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Restless legs syndrome/Willis–Ekbom disease diagnostic criteria: updated International Restless Legs Syndrome Study Group (IRLSSG) consensus criteria – history, rationale, description, and significance

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ABSTRACT

Background: In 2003, following a workshop at the National Institutes of Health, the International Restless Legs Syndrome Study Group (IRLSSG) developed updated diagnostic criteria for restless legs syndrome/Willis–Ekbom disease (RLS/WED). These criteria were integral to major advances in research, notably in epidemiology, biology, and treatment of RLS/WED. However, extensive review of accumulating literature based on the 2003 NIH/IRLSSG criteria led to efforts to improve the diagnostic criteria further.
Methods: The clinical standards workshop, sponsored by the WED Foundation and IRLSSG in 2008, started a four-year process for updating the diagnostic criteria. That process included a rigorous review of research advances and input from clinical experts across multiple disciplines. After broad consensus was attained, the criteria were formally approved by the IRLSSG executive committee and membership.
Results: Major changes are: (i) addition of a fifth essential criterion, differential diagnosis, to improve specificity by requiring that RLS/WED symptoms not be confused with similar symptoms from other conditions; (ii) addition of a specifier to delineate clinically significant RLS/WED; (iii) addition of course specifiers to classify RLS/WED as chronic-persistent or intermittent; and (iv) merging of the pediatric with the adult diagnostic criteria. Also discussed are supportive features and clinical aspects that are important in the diagnostic evaluation.
Conclusions: The IRLSSG consensus criteria for RLS/WED represent an international, interdisciplinary, and collaborative effort intended to improve clinical practice and promote further research.

1. Introduction

Restless legs syndrome (RLS), also known as Willis–Ekbom disease (WED), is a common neurological, sensorimotor disorder. In European and American populations, about 2–3% of adults suffer from clinically significant symptoms [1]. Clinically significant RLS/WED has a substantial negative impact on sleep, quality of life, and health [1–3]. Following a 2003 workshop at the National Institutes of Health (NIH), the International Restless Legs Syndrome Study Group (IRLSSG) developed updated diagnostic criteria that have enabled rapid development of research and treatments for RLS/WED over the past decade [4]. The accumulating research and

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Table 1
International Restless Legs Syndrome Study Group (IRLSSG) consensus diagnostic criteria for restless legs syndrome/Willis–Ekbom disease (RLS/WED).

RLS/WED, a neurological sensorimotor disease often profoundly disturbing sleep and quality of life, has variable expression influenced by genetic, environmental and medical factors. The symptoms vary considerably in frequency from less than once a month or year to daily, and severity from mildly annoying to disabling. Symptoms may also remit for various periods of time. RLS/WED is diagnosed by ascertaining symptom patterns that meet the following five essential criteria, adding clinical specifiers where appropriate.

Essential diagnostic criteria (all must be met):

1. An urge to move the legs usually but not always accompanied by, or felt to be caused by, uncomfortable and unpleasant sensations in the legs.[a,b]
2. The urge to move the legs and any accompanying unpleasant sensations begin or worsen during periods of rest or inactivity such as lying down or sitting.
3. The urge to move the legs and any accompanying unpleasant sensations are partially or totally relieved by movement, such as walking or stretching, at least as long as the activity continues.[c]
4. The urge to move the legs and any accompanying unpleasant sensations during rest or inactivity only occur or are worse in the evening or night than during the day.[d]
5. The occurrence of the above features is not solely accounted for as symptoms primary to another medical or a behavioral condition (e.g. myalgia, venous stasis, leg edema, arthritis, leg cramps, positional discomfort, habitual foot tapping).[e]

Specifiers for clinical course of RLS/WED:[f]

A. Chronic-persistent RLS/WED: symptoms when not treated would occur on average at least twice weekly for the past year.
B. Intermittent RLS/WED: symptoms when not treated would occur on average <2/week for the past year, with at least five lifetime events.

Specifier for clinical significance of RLS/WED:

The symptoms of RLS/WED cause significant distress or impairment in social, occupational, educational or other important areas of functioning by their impact on sleep, energy/vitality, daily activities, behavior, cognition or mood.

[a] Sometimes the urge to move the legs is present without the uncomfortable sensations and sometimes the arms or other parts of the body are involved in addition to the legs.
[b] For children, the description of these symptoms should be in the child's own words.
[c] When symptoms are very severe, relief by activity may not be noticeable but must have been previously present.
[d] When symptoms are very severe, the worsening in the evening or night may not be noticeable but must have been previously present.
[e] These conditions, often referred to as "RLS/WED mimics," have been commonly confused with RLS/WED particularly in surveys because they produce symptoms that meet or at least come very close to meeting criteria 1–4. The list here gives some examples that have been noted as particularly significant in epidemiological studies and clinical practice. RLS/WED may also occur with any of these conditions, but the RLS/WED symptoms will then be more in degree, conditions of expression or character than those usually occurring as part of the other condition.
[f] The clinical course criteria do not apply for pediatric cases nor for some special cases of provoked RLS/WED such as pregnancy or drug-induced RLS/WED where the frequency may be high but limited to duration of the provocative condition.

clinical experience, however, have led to a broad-based consensus for a need to enhance the diagnostic criteria, primarily adding additional elements to improve specificity without changing the fundamental features of RLS/WED diagnosis. In 2012, the IRLSSG revised the 2003 NIH/IRLSSG criteria for RLS/WED [4,5], which are presented here and on the IRLSSG web site (IRLSSG.org).

This 2012 revision of the 2003 NIH/IRLSSG criteria raises two fundamental questions: Why revise them now and how does the revision impact our field, especially for research? By presenting the history, rationale, and significance of the revised criteria, this article addresses these fundamental questions. Furthermore, this article describes in detail the five essential features of the 2012 revised diagnostic criteria and other supportive and associated features of RLS/WED that can aid clinicians and researchers alike in the overall diagnostic assessment. For special populations (i.e. children and cognitively impaired elderly), where the sensory features of RLS/WED may be hard to determine or are unreliable, specific suggestions are discussed. Finally, a consideration of the significance of the revised criteria introduces potential venues for improving our research methods in clinical studies and epidemiology.

It is important to underscore that the 2012 IRLSSG revised criteria represent the only diagnostic criteria developed by a consensus process involving a large international body of RLS/WED clinical and research experts. Through an interdisciplinary, international and evidence-based approach, the IRLSSG sought to avoid three problems. First, the strong interdisciplinary nature of RLS/WED experts reduces the possibility that the diagnostic criteria will be subtly distorted to fit within a framework developed for any one particular discipline. Second, the diversity and global nature of the IRLSSG reduces the risk of cultural bias that might limit the generalizability across racial and ethnic groups. Third, the evidence-based, conservative approach avoids arbitrary and negative impact on validity or significance of prior RLS/WED studies.

