



Original Article

Validation of the Kohnen Restless Legs Syndrome–Quality of Life instrument



Ralf Kohnen ^{a,b}, Pablo Martinez–Martin ^c, Heike Benes ^{d,e}, Claudia Trenkwalder ^{f,g},
Birgit Högl ^h, Elmar Dunkl ⁱ, Arthur S. Walters ^{j,*}

^a Posthumously, Research Pharmaceutical Services, Inc, Fort Washington, PA, USA

^b University of Erlangen, Nuremberg, Germany

^c National Center of Epidemiology and CIBERNED, Carlos III Institute of Health, Madrid, Spain

^d Somi Bene Institute for Medical Research and Sleep Medicine, Schwerin, Germany

^e Medical Center, University of Rostock, Rostock, Germany

^f Department of Neurosurgery, University Medical Center, Goettingen, Germany

^g Paracelsus Elena Clinic, Kassel, Germany

^h Department of Neurology, Medical University of Innsbruck, Austria

ⁱ PRA Health Sciences, Nuremberg, Germany

^j Department of Neurology, Vanderbilt University School of Medicine, Nashville, Tennessee, USA

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ABSTRACT

Background: Due to the symptoms and the sleep disturbances it causes, Restless Legs Syndrome (RLS) has a negative impact on quality of life. Measurement of such impact can be performed by means of questionnaires, such as the Kohnen Restless Legs Syndrome–Quality of Life questionnaire (KRLS-QoL), a specific 12-item instrument that is self-applied by patients. The present study is aimed at performing a first formal validation study of this instrument.

Methods: Eight hundred ninety-one patients were included for analysis. RLS severity was assessed by the International Restless Legs Scale (IRLS), Restless Legs Syndrome–6 scales (RLS-6), and Clinical Global Impression of Severity. In addition the Epworth Sleepiness Scale (ESS) was assessed. Acceptability, dimensionality, scaling assumptions, reliability, precision, hypotheses-related validity, and responsiveness were tested.

Results: There were missing data in 3.58% patients. Floor and ceiling effects were low for the subscales, global evaluation, and summary index derived from items 1 to 11 after checking that scaling assumptions were met. Exploratory parallel factor analysis showed that the KRLS-QoL may be deemed unidimensional, ie, that all components of the scale are part of one overall general quality of life factor. Indexes of internal consistency ($\alpha = 0.88$), item-total correlation ($r_s = 0.32–0.71$), item homogeneity coefficient (0.41), and scale stability (ICC = 0.73) demonstrated a satisfactory reliability of the KRLS-QoL. Moderate or high correlations were obtained between KRLS-QoL scores and the IRLS, some components of the RLS-6, inter-KRLS-QoL domains, and global evaluations. Known-groups validity for severity levels grouping and responsiveness analysis results were satisfactory, the latter showing higher magnitudes of response for treated than for placebo arms.

Conclusions: The KRLS-QoL was proven an acceptable, reliable, valid, and responsive measure to assess the impact of the RLS on quality of life.

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1. Introduction

The Kohnen Restless Legs Syndrome–Quality of Life questionnaire (KRLS-QoL) is a specific measure for assessment of QoL in

patients with RLS [1] (Table 1). The validation study for the questionnaire has only previously been published in abstract form [2]. Our study reports its full validation.

The preliminary version of the KRLS_QoL was a 14-item scale derived from a survey on 721 German patients from self-help groups. Patients reported openly on consequences of their RLS and the reports were qualitatively analysed to obtain the core information for establishing the KQoL-RLS dimensions. A pilot application to 69 RLS patients followed and, subsequently, 12 items were finally

* Corresponding author. Division of Sleep Medicine, Vanderbilt University School of Medicine, Medical Center North A-0118, 1161 21ST Avenue South, Nashville, Tennessee 37232-2551, USA. Fax: +1 615 936 5663.

E-mail address: Arthur.Walters@vanderbilt.edu (A.S. Walters).

Table 1

Kohnen Restless Legs Syndrome–Quality of Life Questionnaire.

Dear patient,

we would like to ask you to evaluate the burden of disease of “Restless Legs Syndrome“ (RLS) on you in this questionnaire. Your answers will allow us to better understand the progress of your disease and how you manage your normal daytime activities with it. If you have any other diseases besides the RLS, please try to assess only the effects of RLS on your quality of life.

Please read the following questions carefully and cross for each question only one answer that matches best your situation. It may be that your symptoms are now different as compared to one year ago or prior to the start of an effective therapy. To evaluate the question how you are feeling at the moment, we ask you to answer all questions for the time period covering the **last four weeks**.

Topic 1 Effects of the RLS symptoms						
1. To what degree do your RLS symptoms disturb your sleep?	not at all	very slightly	slightly	moderately	quite a bit	extremely
<i>e.g. difficulties in falling asleep, awakening at night, pain at night, premature awakening in the morning.</i>						
2. To what degree do your RLS symptoms impair your general performance?	not at all	very slightly	slightly	moderately	quite a bit	extremely
<i>e.g. profession or work in household, planning of daily routine (e.g. seating activities in the morning, walking in the afternoon) or leisure activities.</i>						
3. To what degree do your RLS symptoms impair your mental health / your mood?	not at all	very slightly	slightly	moderately	quite a bit	extremely
<i>e.g. dejection, depression, fear (e.g. fear to go to bed or fear of a worsening of the RLS), unrest, sorrow due to the progress of the disease, of medication intake, of restricted mobility.</i>						
4. Do your RLS-symptoms impair your social activities?	not at all	very slightly	slightly	moderately	quite a bit	extremely
<i>e.g. avoidance or reduction of social activities with your family or with others because you don't want to be a burden to others or you don't want to attract attention since you can't sit still or have to stand up.</i>						
Topic 2 Disturbed sleep and its effects						
5. To what degree do lack of sleep or bad sleep impair your normal daytime activities?	not at all	very slightly	slightly	moderately	quite a bit	extremely
<i>e.g. reduced physical performance, reduced performance in household and/or work, more difficulties in planning the daily activities or impairment of your leisure activities.</i>						
6. To what degree does daytime sleepiness impair your mental health / your mood?	not at all	very slightly	slightly	moderately	quite a bit	extremely
<i>e.g. feeling of weariness, sleepiness, reduced endurance, feeling unenthusiastic, unbalanced, nervous, lack of concentration or exhaustion.</i>						
Topic 3 Effects of other features						
7. To what degree do you feel impaired by side effects of your RLS medication?	not at all	very slightly	slightly	moderately	quite a bit	extremely
<i>e.g. retching and nausea, diarrhea or constipation, sleep disturbances, vertigo, heavy or swollen legs, unease, sweating, dry mouth, etc.</i>						
In case of several side effects: please assess the most pronounced side effect.						
8. To what degree do pains in legs or arms impair your wellbeing or your normal daytime activities?	not at all	very slightly	slightly	moderately	quite a bit	extremely

