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Original article

The reliability, validity and responsiveness of the International Restless Legs Syndrome Study Group rating scale and subscales in a clinical-trial setting

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Abstract

Patients and methods: To assess the reliability, validity, and responsiveness of the International Restless Legs Syndrome Study Group's rating scale (the International Restless Legs Scale (IRLS)) (V2.0), using pooled data from two matching, placebo-controlled studies of ropinirole for treating Restless Legs Syndrome (RLS).

Results: Pooled patient samples comprised 550 patients in the baseline (validation) sample and 439 patients in the week 12 longitudinal (responsiveness) sample. Factor analysis revealed acceptability of the IRLS total score (accounting for 40% of the variance) and that nine of the 10 IRLS items could also be assigned to two distinct subscales, the symptoms or symptoms impact subscales. The IRLS total score, symptoms and symptoms impact subscales had acceptable construct validity, internal consistency reliability ($\alpha = 0.81$, 0.80, and 0.76, respectively), and concurrent validity ($r = -0.68$, -0.52, -0.70, respectively, with the Restless Legs Syndrome Quality of Life questionnaire (RLSQoL) overall life impact score). IRLS scores differed significantly between different levels of sleep problems and Clinical Global Impression (CGI) of health status ($P < 0.0001$), indicating known groups and clinical validity, respectively. Changes in scores differed significantly among CGI 'global improvement' levels ($P < 0.0001$), providing evidence of responsiveness.

Conclusions: The IRLS total score, symptoms, and symptoms impact subscales are reliable, valid, and responsive in a clinical trial setting.

Keywords: IRLS; Restless legs syndrome; Reliability; Validity; Responsiveness; Psychometric analysis

1. Introduction

Restless legs syndrome (RLS) is a neurological disorder characterized by an urgent need to move the limbs (most often the legs) when the patient sits or lies down, usually accompanied by paresthesias (unpleasant sensations, such as 'creeping', 'crawling', 'tingling', 'pulling', or 'pain'). Moving the limbs brings rapid, if variable, relief from the symptoms, but the relief tends to last only as long as the movement continues [1].

The prevalence of RLS increases with age, and the rate in women is about twice that for men [2]. The overall prevalence of RLS appears to vary quite widely, from 2.5 to 15%, depending on the population surveyed [3,4]. There are a number of differential diagnoses, such as leg cramps, paresthesias due to peripheral neuropathy, and arthritic or muscular pain [5]. There are also three major causes of secondary RLS: renal failure, pregnancy, and iron deficiency anemia. Primary RLS has a tendency to run in families. Recent genetic linkage and association studies

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have identified possible areas for a susceptibility gene on chromosomes 12q, 9p, and 14q [6–8]. Each of these susceptibility loci occurs in some RLS families, but not the majority.

RLS becomes worse at night, and clinically significant RLS is usually associated with disruptions to circadian pattern and sleep impairment on a regular basis, leading to fatigue, poor concentration, anxiety, or depression and compromised quality of life [9–13]. It is important, therefore, that measures developed to assess the severity of RLS take into account not only the symptoms themselves, but also the impact of RLS on sleep, mood, and daily functioning. Two disease-specific, clinician-administered measures of RLS symptom severity have been developed and validated: the Johns Hopkins Restless Legs Severity Scale (JHRLSS) [14], and the International Restless Legs Scale (IRLS), developed by the International Restless Legs Syndrome Study Group [1,15]. The JHRLSS was designed as a limited clinical guide based on time of symptom onset. The IRLS, on the other hand, is a more comprehensive measure, consisting of 10 items that address a range of RLS symptoms and their impact on patients' mood and daily life.

Although the original IRLS (Version 1.0) has already been validated [15], it is vital to ensure that the questionnaire also performs well psychometrically when used in different patient groups and as the instrument is further refined through general use. The psychometric properties of the IRLS total score were, therefore, assessed in the patient samples of two recently completed phase-III, multicenter, randomized, double-blind, placebo-controlled studies assessing the efficacy and tolerability of ropinirole, a dopamine agonist, for the treatment of adults with moderate-to-severe RLS: TREAT RLS 1 (Therapy with Ropinirole; Efficacy And Tolerability in RLS 1 [16]), and TREAT RLS 2 [17]. The primary endpoint in both studies was change in IRLS total score.

The findings of two separate psychometric analyses of these studies confirmed the validity of the IRLS total score as the primary measure of overall RLS severity and yielded subscales that were similar to those noted previously [15,18]. The aim of the present study, therefore, was to provide an assessment of the reliability, validity and responsiveness of the IRLS total score and the two potential subscale scores, in a trial patient sample based on the TREAT RLS 1 and 2 studies. The data from both studies were pooled in order to increase the statistical power of the analyses.

2. Methods

2.1. Patient samples

The patient samples from TREAT RLS 1 and 2 were pooled for the present psychometric analysis. Patients were eligible for inclusion in each study if they were at least 18 years of age and had moderate-to-severe RLS (had a baseline IRLS total score of >15 and either had experienced at least 15 nights with symptoms of RLS in the previous month or, if receiving treatment, had symptoms of this frequency before treatment). Patients were excluded from the study if they had any other movement or primary sleep disorder, if they required daytime treatment for RLS, if they were experiencing augmentation or end-of-dose rebound, or if they had secondary RLS. Patients were also excluded if they had a history of alcohol or drug abuse, previous intolerance to dopamine agonists, or were suffering from other clinically relevant conditions affecting assessments.

All patients gave written, informed consent before entering the studies, done according to the principles of the 1996 amendment of the declaration of Helsinki and approved by local ethics committees.

2.2. Clinical trial study design

As matching study designs were used for both studies, it was considered appropriate to pool the data for this analysis. The studies were conducted in a double-blind, randomized, placebo-controlled manner. Patients were recruited from hospitals, sleep centers and neurology clinics in 10 European countries in TREAT RLS 1 (Austria, Belgium, France, Germany, Italy, The Netherlands, Norway, Spain, Sweden and the UK) and in six countries around the world in TREAT RLS 2 (Australia, Canada, Germany, Norway, the UK and the USA). Patients receiving treatment for RLS or treatment known to affect RLS or sleep, or to cause drowsiness, entered a washout phase of either seven consecutive nights or five half-lives of the drug, whichever was the greater. Patients were randomized in a 1:1 ratio to receive once-daily treatment with either ropinirole or placebo for 12 weeks. Ropinirole was initiated at a dose of 0.25 mg/day and titrated upwards during weeks 1–7, either until they were judged to have reached their optimal dose or until they reached the maximum dose of 4.0 mg/day. During the titration period, a maximum of two dose reductions was permitted in the case of adverse events, and doses could then be increased again if the adverse events improved. No further dose changes were permitted after week 7.

The primary endpoint in both studies was change in the IRLS total score, as published previously [16,17]. Secondary endpoints included Clinical Global Impression (CGI) 'global improvement' and 'severity of illness' scores, change in the Restless Legs Syndrome Quality of Life questionnaire (RLSQoL) score, and the medical outcomes study sleep problems index II (MOS sleep scale) score.

2.3. Outcome measures used in psychometric analysis

2.3.1. IRLS

The IRLS was developed and validated by the International Restless Legs Syndrome Study Group [1,15,18].