2. History of RLS/WED diagnostic criteria

Table 1 presents the new, updated IRLSSG diagnostic criteria for RLS/WED and Table 2 presents the historic development of these criteria.

Although RLS/WED was first described by Thomas Willis in 1685 [6], the formal diagnostic criteria start with the seminal monograph "Restless Legs" by Karl-Axel Ekbom in 1945 [7]. He offered the following diagnostic guidance in 1960:

> "The following criteria should be borne in mind. The sensations appear only when the patient is at rest, most often in the evening and early part of the night, and produce an irresistible need to keep the legs moving. Furthermore, the sensations are not felt in the skin but deep down inside the legs [8]."

The essential features of RLS/WED diagnosis have not changed markedly since the description by Ekbom. Uncomfortable sensations and an irresistible urge to move the legs, worsening of symptoms by rest and relief by movement, and initiation or exacerbation of symptoms during the evening/night while at rest have remained the hallmarks of RLS/WED diagnosis. Ekbom's emphasis on sensations, however, has not survived the test of time. What evolved over the next several decades in the diagnostic criteria was a consensus for emphasis on the urge to move or akathisia over the dysesthesias (Tables 1 and 2).

The first formal diagnostic definition for RLS/WED, however, did not exist until publication of Diagnostic Classification of Sleep and Arousal Disorders (DCSAD), from the Diagnostic Classification Committee of the American Sleep Disorders Association in 1979 (Table 2) [9]. Nonetheless, this classification was based neither on broad consensus among clinical experts treating RLS/WED nor on a careful review of the clinical data from the budding research field of RLS/WED. It also reflected the downside of forcing the

Table 2
Evolution of diagnostic criteria for restless legs syndrome/Willis–Ekbom disease (RLS/WED).

1960: Ekbom's "criteria" for RLS
"The following criteria should be borne in mind. The sensations appear only when the patient is at rest, most often in the evening and early part of the night, and produce an irresistible need to keep the legs moving. Furthermore, the sensations are not felt in the skin but deep down inside the legs."
1979: DCSAD restless legs DIMS (or DOES) syndrome – essential features:
DIMS (or DOES) is associated with the "restless legs" syndrome because an individual feels extremely disagreeable deep sensations of creeping inside the calves whenever sitting or lying down. These dysesthesias are rarely painful, but agonizingly relentless, and cause an almost irresistible urge to move the legs, thus interfering with sleep.
1990: ICSD diagnostic criteria for RLS:
A. A complaint of an unpleasant sensation in the legs at night or difficulty in initiating sleep.
B. Disagreeable sensations of "creeping" inside the calves often associated with general aches and pains in the legs.
C. The discomfort is relieved by movements of limbs.
D. Polysomnographic monitoring demonstrates limb movements at sleep onset.
E. No evidence of any medical or psychiatric disorders that account for the movements.
F. Other sleep disorders may be present but do not account for the symptoms.
Minimal criteria: A + B + C.
1995: IRLSSG "minimal" criteria for diagnosis of RLS (1 + 2 + 3 + 4):
1. Desire to move the limbs usually associated with paresthesias/dysesthesias.
2. Motor restlessness.
3. Symptoms are worse or exclusively present at rest (i.e. lying, sitting) with at least partial and temporary relief by activity.
4. Symptoms are worse in evening/night.
2003: NIH/IRLSSG "essential" criteria for diagnosis of RLS:
1. An urge to move the legs, usually accompanied or caused by uncomfortable and unpleasant sensations in the legs. (Sometimes the urge to move is present without the uncomfortable sensations and sometimes the arms or other body parts are involved in addition to the legs.)
2. The urge to move or unpleasant sensations begin or worsen during periods of rest or inactivity such as lying or sitting.
3. The urge to move or unpleasant sensations are partially or totally relieved by movement, such as walking or stretching, at least as long as the activity continues.
4. The urge to move or unpleasant sensations are worse in the evening or night than during the day or only occur in the evening or night. (When symptoms are very severe, the worsening at night may not be noticeable but must have been previously present.)

DCSAD, Diagnostic Classification of Sleep and Arousal Disorders; DIMS, disorder of initiating and maintaining sleep; DOES, disorder of excessive somnolence; ICSD, International Classification of Sleep Disorders; IRLSSG, International Restless Legs Syndrome Study Group; NIH, National Institutes of Health.

diagnosis to fit within the structures used to classify all disorders in a field, in this case that of sleep disorders. The DCSAD classified RLS/WED as a disorder of initiating and maintaining sleep (DIMS) and as a disorder of excessive somnolence (DOES). The DCSAD listed the essential features of "Restless Legs" DIMS (or DOES) syndrome as: "an individual feels extremely disagreeable deep sensations of creeping inside the calves whenever sitting or lying down. These dysesthesias . . . cause an almost irresistible urge to move the legs, thus interfering with sleep." Thus as for Ekbom the DCSAD emphasized 'dysethesias' causing the urge to move, but current studies indicate that the urge to move is primary and may occur without dysesthesias. The DCSAD criteria also omitted a major distinguishing feature of RLS/WED, its diurnal variation. These issues made it difficult to distinguish between RLS/WED and neuropathic pain syndrome. Moreover, the belief then that a disease severely reducing sleep time would produce excessive sleepiness led to classifying the disorder as one with excessive daytime sleepiness. This was done without clinical data supporting the daytime sleepiness and, indeed, most recent studies have documented that on average RLS/WED patients have sleepiness scores within normal limits [2,10,11]. Subsequent research has developed the concept of hyperarousal producing poor sleep without daytime sleepiness in individuals with RLS/WED [11,12].

The first official operational diagnostic criteria for RLS/WED (Table 2) became available when the American Sleep Disorder Association in 1990 published a revision of the DCSAD as the International Classification of Sleep Disorders (ICSD) [13]. This was again done by sleep medicine experts without seeking a broad consensus of RLS/WED experts or a review of existing literature. The ICSD reclassified RLS/WED as one of the "Intrinsic Sleep Disorders" under the subgroup of "dyssomnias" and defined RLS/WED by "disagreeable leg sensations," usually prior to sleep onset, "that cause an almost irresistible urge to move the legs." Forcing diagnosis into the framework for sleep-related disorders led to an emphasis on symptoms at sleep onset and at "night" despite RLS/WED symptoms occurring only during waking and often in the late afternoon and evening.

In response to perceived inadequacy of the 1990 ICSD criteria for RLS/WED, the 28 founding members of the IRLSSG developed in 1995 the first diagnostic criteria based on a broad international consensus of clinical RLS/WED experts [14]. They established "four minimal criteria" for RLS/WED that remain to this day the core of RLS/WED diagnosis (Table 1). This provided a crucial basis that enabled a considerable increase in RLS/WED research. However, as clinical research and experience accumulated, limitations of this 1995 initial IRLSSG formulation of RLS/WED diagnostic criteria became apparent.