(continued on next page)

Table 1 (continued)

Topic 4 Your way of handling the RLS-symptoms						
9. If you use a certain method to ease the symptoms: How burdening is the performance of those measures?	doesn't apply	very slightly	slightly	moderately	quite a bit	extremely
<i>Examples are: walking around, getting up in the night, massage, embalm, cool or warm the legs, gymnastics, etc.</i>						
10. Do you avoid certain activities or situations due to your RLS-symptoms?	never	very rarely	seldom	medium	frequently	almost always
<i>e.g. situations like sitting for a long time during bus-, rail-, car- or flight-trips, visits to theater or cinema, or avoiding of certain situations like stress, overexertion or agitation.</i>						
11. If you have deliberately changed your way of life due to your RLS-symptoms: To what degree do you feel burdened by that?	no change	very slightly	slightly	moderately	quite a bit	extremely
<i>e.g. change in diet (avoid or restrict certain food, alcohol, nicotine, or caffeine), changes in sleep behavior, changes in professional work, avoid social activities, etc.</i>						
Topic 5 At the End: Your overall Quality of Life						
12. Summarizing: To what degree did your RLS-symptoms impair your quality of life during the last 4 weeks?	not at all	very slightly	slightly	moderately	quite a bit	extremely
<i>Please consider your physical and mental health, your physical and general performance, your normal daytime activities, and your social activities.</i>						

Thank you for filling in this questionnaire.

Intellectual property and Contact Information:

The Kohnen RLS-QoL is the result of a joint work undertaken by EURLSSG members. The EURLSSG owns intellectual property over the Kohnen RLS-QoL including but not limited to all and any translations and other derivatives (e.g. electronic versions). The EURLSSG has assigned Mapi ResearTrust for the management of the instrument licenses and permission to use. Please contact the Mapi Research Trust at e-mail:

PRO-information@mapi-trust.org; website: <http://www.proqolid.org>.

selected for the definitive version [1]. The KRLS-QoL is a 12-item self-assessment with questions about physical, mental, social, and functional impact of RLS, as well as coping behavior. The responses range from zero (no impairment at all) to 5 (extreme impairment). Items one to four are focused on “Effects of RLS symptoms”; items 5 and 6 on “Disturbed sleep and its effects”; items 7 and 8 refer to “Effects of other features”; and items nine to eleven compose a “Your way of handling the RLS symptoms” domain. The item 12 summarizes the perceived impact of the RLS on the quality of life as a whole. The time frame is “the last 4 weeks”. To the purpose of the present validation study, a composite score was derived from the KRLS-QoL items one to 11 and was deemed to represent the impact on QoL due to these questionnaire components. The overall QoL impairment by RLS assessed by the item 12 was considered apart, as a global evaluation resulting from a judgment related with the items included plus other aspects not included in the questionnaire. Furthermore, the addition of the global evaluation to the summary score resultant from the other items would be partially redundant.

2. Methods

2.1. Terminology

Health-related quality of life is a patient-reported outcome frequently applied for monitoring the (HRQoL) effect of interventions in clinical trials and the impact of health status disorders on physical, mental, and social domains, a multidimensional perspective derived from the World Health Organization definition of health [3,4]. The term “quality of life” (QoL) is a wider construct than “health-

related quality of life” health being only one of its determinants, but in the clinical setting both terms are used indistinctly. We will refer hereafter to health-related quality of life as QoL, understood as “the perception and evaluation by patients themselves of the impact that the disease and its consequences have on their life” [5]. HRQoL is usually assessed by means of questionnaires (QoL scales or measures) that may be generic, both for evaluating the most important health domains in general population or any condition, and specific for populations which assess specific areas of interest for certain illnesses, populations or symptoms.

2.2. Patients

The sample for the present study comes from four multicenter, double-blind, randomized active or placebo-controlled clinical trials [6–11] and has been previously described [12]. In summary, the inclusion criteria for these studies were: both gender patients, aged 18 to 75 (cabergoline trials: CALDIR, CABAS-0067-031: [CT.gov](http://www.ct.gov) Identifier: NCT00625547; CATOR, CABAS-0067-033: [CT.gov](http://www.ct.gov) Identifier: NCT00627003) or 18 to 80 (lisuride trials: TULIR 02/01, EudraCT Number: 2004-001589-42; TULIR 03/01, EudraCT Number: 2005-003549-16) years, experiencing all four clinical manifestations of RLS according to the IRLSSG Criteria [13]. Severity of symptoms had to be at least moderate (IRLS total score at baseline ≥ 10 for cabergoline trials; ≥ 15 for lisuride trials), and a “severity at night” score of ≥ 4 (cabergoline trials) in the RLS-6 rating scale. Patients were either denovo or unsatisfied with previous RLS therapy.

Exclusion criteria were: 1) Secondary RLS, iron deficiency, or other clinically relevant concomitant diseases, relevant findings in ancillary tests, and skin disorders on application area (lisuride patch trials)

[8,9]. Uremic RLS patients were allowed in the lisuride studies and there were seven such patients. 2) Established or suspected hypersensitivity to the tested drug or non-response/intolerability to previous cabergoline or L-dopa therapy (CBG) [6,7]. 3) Concomitant use of drugs with a probable influence on RLS or sleep structure were not permitted and had to be discontinued at the start of the washout period one week before baseline. 4) Previous treatment with cabergoline [6] or discontinuation of the drug in less than two months prior to screening [7]. Women of child-bearing potential had to use a reliable method of contraception. Patients were recruited in outpatient unit of neurological hospitals or in private neurological sleep laboratories.

2.3. Ethical issues

All four studies were approved by the corresponding Ethics Committees and patients signed their informed consent before inclusion in the study.

2.4. Assessments

In addition to the KRLS-QoL the following assessments were applied: International Restless Legs Scale (IRLS), version for clinical trials [14], Restless Legs Syndrome-6 scales (RLS-6) [12], Epworth Sleepiness Scale (ESS) [15], and Clinical Global Impression of Severity (CGIS) [16].

The RLS-6 includes six items, each one scoring on a 0–10 scale from 0 (no symptoms) to 10 (very severe). In addition to questions about satisfaction with sleep and sleepiness, the scales rate the severity of RLS for the past week under different circumstances and times of day: during the night, during the day while sitting or lying, and during the day when moving around. The RLS-6 scale was not designed to calculate a total score, but to assess the following 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); 4) RLS during activity (item 5) which really is 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 [17]. The scale is applied under conditions of a face-to-face interview with the patient where clarifications regarding the questions can be made to the patient, but the scale can also be self-completed. It is the most extensively used of the RLS severity scales in research studies of all types. It has excellent clinimetric properties and is used as the benchmark outcome measure for treatment trials in RLS [18].

The ESS and CGIS are generic scales. The ESS is a 8-item scale to assess excessive daytime somnolence and the CGIS provides a clinician-based subjective score of severity from 0 (not assessed) to 7 (among the most extremely ill patients).

2.5. Data analysis

A database for the present study was created from the previously mentioned studies [6–11] and submitted to the National Center of Epidemiology (ISCIII, Madrid, Spain). Descriptive statistics (central tendency and dispersion, proportions) were applied to the variables in the study to characterize the sample.

Main variables in the study did not get a normal distribution (graph plot, Shapiro-Francia test); therefore, non-parametric statistics were used. In addition to the perceived global impact (item 12), a RLS-related quality of life index based on the scale components was derived as arithmetic mean of the item 1 to 11 scores (KRLS-QoL Index). The following clinimetric attributes were determined and tested against the corresponding standard values:

Acceptability: Percentage of missing data (standard <10%) [19]; mean and median closeness; range of scores; skewness (between –1 and +1) [20]; and floor and ceiling effect (<15%) [21].

Scaling assumptions were explored to determine the appropriateness of summing up the KRLS-QoL items 1 to 11. To this purpose, the range of means, standard errors of the mean, variances, and CI95% distribution, that must be roughly equivalent, were determined [22,23].

Dimensionality: It was explored by factor analysis, principal component factor. The number of factors was chosen according to the Kaiser criterion (eigenvalue >1) and scree plot inspection. Bartlett sphericity index for suitability of the analysis ($P < 0.05$) and Kaiser-Meyer-Olkin for sampling adequacy (>0.60) were considered [24]. The final number of advised dimensions was explored by Parallel factor analysis using Unweighted least squares and Exploratory maximum likelihood methods [25].

Internal consistency: Cronbach's alpha index, as reliability index (standard, >0.70) [26]; item-total corrected correlation (standard, $r \geq 0.30$) [19]; and item homogeneity coefficient (standard >0.40) [27] were determined for items 1 to 11.

Test-retest: A group of 78 patients were considered "stable" during a homogeneous follow-up period of 90 ± 7 days. The stability was determined by a change lower than ± 3 points in the IRLS total score. This limit value was derived from two thresholds indicative of a real change: $\frac{1}{2}$ standard deviation at baseline = 3.17 [28,29] and the standard error of the difference baseline–follow-up = 3.27 [30]. Weighted kappa with quadratic weights for items and intraclass correlation coefficient (ICC, one-way, individual) for the KRLS-QoL Index were applied. The standard error of measurement, based on the baseline standard deviation and the ICC of the KRLS-QoL Index, was calculated [31,32].

Hypotheses testing: An *a priori* close association ($r \geq 0.50$) was expected between the KRLS-QoL and total scores of measures for RLS severity and impact, whereas moderate ($r = 0.35–0.50$) or low correlations ($r < 0.35$) were expected with other variables in the study. Internal validity between KRLS-QoL domains would be considered satisfactory with correlation coefficient values 0.30–0.70 [19,20] and a high correlation was hypothesized between the overall QoL evaluation (KRLS-QoL Item 12) and the KRLS-QoL Index. Known-groups validity was determined for severity categories of RLS based on the IRLS scores, CGIS, and duration of the RLS. For the continuous variables, grouping was carried out according to median and interquartile range. A significant increase of the RLS-6 scores was expected with increasing RLS severity, whereas the difference for duration categories could be non-significant. Kruskal-Wallis test with Bonferroni correction was applied for comparisons.