In 2002, the IRLSSG, WED Foundation, and the National Institute on Aging, in partnership with other branches of the National Institutes of Health, sponsored an RLS/WED diagnosis and epidemiology workshop to revise the 1995 IRLSSG criteria. During the workshop, the 1995 IRLSSG criteria were updated and rephrased to incorporate new scientific knowledge about RLS/WED and to provide better reliability and validity for RLS/WED diagnosis by researchers and clinicians alike [4]. First, the somewhat confusing "motor restlessness" criterion for diagnosis of RLS/WED was replaced by "urge to move," which became clearly the single most prominent feature of RLS/WED. Second, relief of symptoms by movement and exacerbation of symptoms by inactivity became separate criteria to emphasize the need for clear ascertainment of these features of RLS/WED. Third, the workshop also addressed new diagnostic criteria for two special populations – children and the cognitively impaired elderly – plus diagnostic criteria for the treatment emergent problem of augmentation.

These criteria were published in 2003 and are often referred to as the "NIH/IRLSSG criteria" for RLS/WED diagnosis. They remain the fundamental basis for diagnosing RLS/WED, and care needs to be taken in revising these criteria so as not to raise unnecessary questions about the validity of the large number of RLS/WED studies based on these criteria.

3. Rationale for revision of the 2003 NIH/IRLSSG criteria

The 2003 NIH/IRLSSG criteria contributed to several milestones in the field of RLS/WED research. First, the workshop's recommendation for a simple three-item questionnaire based on the 2003 NIH/IRLSSG criteria led to epidemiological studies revealing that 7–10% of the general adult population in Europe and the USA have symptoms meeting the RLS/WED diagnostic criteria, and 2–3% of the total population (20–40% of all reporting RLS/WED symptoms) have significant suffering associated with their symptoms [1,15]. Second, clarification of the essential diagnostic features of RLS/WED aided clinical trials that led to regulatory approval of dopamine agonists for treatment of moderate-to-severe RLS/WED in both Europe and the USA [16–18]. For the first time, RLS/WED sufferers had effective medication readily prescribed by experts and primary care physicians alike. Finally, the 2003 NIH/IRLSSG criteria provided a basis for a large series of studies that demonstrated multiple aspects of RLS/WED biology, e.g. low brain iron [19–24], peripheral iron relation to RLS/WED severity [25–28], pain sensory abnormalities [29,30], cortical and spinal excitability [31], hypoxic pathway activation [32–34], and genetic factors of RLS/WED [35–42].

Nonetheless, rapid progress in the field of RLS/WED over the past several years revealed limitations of the 2003 NIH/IRLSSG criteria. Whereas a proliferation of epidemiological studies led to identification of important risk factors for RLS/WED in the community, wide variability of RLS/WED prevalence in different countries became controversial. The three- or four-item questionnaires covering the 2003 criteria, intended to screen for RLS/WED, led to excessively high prevalence estimates in some studies. Moreover, these questionnaires, designed to screen for RLS/WED, became increasingly and erroneously used in the primary care setting for diagnostic purposes without careful consideration of either clinical significance or differential diagnosis. Furthermore, the direct-to-consumer marketing practices by pharmaceutical companies (that failed adequately to discriminate milder from more severe forms of RLS/WED) became a target for accusations of "disease-mongering" within the medical field and popular media. Perception of RLS/WED as a frivolous, "lifestyle" condition demeaned the terrible suffering of affected individuals and increased the need to define "clinically significant" RLS/WED.

Relying on simple three- to four-item questionnaires based on the four essential criteria of the 2003 NIH/IRLSSG criteria also raised concerns about validity of diagnosis, particularly about its specificity. Several recent studies have demonstrated that the four-item questionnaires lead to low positive predictability of RLS/WED (e.g. 50–60%) [43–45]. The problem of "false positives" appeared to be largely due to lack of consideration of differential diagnosis during the diagnostic evaluation. Major features of RLS such as restlessness, akathisia, or sensory misperception in the extremities occur in many neurological diseases and may be difficult to disentangle from restless legs symptoms. Other frequently occurring conditions may closely "mimic" RLS symptoms requiring attention to differential diagnosis [46].

The danger of potential inclusion of "false positives" in studies based on the 2003 NIH/IRLSSG criteria is even more magnified in research on the etiopathogenesis of RLS/WED in non-epidemiologic studies. Inclusion of "false positive" RLS/WED in pathophysiological studies that rely on smaller sample sizes could lead to erroneous study findings and difficulty in replication of results, impeding progress in the field. The need for a fifth criterion to improve specificity by requiring consideration of differential diagnosis, particularly for the common RLS/WED "mimics," became persuasive.

Thus, the current 2012 IRLSSG consensus diagnostic criteria provide guidance in differential diagnosis in order to improve specificity of diagnosis in both clinical and research settings. The 2012 consensus criteria also address the issues of "clinical significance" and "clinical course" in order to emphasize the heterogeneity of RLS/WED manifestations in individual patients and to aid clinicians and researchers in identifying and characterizing subtypes of RLS/WED.

4. Process for revising the diagnostic criteria

In recognition of the developing need to revise the diagnostic standards for RLS/WED, the IRLSSG and WED Foundation sponsored a one-day clinical standards workshop (chair: Richard Allen) on October 26th, 2008, at the Johns Hopkins Mount Washington Conference Center, Baltimore, MD, USA. Members of the IRLSSG were invited to update and revise the 2003 diagnostic criteria for RLS/WED. To address specific aspects of the 2003 criteria the attendees were assigned to three different workgroups based on their research and clinical expertise: differential diagnosis, clinical significance, and objective testing.

Prior to the clinical standards workshop, individual members of each workgroup submitted written briefs with suggestions on the assigned topics to their respective workgroup chairs, who moderated the pre-meeting dialogue over internet- and teleconferences. During the workshop, each workgroup met separately to discuss and debate on their assigned topics until they reached consensus. Experts from other fields (e.g. dementia and depression) presented their perspectives on diagnostic criteria in other clinical conditions to inform and facilitate the process of developing consensus among members of the workgroup. Subsequently, the chair of each workgroup presented the group's consensus recommendations to all of the attendees of the workshop for additional open discussion. Then, the chair of the workshop assembled the products of the three workgroups into preliminary, revised consensus diagnostic criteria for RLS/WED, and further refined them for consistency in content and language. After the workshop, the preliminary, revised diagnostic criteria were distributed to the IRLSSG membership for further input and discussion.