Responsiveness: It was defined as the ability of the RLS-6 to detect a change. To this purpose, the analysis was carried out on data from those patients who participated in the placebo-controlled lisuride clinical trials [8–11] and were followed-up for a similar period (mean, 90 days; SD, 3.9; range: 83–97). This sample was composed of 82 patients in the placebo arm and 179 in the lisuride branch. Patients in the cabergoline trials [6,7] could not be included as their follow-up was too variable to the purpose of the analysis (mean, 140.5 days; SD, 81.1; range 7–231). For the analysed patients, no statistical differences between arms were found for age, gender, age at onset, and RLS duration at baseline. The following responsiveness parameters were determined: Relative change [33], Wilcoxon and Mann-Whitney tests (for intra- and inter-groups comparisons), effect size, standardized response mean, and correlation of change between KRLS-QoL index and item 12 with change in RLS severity measures (IRLS, RLS-6, CGIS) were calculated [34,35].

Analysis was carried out with Stata 13 (Stata Corp., 4905 Lakeway Drive College Station, Texas 77845 USA) and Factor 9.2 (Univ. Rovira I Virgili, Tarragona, Spain).

3. Results

Eight hundred ninety-three patients, mean (\pm SD) age 58.73 ± 11.46 (range: 21.90–82.34) years, 71.56% women, were included in the study. Their body mass index was 26.55 ± 4.10 (range: 16.90–44.98). Historical and evaluative data related with the RLS are shown in the Table 2.

In the KRLS-QoL there were 1 or 2 missing data in items 5 to 12 in 9 cases and 29 in the item 7, with 861 patients (96.42%) providing fully completed questionnaires. Imputation by the individual's mean [36] was carried out if the proportion of missing data was $\leq 25\%$. Two patients were excluded because they had more than 30% of empty boxes. Therefore, the final sample for the KRLS-QoL validation analysis was 891 patients (99.78%). Table 1S (Supplementary material) shows the results of the Acceptability parameters. The range of scores for all items was 0–5 and 0.36 to 5 for the KRLS-QoL index. Data related to scaling assumptions are displayed in the Table 2S (Supplementary material). The range of values for each tested parameter was quite narrow, supporting the appropriateness of their summed scores for obtaining the summary index.

The exploratory factor analysis (Bartlett test, $P < 0.00001$; Kaiser-Meyer-Olkin test = 0.90) identified two factors (explaining 56.85% of the variance) after orthogonal and promax rotations: Factor 1, Impaired health by symptoms, included the items 1, 2, 3, 5, 6, 8, and 12, and Factor 2, Burden of symptoms, included items 7, 10 and 11. Items 4 (Impairment of social activity) and 9 (Burden of relief methods) did not load clearly on any factor. The parallel factor analysis advised for considering only 1 dimension in the scale (Comparative Fit Index = 0.95, 1.32; Goodness of Fit Index = 1.00; Adjusted Goodness of Fit Index = 0.99).

Cronbach's alpha (items 1 to 11) was 0.88, item-total correlation ranged from 0.32 (Item 7) to 0.71 (Items 2 and 5), the inter-item correlation from 0.11 (item 1 with item 7) to 0.77 (item 5 with item 6), and the item homogeneity coefficient was 0.41. Concerning the test-retest analysis, kappa values were 0.43 (Item 7) to 0.64 (Item 4) and the ICC for the KRLS-QoL Index, 0.73. For the Item 12, impairment of QoL by RLS, kappa was 0.56.

Both the KRLS-QoL Index and Domain 5 (Item 12) reached moderate or high correlations with the IRLS total scores and subscores of severity, moderate or low with the components of the RLS-6 and CGIS, and weak to negligible with other variables in the study (Table 3S, Supplementary material). The correlation coefficient values were lower for the Item 12, except for the variables related with age (age at study, age at onset) (Table 3S, Supplementary material). The correlation among KRLS-QoL domains was 0.42–0.74 and between KRLS-QoL Index and Item 12 was 0.74.

In regard to the known-groups validity, the KRLS-QoL Index and Item 12 significantly increased their scores with increasing RLS se-

Table 2
Descriptive data of the Restless Legs Syndrome and scales in the sample.

	Mean	SD	Min.	Max.
RLS duration (a)	13.40	13.24	0	59.70
Duration of treatment (b)	2.69	2.95	0	21.93
Age at onset	45.34	16.21	3.63	78.68
IRLS Total score	27.48	6.34	9	40
IRLS Subscore severity	19.45	3.89	6	24
IRLS Subscore impact	6.36	3.05	0	12
RLS-6 – Sleep quality	12.25	4.36	0	20
RLS-6 – Nighttime	12.82	4.80	1	20
RLS-6 – Daytime	4.90	2.62	0	10
RLS-6 – Mimics	1.59	2.06	0	10
Clinical Global Impression	4.83	0.94	1	7
Epworth Sleepiness Scale	7.85	4.95	0	22

N = 893, except (a), n = 704, and (b), n = 891.

Abbreviations: SD: standard deviation; Min.: Minimum; Max.: Maximum; RLS-6: Restless Legs Scale – 6 items; IRLS: International Restless Legs Scale.

Table 3

Known-groups validity of the Kohnen Restless Legs Syndrome–Quality of Life questionnaire.

Categories	n	KRLS-QoL Index		KRLS-QoL Item 12	
		Mean	SD	Mean	SD
RLS Duration (years)*					
<3.30	220	2.47	0.91	3.22	1.10
3.30–8.86	224	2.45	0.90	3.17	1.03
8.87–19.77	222	2.48	0.92	3.15	1.11
≥ 19.78	225	2.72	0.91	3.23	1.21
P	–	0.003		0.56	
IRLS score					
<23	205	1.79	0.76	2.31	1.13
23–27	218	2.16	0.68	2.87	1.00
28–31	198	2.62	0.70	3.42	0.79
≥ 32	270	3.33	0.64	3.95	0.76
P	–	0.0001		0.0001	
CGI-Severity					
Normal (1)	3	1.58	1.23	1.67	2.08
Mild (2, 3)	49	2.09	0.96	2.65	1.13
Moderate (4)	267	2.13	0.76	2.82	1.07
Severe (5)	351	2.53	0.89	3.19	1.10
Very severe (6, 7)	221	3.12	0.77	3.80	0.87
P	–	0.0001		0.0001	

(P) Kruskal-Wallis test. Significance after Bonferroni correction, $P < 0.0083$.