Over the next year, there was extensive dialogue and interaction among members of the IRLSSG, and the diagnostic criteria were adjusted based on this input from RLS/WED experts around the world. The final version of the new, consensus diagnostic criteria was submitted to the Executive Committee of the IRLSSG for approval at its annual meeting in fall 2011. Preliminary approval was given, contingent upon another review period by the IRLSSG membership. This review period ended in spring of 2012, and the IRLSSG approved the final version which became available on the IRLSSG web site (www.irlssg.org). Table 1 lists the final version of the criteria.

Overall, this was a four-year process, which was systematically structured to ensure broad-based input and consensus among IRLSSG members who represented various disciplines and international clinical and research groups. IRLSSG members who participated in development of these revised criteria are listed in the Acknowledgements section of this article.

5. IRLSSG consensus diagnostic criteria

RLS/WED, a neurological sensorimotor disease ... is diagnosed by ascertaining symptom patterns that meet the following five essential criteria adding clinical specifiers where appropriate.

RLS/WED arises from dysfunction of the central nervous system that leads to both sensory and motor symptoms. No biological assay is available to make a diagnosis of RLS/WED. Clinical diagnosis of RLS/WED is based on clinician interaction with the patient and assessment by the clinician of the patient's subjective reports in compari-

son to the essential features of RLS/WED. Regarding the interactive clinical nature of RLS/WED diagnosis, Ekbom wryly observed that "in typical cases [diagnosis] is very easy, provided that the physician knows of the disease and the patient describes his complaints properly" [7]. Indeed, the subjective and interactive nature of RLS/WED diagnosis relies on the expertise of the clinician regarding the symptomatology of RLS/WED, as well as the cooperation and capacity of the patient. The art of drawing out appropriate responses by probing questions, often repeated or rephrased, in order to refine the phenomenology of each feature is a task assigned to the clinician, who should systematically address each of the diagnostic features.

5.1. Five essential diagnostic criteria (all must be met) (Table 1)

(1) An urge to move the legs usually but not always accompanied by or felt to be caused by uncomfortable and unpleasant sensations in the legs.

The first criterion for diagnosis of RLS/WED is unchanged from the 2003 NIH/IRLSSG diagnostic criteria for RLS/WED. An urge to move the legs remains the key diagnostic feature of RLS/WED. This is usually accompanied by "hard to describe" unpleasant sensations in the legs. Note the three separate components of this criterion: urge to move (or akathisia), legs, and sensations (dysesthesias). "Unpleasant sensations" in the legs are neither sufficient nor necessary for the diagnosis of RLS/WED. "Urge to move" the legs must be present and is sufficient for the diagnosis.

Often the urge to move and the accompanying sensory symptoms are intermingled together and difficult to separate symptomatically or temporally. Patients with clinically significant RLS/WED, however, can often clearly delineate them. Some patients describe only an urge to move and are unaware of any "uncomfortable and unpleasant" sensations, especially when their RLS/WED symptoms are mild. The uncomfortable sensations are described as painful in up to 30–50% of RLS/WED patients but isolated pain without an urge to move does not constitute RLS/WED [10,47,48].

For children, the description of these feelings should be in their own words, which often differ from those used by adults. Examples are provided in a separate article on the pediatric diagnosis of RLS/WED [49].

Despite being called restless 'legs' syndrome, RLS/WED may also involve the arms or other body parts. Arm involvement is reported in 21–57% of cases [10,47,48,50,51]. RLS/WED symptoms, when they are more severe, may spread to other body parts, including the hips, trunk, and even rarely the face [52], but the legs must be affected and are usually affected first and more severely than are other body parts. Atypical cases of RLS/WED have been described with the arms affected predominantly and little or no involvement of the legs [53,54]. These cases responded to dopaminergic treatment and appear to be a variant of RLS/WED, but are rare, and the IRLSSG felt that these are best classified as an RLS/WED variant rather than include them in an expanded definition of RLS/WED.

Although the plural "legs" is used in this diagnostic criterion, this is meant as a general concept and does not exclude RLS/WED symptoms occurring in only one leg. RLS/WED typically involves symptoms in both legs but not necessarily at the same time or symmetrically. Symptoms may occur only in one leg and then move to the other or occur in the other on a different day. Purely unilateral symptoms only in one leg occur with RLS/WED and in some cases may relate to unilateral neurological conditions.

The location of symptoms in the legs also varies considerably both between patients and over time for a patient. The middle portions of the calves and thighs are affected most commonly with RLS/WED [7,51]. Involvement of feet or joints is not prominent in contrast to the distal, "stocking" pattern with polyneuropathy and the joint predominant pattern with arthritis. The sensations may start and occur primarily above the knee. When there is a pattern of progression, within an episode or over time, the increasing severity typically involves spread to more of the lower limbs and to other body parts, particularly the arms.

(2) The urge to move the legs and any accompanying unpleasant sensations begin or worsen during periods of rest or inactivity such as lying down or sitting.

The most important change in the second diagnostic criterion is the coupling of the "urge to move" and "unpleasant sensations." Previously, the diagnostic criteria required presence of either "urge to move" or "unpleasant sensations." Changing the previously used disjunctive "or" to the conjunctive "and" serves to increase specificity of the diagnostic criteria and reduce confusion over the primacy of "urge to move" in the diagnosis of RLS/WED.

Criterion 2 describes a key diagnostic feature of RLS/WED – inactivity or rest initiates or exacerbates RLS/WED. This criterion has been validated by a series of pioneering studies conducted by Montplaisir et al., who, based on the suggested immobilization test (SIT) paradigm, examined the effects of immobility on RLS/WED [55]. Compared to normal controls, patients with RLS/WED exhibit pronounced sensory symptoms in the legs and periodic leg movements while resting and awake that increase with the duration of rest. This exacerbation with duration of rest has been confirmed in subsequent studies [56,57].

(3) The urge to move the legs and any accompanying unpleasant sensations are partially or totally relieved by movement, such as walking or stretching, at least as long as the activity continues.

Besides the coupling of the "urge to move" and "unpleasant sensations," there is no change in this criterion from the 2003 NIH/IRLSSG criteria for RLS/WED. The clinician should note three important features of this criterion: relief vs resolution, immediacy, and persistence. In addition, interaction with RLS/WED severity is addressed in Table 1, footnote c.

RLS/WED patients, when asked about the effect of activity on RLS/WED, may confuse relief with resolution of symptoms. For example, they may mistakenly report that walking produces little or no "relief" because as soon as they stop the symptoms return. Clearly, temporary relief occurred during the activity, contrary to their self-report. It is important to understand that response to movement for this criterion is fulfilled by temporary relief, not necessarily complete resolution of the symptoms.

RLS/WED patients generally feel at least some symptomatic relief almost immediately with the start of activity or very soon thereafter. This should be differentiated from a delayed response to physical exercise or strenuous activity. The simple act of moving or walking usually suffices. The relief should persist as long as the activity persists. Symptoms should generally not return with continued activity, nor start or become worse during periods of activity.

Individuals with very severe RLS/WED may, however, report minimal or no relief of symptoms even after a prolonged period of activity such as walking, pacing, bending, or moving. Often there is some minimal sense of relief with significant levels of activity, but this may be hard for the patient to discern. The diagnosis in these very severe cases requires adjustment of the expected symptom relief from motor activity. These patients are deemed to meet criterion 3 if they report either some minimal transitory relief or if they were able to obtain relief with movement earlier in the course of their RLS/WED when the symptoms were milder (Table 1, footnote c).

(4) The urge to move the legs and any accompanying unpleasant sensations during rest or inactivity only occur or are worse in the evening or night than during the day.

Table 3
Criterion 5. Differential diagnosis of restless legs syndrome/Willis–Ekbom disease (RLS/WED).

Common conditions
Leg cramps[a]
Positional discomfort[a]
Local leg injury
Arthritis
Leg edema
Venous stasis
Peripheral neuropathy[a]
Radiculopathy[a]
Habitual foot tapping/leg rocking
Anxiety
Myalgia
Drug-induced akathisia
Less common
Myelopathy
Myopathy
Vascular or neurogenic claudication
Hypotensive akathisia
Orthostatic tremor
Painful legs and moving toes

[a] More likely to fulfill all of criteria 1–4. Any of these conditions can coexist with RLS/WED (see text).

Circadian variation of symptoms is a unique diagnostic feature of RLS/WED that aids case ascertainment. It occurs predictably across the 24 h day, modulating response to other factors that provoke symptoms such as inactivity [58–60]. Studies validating this criterion have demonstrated that the circadian variation in symptoms occurs independently of activity, sleep deprivation, or sleep–wake state [58,59,61,62]. Suggested immobilization tests show that the effect of rest in provoking RLS/WED symptoms increases markedly across the day [55,56,60,63,64]. The symptoms are most pronounced in the evening and night with relative improvements late in the sleep period or early morning. There are few if any RLS/WED symptoms in the morning, which appears to be a relatively "protected period" for RLS/WED symptoms. Afternoon symptoms are, however, not uncommon particularly when the patient has longer periods of inactivity [65].

Clinicians should inquire about symptoms when resting in the morning compared to evening or night. The critical clinical question for this criterion involves ascertaining circadian differences in symptom response to rest. Patients with RLS/WED should report fewer symptoms when resting in the morning than in the evening or night.

Patients with very severe RLS/WED, however, may have relentless symptoms persisting throughout the day and night without any noticeable circadian variation. Nevertheless, they are deemed to meet this criterion if circadian variation of their symptoms was present earlier in the course of their RLS/WED, when their symptoms were milder (Table 1, footnote d).

(5) The occurrences of the above features is not solely accounted for as symptoms primary to another medical or behavioral condition (e.g. myalgia, venous stasis, leg edema, arthritis, leg cramps, positional discomfort, habitual foot tapping).

The fifth criterion is a new addition to the revised IRLSSG criteria for RLS/WED. It is intended to increase the specificity of the diagnostic criteria while understandably sacrificing some sensitivity in detection of RLS/WED. A diagnosis of RLS/WED is made after careful consideration of differential diagnoses and exclusion of mimicking conditions [46,66]. These mimics have been confused with RLS/WED, particularly in written surveys, because they produce symptoms that meet (or at least come very close to meeting) criteria 1–4. The list in the diagnostic criterion gives some examples that have been noted as particularly common in epidemiological studies and clinical practice. Table 3 gives a more complete list of common and less common conditions that can be mistaken for RLS/WED. Features not typical of RLS/WED but indicating possible "mimic" conditions are knotting of the muscle (leg cramps), relief with a simple postural shift (positional discomfort), limitation to joints or joint erythema (arthritis), muscle soreness (myalgias), numbness (neuropathy), and swelling (venous stasis, leg edema) [46,51,66]. Adding differential diagnosis to the diagnostic criteria in diagnostic questionnaires or scales produces much-improved agreement with clinical expert diagnosis that exceeds 90% [43,44,67,68].

However, someone with RLS/WED may have one or more of these other conditions in addition to RLS/WED, e.g. RLS/WED and peripheral neuropathy [46]. This situation requires focus on the differentiating characteristics of each condition for both diagnosis and assessment of impact. Then the clinician can use this information to reach appropriate treatment decisions.

5.2. Specifiers for RLS/WED

Specifiers for clinical course and clinical significance have been added to characterize RLS/WED more completely. When diagnostic criteria are met, specifiers should be applied, when appropriate. These specifiers define more homogeneous subgroups for research and for treatment planning.

5.2.1. Specifiers for clinical course of RLS/WED

(A) Chronic-persistent RLS/WED: symptoms when not treated would occur on average at least twice weekly for the past year.

(B) Intermittent RLS/WED: symptoms when not treated would occur on average <2/week for the past year, with at least five lifetime events.

Clinical course was unanimously judged to be an important distinction among RLS/WED patients. Some have sporadic and infrequent episodes of RLS/WED symptoms whereas others have them regularly. The latter are more likely to seek treatment and represent those seen most often in clinical practice. Population-based surveys, however, indicate that many have RLS/WED symptoms only intermittently. The REST general population survey found that of all those reporting RLS/WED symptoms during the past year, 30% had symptoms less than once a week and 12.5% had symptoms about once week. Of the remaining 57.5% with symptoms occurring twice a week or more, the majority (66%) also reported the symptoms as moderate to severely disturbing [1]. This last group is often referred to as RLS/WED sufferers. Since most of the patients with symptoms at least twice a week for the past year also reported them as distressing, this was considered to be a critical level of frequency of symptoms defining chronic-persistent RLS/WED.

There is a wide range of symptom frequency for those with symptoms less than twice a week. The question arises: what is the minimal number of RLS/WED symptom episodes required to make a diagnosis of RLS/WED? A strong consensus emerged among the RLS/WED experts that the field needs to continue investigating all severity, including the milder, infrequent forms of RLS/WED. Restricting RLS/WED diagnosis to the more frequent form of RLS/WED may be of clinical utility, but would restrict research to the more severe spectrum of RLS/WED. More importantly, there was no good reason or any data to set a minimum number of episodes to define RLS/WED except to have enough episodes to establish a nocturnal clinical pattern. It was agreed that a minimum of five RLS/WED episodes, all occurring in the evening or night, would suffice to establish a nocturnal circadian pattern since the probability

that all five would occur by chance only in the nocturnal half of the 24 h day–night cycle is 0.031. This was accepted as the minimum number of lifetime events required to make the diagnosis of RLS/WED.