Abbreviations: SD: Standard deviation; CGI: Clinical Global Impression; RLS-6: Restless Legs Scale – 6 items; IRLS: International Restless Legs Scale; RLS: Restless Legs Syndrome.

* Categories according to interquartile range.

verity levels based on the IRLS and CGIS scores, but no with duration of the disorder (Table 3).

Concerning the responsiveness parameters (Table 4), both KRLS-QoL Index and Item 12 performed similarly, the latter showing a trend to reach slightly higher values for most of the parameters than the KRLS-QoL Index, except for correlations of change. Although a significant placebo effect was present in this study, the responsiveness data clearly indicated a higher effect for the group in active treatment.

4. Discussion

The present study follows the development and initial testing of the KRLS-QoL, a specific instrument for QoL assessment in RLS [1,2,37]. A wide sample of patients with moderate RLS symptoms on average were evaluated with the tested questionnaire and additional recognized measures for RLS.

The results of the present study support the use of the KRLS-QoL as an acceptable, reliable, valid, and responsive instrument for assessment of the QoL deterioration caused by the RLS and the results of the psychometric properties that were explored in the early validation study [2] were overwhelmingly confirmed in this new analysis.

Missing data were $< 4\%$ and allowed imputation for obtaining a final full computable sample of 891 patients (99.78%). The item with more missing scores was item 7, related with side effects of medication for RLS. There are several explanations for this finding, such as uncertainty to choose a response by those patients without treatment or to identify some symptoms as side effects, etc. A proposal for decreasing this problem could be to indicate that patients without treatment should mark "0". Nonetheless, data quality could be considered excellent.

Variance, standard error of the mean, and confidence interval 95% provided relatively near values among items 1 to 11 in the scale, giving support for obtaining an Index representative of the RLS-related quality of life on the basis of those components. In health-related quality of life measures with several dimensions, summary indexes have proved to be helpful reducing profile data to a figure

Table 4

Kohnen Restless Legs Syndrome–Quality of Life questionnaire responsiveness data.

			KRLS-QoL Index	KRLS-QoL Item 12
Mean ± SD	Placebo	Baseline	2.53 ± 0.83	3.13 ± 1.00
		Follow-up	1.92 ± 1.17	2.27 ± 1.44
		Difference	0.61 ± 1.02	0.87 ± 1.37
	Lisuride	Baseline	2.64 ± 0.83	3.35 ± 0.98
		Follow-up	1.54 ± 1.15	1.84 ± 1.44
		Difference	1.10 ± 1.11	1.52 ± 1.50
Relative change (5)	Placebo		–24.11	–24.48
	Lisuride		–41.62	–45.10
Difference intra-group*	Placebo		(z = 1.84) P < 0.0001	(z = 4.83) P < 0.0001
	Lisuride		(z = 9.69) P < 0.0001	(z = 9.83) P < 0.0001
Difference inter-groups†			(z = –3.58) P = 0.0003	(z = –3.34) P = 0.0008
Effect size	Placebo		0.73	0.87
	Lisuride		1.34	1.55
Standardized response mean	Placebo		0.60	0.64
	Lisuride		1.00	1.01
Correlation of change (Placebo Lisuride)	International Restless Legs Scale		0.62 0.74	0.53 0.70
	RLS-6 Sleep quality		0.42 0.65	0.42 0.56
	RLS-6 Nighttime manifestations		0.54 0.68	0.55 0.65
	RLS-6 Daytime manifestations		0.43 0.60	0.36 0.54
	RLS-6 Mimics		0.16 0.35	0.07 0.35
	Clinical Global Impression of Severity		0.55 0.62	0.43 0.53

* Wilcoxon test.

† Mann-Whitney test.

representative of the impact by the disorder [38–40]. Such summary score is not equivalent to the single-item overall quality of life appraisal, a direct judgment including those aspects considered into the profile plus others [41–43].

The KRLS-QoL domains and Index showed acceptability results into the range of standard values, with close median to mean values, absence of significant floor or ceiling effects, and items covering the full range of potential scores without skewness (except a marginal skewness for item 7). In summary, the parameters referred to KRLS-QoL acceptability are deemed satisfactory.

As in the early validation report [2], two factors (with similar composition) and almost equivalent explained variance (56.67% vs. 56.85%) were found, although the Parallel analysis showed that the scale can be considered unidimensional and, therefore, with all items grouped around a single construct, namely QoL. Cronbach's alpha value was also almost equivalent to the previous study (0.89 vs. 0.88), and indicative of a satisfactory internal consistency. Other parameters of reliability, including item-total correlation and homogeneity index resulted over the adequacy threshold for these scale properties. The stability of KRLS-QoL scores was moderate to substantial for the items and acceptable for the Index. It is relevant to emphasize that the considered re-test was performed three months after the first application, a long period in comparison with the usual two to four weeks span. This fact probably has allowed some bias (for example, regression to the mean, variation in the reaction, etc.) that decreased the reproducibility of the scores.

Concerning the convergent validity of the scale, high correlations were found between KRLS-QoL index and Item 12 and the IRLS (total and impact scales, mainly) and RLS-6 Sleep quality domain. The correlation between other KRLS-QoL components and these scales and CGIS ranged from weak to strong (Table S3, Supplementary material). Again, the most relevant results were almost coincided with the previous validation study [2] and, as a whole, performed as hypothesized. To be highlighted of note, a weak to negligible association was found with age, duration of RLS, and ESS.