It is recommended by the IRLSSG that for most cases the clinical course of RLS/WED be identified as either A or B above, in both clinical practice and research studies. However, research to date does not support application of these course specifiers for children or some cases of provoked RLS/WED, such as pregnancy- or drug-induced RLS/WED.

5.2.2. Specifier for clinical significance of RLS/WED

The symptoms of RLS/WED cause significant distress or impairment in social, occupational, educational or other important areas of functioning by their impact on sleep, energy/vitality, daily activities, behavior, cognition or mood.

Addition of a specifier for clinical significance of RLS/WED affirms the dimensional aspects of RLS/WED, which has a spectrum of severity that varies from mildly annoying to crippling symptoms. No consensus was reached in terms of the specific frequency and duration of RLS/WED to specify "clinical significance." However, several functional domains have been provided to the clinician for evaluation of clinical significance. Disruption of sleep is a common and distressing impact of RLS/WED [10,45,69–75]. The severity and health impact of RLS/WED both correlate with sleep disturbance [45,75]. Compared to controls, sleep quantity, sleep adequacy, and sleep problem measures are worse in RLS/WED patients [45]. Disturbed sleep is objectively found on polysomnography in RLS/WED, with longer latency to persistent sleep and increased arousal index the most consistent findings [69,76,77]. Resultant fatigue, due to loss of sleep or exhausting restlessness in the evening, is also common and clinically important. Using standard health-related quality of life (HRQoL) measures, physical and mental health scores are lower for individuals with RLS/WED [1,2,70,78–90]. These HRQoL impairments are strongly associated with RLS/WED severity [45,78,79] and improve with treatment of RLS/WED [91–94]. In addition, depressive and anxiety disorders are common in individuals with RLS/WED, correlate with severity of RLS/WED, and improve with treatment of RLS/WED [74,75,88,95–99]. Overall, the careful assessment of impact is crucial when determining clinical significance and making individual treatment decisions.

6. Features supporting the diagnosis of RLS/WED

RLS/WED has both a motor sign and several common clinical patterns that can support a diagnosis, particularly when there is some lack of diagnostic certainty (Table 4).

Table 4
Clinical features supporting the diagnosis of restless legs syndrome/Willis–Ekbom disease (RLS/WED).

The following features, although not essential for diagnosis, are closely associated with RLS/WED and should be noted when present:
1. Periodic limb movements (PLM): presence of periodic leg movements in sleep (PLMS) or resting wake (PLMW) at rates or intensity greater than expected for age or medical/medication status.
2. Dopaminergic treatment response: reduction in symptoms at least initially with dopaminergic treatment.
3. Family history of RLS/WED among first-degree relatives.
4. Lack of profound daytime sleepiness.[a]

[a] RLS/WED shares this characteristic with other hyperarousal conditions including insomnia disorder.

6.1. Periodic leg movements

RLS/WED has one identified sign: periodic leg movements (PLMs). PLMs can occur in sleep (PLMS) or wakefulness (PLMW). Lugaresi's seminal work recognized that PLMS occur commonly in RLS/WED patients [100]. Montplaisir further documented that excessive PLMS occur in about 80–89% of RLS/WED patients seen in a clinic setting and that excessive periodic leg movements also occur in quiet waking (PLMW) during the sleep period [69,101]. The amount of PLMS but not PLMW during the sleep period relates well to RLS/WED severity [69]. More recent studies have documented a bimodal distribution of the inter-movement intervals for PLMs that divide into short (<10 s) and long (10–90 s) inter-movement intervals [102], with the second interval range being representative of the typical periodic activity. PLMW of RLS/WED patients during the sleep period have mostly short inter-movement intervals (<10 s). The PLMS of RLS/WED patients, in contrast, have mostly long inter-movement intervals (10–90 s) [103].

Contrary to initial expectations, PLMS are not directly related to the primary RLS/WED morbidity of sleep disturbance [69], rather they may reflect some RLS/WED biology partially independent of that. They occur with significant transient changes in electroencephalogram [104–106], heart rate [107–110] and blood pressure [110–113] that may reflect a process producing the increased risk of cardiovascular disease observed with RLS/WED in several [110,111,113–115] but not all [116] studies. Presence vs absence of PLMS may also define a different clinical expression of RLS/WED biology [35,117].

The amount of PLMS, although fairly sensitive for RLS/WED, is not very specific [101] as it has been found to be high in several other medical conditions [118–122], with many medications [123,124], and frequently among adults aged >45 years [76,118–120,125,126]. Recently developed measures of the relative number of long-interval to all leg movement intervals (periodicity index) and time-of-night expression enhance the specificity of PLMS for RLS/WED [102,127,128]. PLMS measures support the diagnosis when present in a pattern or amount different than expected for age without evidence for other disease states or medication that may induce or aggravate PLMS. Their presence and responsiveness to treatment become particularly important to the extent that they might relate to cardiovascular risk factors of RLS/WED.

Unlike PLMW during the sleep period, those during 1 h of resting waking in a suggested immobilization test (SIT) before sleep have promisingly high sensitivity and specificity for RLS/WED, when combined with subjective leg discomfort scores [55,129]. Measuring PLMW by the SIT might also provide a measure of severity and treatment response for RLS/WED [57].

6.2. Dopaminergic treatment response

Most RLS/WED patients show at least some initial clinical benefit of fast-acting dopaminergic medications, e.g. levodopa and dopamine agonists. In one small clinical trial using levodopa treatment, there was 100% sensitivity but only 80% specificity for ascertaining RLS/WED [130]. These data, however, come from a highly selected patient population at one clinical center and cannot be considered representative of the entire RLS/WED population. Larger clinical trials with more diverse patient populations show a good clinical response to dopamine agonist treatment in only about 60–75% [93,130,131]. Thus, in general clinical practice, failure ever to respond to dopaminergic treatment should raise some concern about the accuracy of diagnosis, but it does not preclude a diagnosis of RLS/WED.

6.3. Family history of RLS/WED among first-degree relatives

RLS/WED has been noted to occur frequently in families, indicating significant genetic or shared environmental factors for the disease [35,69,132]. One study found that 20% of consecutive RLS/WED patients in two clinical settings reported RLS/WED among their first-degree relatives [133]. This was true for only 3.5% of clinical patients without RLS/WED. In addition, twin studies have shown high concordance for RLS/WED [42,134,135]. Thus, the presence of RLS/WED among first-degree relatives is supportive of the diagnosis.