The internal validity (inter-domains correlations) was into the standard values and the correlation between KRLS-QoL index and

global QoL evaluation (Domain 5. Item 12) was 0.74, demonstrating close association but no equivalence of both estimations [41–43], a fact observed in similar circumstances with measures for other constructs [44–46]. Therefore, the RLS-QoL allows one to assess the impact on QoL of several RLS specific aspects as well as a global appraisal directly estimated by the patient.

Known-groups validity analysis, as expected, showed significant higher impact on the QoL for increasing levels of severity according the IRLS and CGIS (Table 3). The association between RLS duration categories and RLS-QoL scores was lower, reaching non-significant values for the Domain 5. Item 12.

A remarkable placebo effect has been previously observed in RLS studies, both with the IRLS and RLS-6 in this series [12] and also is found with the KRLS-QoL. Nonetheless, the responsiveness parameters of this scale showed a considerable decrease in scores, relative change, significant change between baseline and follow-up evaluations (both intra- e inter-groups), for placebo and lisuride groups, with higher magnitudes for the latter. Effect size and standardized response mean resulted large for lisuride and moderate, as a whole, for placebo. The correlations of change were high with the IRLS for both groups and moderate to high with RLS-6 Sleep quality and Nighttime manifestations (Table 4), and constantly higher for the lisuride group. Differences between values with KRLS-QoL Index and Domain 5. Item 12 were marginal. Therefore, KRLS-QoL is deemed a responsive measure with two useful summary figures.

A relevant limitation of the study is related to the origin of the data, as patients were selected for clinical trials and the study was not designed for validation of a health measure. Nonetheless, the sample size, the high quality of the data and the implementation of a therapeutic intervention that allowed testing the questionnaire responsiveness provide strength to the findings.

The KRLS-QoL is one of the three questionnaires for measuring the impact of RLS on the patients QoL identified by the Movement Disorder Society Task Force (MDS-IF) that carried out a systematic review of this kind of instruments [37]. The Abetz RLS-QoL is a 18-item questionnaire providing four-week time frame assessment. A summary score derived of 10 of the 18 items is obtained

Table 5
Detailed analysis of RLS Quality of Life instruments.

Name of Instrument	Subjects	IRR by Kappa or ICC or other Test-Retest	CA, FA	CRIT, CONV, DIV, KG	RESPONSE ES
RLS-QOL-Abetz	85 for initial validation. 519 for additional validation and responsiveness.	Test-Retest ICC = 0.79	CA = 0.92. Three factors with 72% variance	CONV $r = 0.5$ with MCS of SF-36. Item-scale correlations 0.5 to 0.9. KG $P < 0.0001$.	$R = -0.51$, $P < 0.0001$ ES 0.54 to 1.51.
RLS-QLI	574 with mean age 54.5 yrs, ratio of 1M:2F.	Test-Retest subscales 0.81 to 0.93	CA of subscales 0.85 to 0.91. Four factors with 73.3% of variance.	CRIT subscales to IRLS $r = -0.43$ to -0.77 . Correlation between subscales 0.48 to 0.63. CONV subscales $r = 0.26$ to 0.62.	
RLS-QOL – Kohnen	893 with mean age 58.73 yrs and 71.56% women	Test-retest Kappa for individual items 0.43 to 0.64. ICC for Index = 0.73	CA = 0.88. Two factors with 56.85% of the variance.	Correlation between domains $r = 0.42$ to 0.74. Correlations for Index to IRLS = 0.68. K-G Index to IRLS severity $P < 0.0001$. Correlation of Index TO RLS-6 items = 0.33 to 0.57	RC placebo: -24.11% RC lisuride: -41.62% ES placebo = 0.73. ES lisuride = 1.34

Abbreviations: IRR, interrater reliability as measured by Cohen K or intraclass correlation (ICC) or other; CA, Cronbach α , which is a measure of the internal consistency of the instrument; FA, factor analysis which is a method applied to inform about the dimensionality of the instrument (construct validity); CRIT, criterion validity which means comparison of the instrument to a gold standard; CONV, convergent validity which refers to the correlation of the instrument with another measure of RLS or its comorbidities; DIV, divergent or discriminant validity which refers to the correlation of the instrument with another measure not related to RLS; K-G, Known-groups (discriminative) validity which refers to the ability of the instrument to detect differences between groups at a point in time; Response, responsiveness which is a measure of change of an instrument over time with or without treatment; RC, relative change; ES, effect size.

with the other items, some scored as continuous and others as categorical variables, being excluded of this score by different reasons [47]. It has shown excellent attributes (acceptability, reliability, and responsiveness) and met the MDS-TF criteria to be “Recommended” as a valid instrument for assessment of QoL in RLS. The Restless Legs Syndrome Quality of Life Instrument (RLS-QLI) is a 17-item questionnaire with four scales identified through factor analysis: Daily Function, Social Function, Sleep Quality, and Emotional Well-Being [48]. It evaluates the RLS impact on the past 30 days and although the tested clinimetric properties resulted satisfactory, there was not information about the responsiveness and a diagnosis of true RLS in the subjects participating in the validation study could not be assured. Therefore, the RLS-QLI was qualified “Suggested” by the MDS-TF. The KRLS-QoL was classified as suggested on the basis of preliminary data of validity [2], but there were not data on stability and responsiveness reaching a recommendation of “Suggested” [37]. The present study completes this gap and would allocate this questionnaire as a valid, “Recommended” alternative measure for assessment of QoL in RLS.

Overall the Abetz RLS-QOL, the RLS-QLI and the KRLS-QOL have comparable psychometric properties and are good measures of RLS QOL under baseline conditions as can be seen by a comparison of all three scales in Table 5. However, only the Abetz-QOL and the KRLS-QOL have been shown to be responsive to change under therapeutic conditions (Table 5).