6.4. Lack of expected daytime sleepiness

Patients with moderate-to-severe RLS/WED have chronic short sleep times but generally do not report a level of daytime sleepiness that would be expected for the degree of sleep loss [2,11,12]. They usually have mean Epworth Sleepiness Scale scores that are only slightly elevated and within the range of normal [2,10,75,116,136]. Younger patients with mild RLS/WED, however, may report some mild levels of daytime sleepiness [137]. Nonetheless, for the majority of patients with RLS/WED, this lack of profound daytime sleepiness, in spite of poor sleep, is a characteristic but counterintuitive finding. They can suffer other consequences of sleep deprivation such as fatigue, reduced concentration, and depression, but do not usually nap. Recognition of this feature supports an RLS/WED diagnosis, but, more importantly, alerts the clinician to other possible etiologies in cases where there is excessive sleepiness. Profound sleepiness in any except the most severely affected RLS/WED patient should prompt evaluation for another cause, such as sleep apnea, narcolepsy, or medication effect [138].

7. Features to be considered for a comprehensive diagnostic assessment of RLS/WED

The clinical features presented in Table 5 are particularly important for completing a full diagnostic assessment of RLS/WED status. These features may also impact treatment options. Some are common to other conditions, but, as explained below, they all have particular significance for RLS/WED.

7.1. Gender

Gender is a significant factor related to risk of RLS/WED. RLS/WED occurs in adults aged >35 years about twice as frequently for women as for men [1,15,132]. There is, however, little or no gender difference for adults aged <35 years or for children [1,139,140]. This gender difference may be largely secondary to pregnancy since nulliparous women appear to have about the same prevalence of RLS/WED as males (see Section 7.8) [82,141].

Table 5
Features significantly impacting diagnostic assessment of restless legs syndrome/Willis–Ekbom disease (RLS/WED).

1. Gender.
2. Age and age of onset of RLS/WED.
3. History of the course of the disease (e.g. periods of increases, decreases, remissions, stable unchanging or fluctuating symptoms).
4. Sleep disturbance.
5. Degree of pain vs discomfort for RLS/WED symptoms.
6. Parts of the body involved.
7. Daily pattern of symptoms and activity levels.
8. History of pregnancy (number of pregnancies and RLS/WED status during and after pregnancy).
9. History of iron deficiency.

7.2. Age of onset of RLS/WED

The age of onset ranges from childhood to age >90 years. The later in life RLS/WED starts, the more rapid the onset and greater likelihood it is associated with another medical condition, e.g. neuropathy, iron deficiency, renal disease [142,143].

7.3. History of the course of the disease

The history of the course of the disease may indicate future course. In particular, a history of remission and relapse in symptoms should be noted as a possible indicator of similar events in the future. In one clinical population of adults with RLS/WED, one-third reported onset before age 10 years [144]. The typical pattern of an insidious onset with gradual progression to a clinically significant disease was reported to occur for most with early age of onset [142]. Some, however, reported relatively rapid symptom development with a variable degree of symptom progression after onset [144]. A large study that included clinical cases and affected family members reported RLS symptoms over time as follows: progressive in 36%, stable in 41%, diminished in 15%, and remitted in 8% [132]. However, incidence studies report remission in about 50%, which may reflect inclusion of milder cases in those studies [145–147]. Given the variable natural course of the disease, the diagnostic evaluation should consider the disease course for an individual patient and plan long-term treatment options accordingly [148].

7.4. Sleep disturbance

Sleep disturbance is a common and distressing aspect of RLS/WED [45,69–71,74]. Epidemiological data indicate that about 75% of RLS/WED patients likely to seek treatment will report sleep disturbance characterized by waking disrupting sleep onset and/or sleep maintenance [1,70]. Individuals with moderate-to-severe RLS/WED have chronic sleep loss with total sleep times of 4.5–6 h a night [45,76,149,150]. The sleep disturbance correlates with RLS/WED severity and the sleep disturbance itself is a primary source of the health impact of RLS/WED [75,151]. Improving sleep should therefore be one of the primary goals for RLS/WED treatment.

However, most patients with poor sleep do not have RLS/WED. In one population-based study, 10% of patients with poor sleep reported RLS/WED symptoms [45]. Moreover, sleep disturbance, while expected for the moderate-to-severe RLS/WED patient, may be minimal or not present at all for milder RLS/WED. Some individuals with mild RLS/WED even report going to sleep to get relief from their RLS/WED symptoms by sleeping through them.

7.5. Degree of pain versus discomfort

The degree of pain versus discomfort relates to a dimension of severity of the disease [152]. About one-half of RLS/WED patients report the symptoms as painful, not just uncomfortable [10,47,48,153]. However, they usually describe the symptoms as more of an ache rather than a sharp pain [152–154]. RLS/WED symptoms differ from those of neuropathy by not typically including superficial numbness or burning.

7.6. Parts of the body involved

The parts of the body involved should be carefully documented at the time of diagnosis to provide a pre-treatment baseline needed for evaluating any future progression of symptoms. It should be noted that symptoms are typically felt deep inside the muscles, in the middle portions of the lower limbs, especially the calves [51]. Although

the feet or joints may be involved, RLS/WED sensations should rarely be exclusively or predominantly located in these areas [7,51]. The symptoms do not follow a classic distal to proximal progression, providing a feature that differentiates RLS/WED from polyneuropathy [7,69]. Symptoms are usually bilateral, at least to some extent, although not necessarily at the same time [51]. If the symptoms are strictly and consistently localized to one limb, then further neurological evaluation should be considered [51,155].

7.7. Daily pattern of symptoms and activity levels

Documenting the usual time each day of symptom onset and duration assists in treatment planning, as well as in evaluating for future disease progression and possible augmentation. Onset of RLS/WED occurs earlier in the day for more severe RLS/WED [156] and changes to earlier in the day with natural progression and development of augmentation [4,157,158]. RLS/WED symptoms are increased by lack of activity [55,64] and evaluating time of onset each day needs to be done mindful of the daily activity level and lifestyle of the patient. Timing of treatment and choice of longer- vs shorter-acting medication also depend on the patterns of symptom expression.

7.8. History of pregnancy

A history of pregnancy increases the risk of RLS/WED in later life about twofold [82,141,159,160] and transient RLS/WED during pregnancy confers an approximately fourfold increased risk of developing chronic RLS/WED [161]. Accordingly, a woman's history of pregnancy and RLS/WED status during pregnancy should be noted.

7.9. History of iron deficiency

A history of iron deficiency indicates an increased risk of recurring or persisting iron deficiency that could impact RLS/WED symptoms. Evaluation of iron status and possible iron treatments should be considered in patients with a past history of iron deficiency [162,163], particularly childhood iron deficiency [27,164–167].