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Intellectual property and Contact Information:

The Kohnen RLS-QOL is the result of a joint work undertaken by EURLSSG members. The EURLSSG owns intellectual property over the Kohnen RLS-QOL 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 contact the Mapi Research Trust at e-mail: PRO-information@mapi-trust.org; website: <http://www.proqolid.org>.

Conflict of interest

Ralf Kohnen: Board membership for UCB Pharma, Mundipharma. Employee of Research Pharmaceuticals Services, Inc. Fort Washington, PA.

Pablo Martinez-Martin: Board membership for Abbvie. Lectures/Speakers Bureau for Abbvie, Viguera.

Heike Benes: Lectures/Speakers Bureau for Mundipharma, UCB Pharma.

Claudia Trenkwalder: Board membership for Mundipharma, UCB Pharma, Boehringer-Ingelheim, Novartis, Britannia, Destin, Vifor.

Birgit Hogl: Research grant from UCB Pharma. Consultant/Honorarium from Mundipharma, Otsuka and UCB Pharma. Support/travel and other purposes from Habel, Medizintechnik and Vivisol, Austria. Payment for lectures from Otsuka, UCB Pharma, Mundipharma, Abbvie and Lundbeck.

Elmar Dunkl: Research employee of PRAHS Pharmaceutical.

Arthur S. Walters: Restless Legs Syndrome (RLS) medical advisory board for UCB Pharma. Grants for RLS research from UCB Pharma, Mundipharma, and Xenoport.

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.2016.04.019>.

Appendix: Supplementary material

Supplementary data to this article can be found online at <doi:10.1016/j.sleep.2016.04.019>.

References

- [1] Kohnen R, Benes H, Heinrich CR, et al. Development of the disease-specific Restless legs Syndrome Quality of Life (RLS-QOL) questionnaire. *Mov Disord* 2002;17(Suppl. 5):232.
- [2] Kohnen R, Beneš H, Högl B, et al. Disease-specific Quality of Life (QoL) in Restless Legs Syndrome (RLS): validation of the RLS-QoL Questionnaire. *Sleep Med* 2011;12(Suppl. 1):S118.
- [3] World Health Organization. Handbook of basic documents. 5th ed. Geneva: WHO, Palais des Nations; 1952. p. 3–20.
- [4] Schipper H, Clinch JJ, Olweny CLM. Quality of life studies: definitions and conceptual issues. In: Spilker B, editor. Quality of life and pharmacoeconomics in clinical trials. 2nd ed. Philadelphia: Lippincott-Raven Publishers; 1996. p. 11–23.

- [5] Martinez-Martin P. An introduction to the concept of "quality of life in Parkinson's disease". *J Neurol* 1998;245(Suppl. 1):S2–6.
- [6] Oertel WH, Benes H, Bodenschatz R, et al. Efficacy of cabergoline in restless legs syndrome: a placebo-controlled study with polysomnography (CATOR). *Neurology* 2006;67:1040–6.
- [7] Trenkwalder C, Benes H, Grote L, et al. Cabergoline compared to levodopa in the treatment of patients with severe restless legs syndrome: results from a multi-center, randomized, active controlled trial. *Mov Disord* 2007;22:696–703.
- [8] Benes H, Kohnen R. Transdermal Lisuride in patients with severe Restless Legs Syndrome: results from a placebo – and ropinirole-controlled, double-blind, randomized, multicenter, 12-week efficacy and tolerability study. *Sleep* 2008;31(Abtract Suppl.):A266–7.
- [9] Benes H, on behalf of the TULIR Study Group. Transdermal lisuride. New results and insights. *J Sleep Res* 2006;15(Suppl. 1):177.
- [10] Benes H, Horowski R, Palla D, et al. Lisuride in restless legs syndrome. *Parkinsonism Relat Disord* 2005;11(Suppl. 2):270.
- [11] Benes H, on behalf of the TULIR Study Group. Transdermal Lisuride in patients with idiopathic Restless Legs Syndrome: results from a placebo-controlled, double-blind, randomized multicenter, 12-week, dose finding study. *Sleep Med* 2005;6(Suppl. 2):S156.
- [12] Kohnen R, Martinez-Martin P, Benes H, et al. Rating of daytime and night-time symptoms in RLS: validation of the RLS-6 scale of restless legs syndrome/Willis-Ekbom disease. *Sleep Med* 2016;20:116–22.
- [13] Allen RP, Picchiatti D, Hening WA, et al. Restless legs syndrome: diagnostic criteria, special considerations, and epidemiology. A report from the restless legs syndrome diagnosis and epidemiology workshop at the National Institutes of Health. *Sleep Med* 2003;4:101–19.
- [14] Hening WA, Allen RP. Restless legs syndrome (RLS): the continuing development of diagnostic standards and severity measures. *Sleep Med* 2003;4:95–7.
- [15] Johns MW. A new method for measuring daytime sleepiness: the Epworth sleepiness scale. *Sleep* 1991;14:540–5.
- [16] Guy W, editor. ECDEU assessment manual for psychopharmacology – revised. Rockville, MD, USA: Department of Health, Education, and Welfare; 1976. p. 218–22 DHEW Publ No ADM 76-338.
- [17] Allen RP, Kushida CA, Atkinson MJ, et al. Factor analysis of the International Restless Legs Syndrome Study Group's scale for restless legs severity. *Sleep Med* 2003;4:133–5.
- [18] Walters AS, Frauscher B, Allen R, et al. Review of severity rating scales for the Restless Legs Syndrome: critique and recommendations. *Mov Disord Clin Pract* 2014;1:317–24.
- [19] Hobart JC, Riazi A, Lamping DL, et al. Improving the evaluation of therapeutic interventions in multiple sclerosis: development of a patient-based measure of outcome. *Health Technol Assess* 2004;8:9.
- [20] van der Linden FA, Kragt JJ, Klein M, et al. Psychometric evaluation of the multiple sclerosis impact scale (MSIS-29) for proxy use. *J Neurol Neurosurg Psychiatry* 2005;76:1677–81.
- [21] McHorney CA, Tarlov AR. Individual-patient monitoring in clinical practice: are available health status surveys adequate? *Qual Life Res* 1995;4:293–307.
- [22] Smith SC, Lamping DL, Banerjee S, et al. Measurement of health-related quality of life for people with dementia: development of a new instrument (DEMQOL) and an evaluation of current methodology. *Health Technol Assess* 2005;9:1–93.
- [23] Hobart J, Lamping D, Fitzpatrick R, et al. The Multiple Sclerosis Impact Scale (MSIS-29). A new patient-based outcome measure. *Brain* 2001;124:962–73.
- [24] Beavers AS, Lounsbury JW, Richards JK, et al. Practical considerations for using exploratory factor analysis in educational research. *Pract Assess Res Eval* 2013;18:6.
- [25] Timmerman ME, Lorenzo-Seva U. Dimensionality assessment of ordered polytomous items with Parallel Analysis. *Psychol Methods* 2011;16:209–20.
- [26] Scientific Advisory Committee of the Medical Outcomes Trust. Assessing health status and quality-of-life instruments: attributes and review criteria. *Qual Life Res* 2002;11:193–205.
- [27] Clark LA, Watson D. Constructing validity: basic issues in objective scale development. *Psychol Assess* 1995;7:309–19.
- [28] Norman GR, Sloan JA, Wyrwich KW. Interpretation of changes in health-related quality of life. The remarkable universality of half a standard deviation. *Med Care* 2003;41:582–92.
- [29] Sloan JA, Cella D, Hays RD, et al. Clinical significance of patient-reported questionnaire data: another step toward consensus. *J Clin Epidemiol* 2005;58:1217–19.
- [30] Fitzpatrick R, Norquist JM, Jenkinson C. Distribution-based criteria for change in health-related quality of life in Parkinson's disease. *J Clin Epidemiol* 2004;57:40–4.
- [31] Mokkink LB, Terwee CB, Patrick DL, et al. The COSMIN study reached international consensus on taxonomy, terminology, and definitions of measurement properties for health-related patient-reported outcomes. *J Clin Epidemiol* 2010;63:737–45.
- [32] Wyrwich KW, Nienaber MA, Tierney WM, et al. Linking clinical relevance and statistical significance in evaluating intraindividual changes in health-related quality of life. *Med Care* 1999;37:469–78.
- [33] Deyo RA, Centor RM. Assessing the responsiveness of functional scales to clinical change: an analogy to diagnostic test performance. *J Chronic Dis* 1986;39(11):897–906.
- [34] Terwee CB, Dekker FW, Wiersinga WM, et al. On assessing Responsiveness of health-related quality of life instruments: guidelines for instrument evaluation. *Qual Life Res* 2003;12:349–62.
- [35] Wyrwich KW, Bullinger M, Aaronson N, et al. Estimating clinically significant differences in quality of life outcomes. *Qual Life Res* 2005;14:285–95.
- [36] Shrive FM, Stuart H, Quan H, et al. Dealing with missing data in a multi-question depression scale: a comparison of imputation methods. *BMC Med Res Methodol* 2006;6:57.
- [37] Walters AS, Frauscher B, Allen R, et al. Review of quality of life instruments for the restless legs syndrome/Willis-Ekbom Disease (RLS/WED): critique and recommendations. *J Clin Sleep Med* 2014;10:1351–7.
- [38] Ware JE, Kosinski M, Bayliss MS, et al. Comparison of methods for scoring and statistical analysis of SF-36 health profile and summary measures: summary of results from the Medical Outcomes Study. *Med Care* 1995;33:AS264–79.
- [39] Jenkinson C, Fitzpatrick R, Peto V, et al. The Parkinson's Disease Questionnaire (PDQ-39): development and validation of a Parkinson's disease summary index score. *Age Ageing* 1997;26:353–7.
- [40] EuroQol Group. EQ-5D-3L User Guide. Basic information on how to use the EQ-5D-3L instrument. Rotterdam, The Netherlands: EuroQol Research Foundation; 2015. Version 5.1. <www.euroqol.org>.
- [41] Spilker B. Introduction. In: Spilker B, editor. *Quality of life and Pharmacoeconomics in Clinical Trials*. 2nd ed. Philadelphia: Lippincott-Raven; 1996. p. 1–10.
- [42] Fayers PM, Machin D. *Quality of life. The assessment, analysis and interpretation of patient-reported outcomes*. 2nd ed. Chichester, England: John Wiley & Sons Ltd.; 2007. p. 31–48.
- [43] Wu CH, Yao G. Examining the relationship between global and domain measures of quality of life by three factor structure models. *Soc Indic Res* 2007;84:189–202.
- [44] Locker D, Dunt D. Theoretical and methodological issues in sociological studies of consumer satisfaction with medical care. *Soc Sci Med* 1978;12:283–92.
- [45] Veenhoven R. The study of life satisfaction. In: Saris WE, Veenhoven R, Scherpenzeel AC, et al., editors. *A comparative study of satisfaction with life in Europe*. Budapest: Eötvös University Press; 1996. p. 11–48.
- [46] Frager DC, Coyne L, Lyle J, et al. Which treatments help? The patient's perspective. *Bull Menninger Clin* 1999;63:388–400.
- [47] Abetz L, Vallow SM, Kirsch J, et al. Validation of the Restless Legs Syndrome Quality of Life questionnaire. *Value Health* 2005;8:157–66.
- [48] Atkinson MJ, Allen RP, DuChane J, et al. Validation of the Restless Legs Syndrome Quality of Life Instrument (RLS-QLI): findings of a consortium of national experts and the RLS Foundation. *Qual Life Res* 2004;13:679–93.