8. Pediatric diagnostic criteria

The 2003 NIH/IRLSSG criteria included separate criteria for children and defined definite, probable, and possible pediatric RLS/WED [4]. Based on new research, the pediatric RLS/WED diagnostic criteria have been simplified and integrated with the newly revised adult RLS/WED criteria. Table 1, footnote b of the new criteria emphasizes the importance of symptom description in the child's own words for criterion 1, and footnote f indicates that the clinical course criteria do not apply for pediatric cases. In a related publication, pediatric aspects of diagnosis, differential diagnosis, comorbidity, and clinical significance are described in detail [49]. In addition, updated research criteria for probable and possible pediatric RLS/WED are defined.

9. Diagnosis for cognitively impaired seniors

The 2003 NIH/IRLSSG diagnostic criteria included separate consideration for the cognitively impaired elderly. Some ongoing studies have sought behavioral observations that might be used to identify RLS/WED in this population but none of these have yet published satisfactory results. Cognitive and communication problems distort the description of core RLS/WED symptoms. The situation is further complicated by the large increase in PLMS and PLMW at night with age [125] and the difficulty of even looking at PLMW while resting in this population. At this point, a valid assessment method for diagnosis of RLS/WED for cognitively impaired elders remains unavailable. A potential approach is consideration of cognitively impaired seniors with low or low–normal serum iron status combined with high rates of PLMW or PLMS. This population might deserve special attention for possible RLS/WED and might, like non-demented elderly, benefit particularly from iron treatments [168–171].

10. Comparison to the diagnostic and statistical manual of mental disorders, fifth edition (DSM-5) and the international classification of sleep disorders, third edition (ICSD-3) diagnostic criteria for RLS/WED

Previously, RLS/WED was not listed in DSM-IV and was subsumed under the diagnostic category of Dyssomnia Not Otherwise Specified. However, in the recently released fifth edition of DSM, RLS/WED is elevated to a separate diagnostic entity based on the public health significance of the condition, scientific progress made by RLS/WED researchers, and on the necessity of defining a clinically significant condition that is commonly encountered in daily psychiatric practice [172]. There are several important distinctions between the IRLSSG revised criteria and the DSM-5 criteria.

First, the IRLSSG revised criteria (Table 1) do not include the DSM-5 requirement for frequency (at least three times per week) and duration (at least three months). While arbitrary cut-offs to restrict RLS/WED diagnosis to a more frequently occurring and longer duration condition might lead to improved diagnostic specificity and reliability in primary care or psychiatric practice, it trivializes the potential clinical significance of the intermittent subtype or recent-onset RLS/WED.

Second, the IRLSSG revised criteria define a full spectrum of RLS/WED while the DSM-5 criteria for RLS/WED define a narrower clinical spectrum of RLS/WED by requiring the RLS/WED symptoms to be "accompanied by significant distress or impairment in social, occupational, education, academic, behavioral or other important areas of functioning." This conflates clinical impact with presence of the defining symptoms and will be impacted by lifestyle (e.g. sedentary or physically active work) as well as the severity of the disorder itself.

In comparison to the DSM-5 criteria, the recently released ICSD-3 diagnostic criteria for RLS/WED are more analogous to the IRLSSG revised criteria [173]. The five essential criteria of the IRLSSG are required for ICSD-3 diagnosis of RLS/WED. Another notable concurring element between the ICSD-3 and IRLSSG revised criteria is the absence of frequency and duration requirements that are prominent in DSM-5 diagnostic criteria.

A notable difference between the ICSD-3 and IRLSSG revised criteria is how each handles the issue of clinical significance. ICSD-3 diagnostic criteria feature a clinical significance criterion that is similarly worded to the IRLSSG diagnostic specifier for clinical significance. For the ICSD-3 diagnosis of RLS/WED, this criterion "must be met." Yet there is a footnote to this criterion that allows omission for "certain research applications, such as genetic or epidemiological studies..." A concern regarding this ICSD-3 approach is potential arbitrary omission or inclusion of the clinical significance criterion and a subsequent problem of generalizability across RLS/WED studies. In contrast, the IRLSSG revised criteria aimed to provide a consistent case definition of RLS/WED for all clinical and research settings, while highlighting clinical significance as a diagnostic specifier.

The other diagnostic feature that neither DSM-5 nor ICSD-3 criteria address is the varying course of RLS/WED. The IRLSSG specifiers for clinical course of RLS/WED (Table 1) divide the RLS/WED spectrum into intermittent and chronic-persistent types. There is,

indeed, a dimensionality of RLS/WED, from mild, infrequent episodes to severe, chronic-persistent RLS/WED. Together with the specifier for clinical significance, the IRLSSG revised criteria provide to clinicians flexibility to make individualized treatment decisions with RLS/WED patients [174,175]. Furthermore, this dimensional approach avoids a dichotomous categorization based on frequency of symptoms, where intermittent but severe RLS/WED and mild but persistent RLS/WED would not even be classified as RLS/WED [172]. In addition, it retains the important concept of mild RLS/WED for research applications, such as genetic, epidemiological, and treatment studies [115,176,177]. Moreover, the concept of subclinical or latent disease, which is well described for conditions such as hemochromatosis, celiac disease, and prostate cancer, is an important clinical concept for RLS/WED, a condition that can remit based on iron, renal, or pregnancy status [161,162,178–180].

11. Significance of the new diagnostic criteria and specifiers

The new diagnostic criteria address two important areas for RLS/WED clinicians and researchers: a more rigorous approach to RLS/WED case ascertainment to achieve improved validity and better characterization of clinical and research samples by specifying clinical course and clinical significance.

Ensuring attention to the differential diagnosis required by the new fifth criterion encourages development of standardized and validated methods for improved case ascertainment. This is particularly important for survey studies relying upon participant completion of a questionnaire. Questionnaire studies with only the four diagnostic criteria have high sensitivity (e.g. 86%) but low specificity (e.g. 45%) [44]. When used in general population studies this yields positive predictive values of, at best, about 50–55% for identification of RLS/WED [45,181]. Adding questions excluding common mimics can improve specificity with only a small loss of sensitivity; e.g. the Cambridge–Hopkins diagnostic questionnaire with questions excluding common mimics has a specificity of 94.4% and sensitivity of 87.2% [43].

Whereas identification of the clinical features of RLS/WED has always been a critical part of the diagnostic or ascertainment process for RLS/WED, the clinical specifier for course of the disorder provides for identification of those whose symptoms are stable and frequent enough to be in need of medical attention. It does not, however, preclude identification or treatment of those with less stable or frequent RLS/WED symptoms. In addition, the clinical significance specifier for RLS/WED lists several major domains that are affected by the disease, which aids clinicians and researchers alike in assessing impact.

12. Conclusions and future directions

The revised diagnostic criteria aim to contribute to the field by improving diagnostic validity and case ascertainment and by facilitating clear communication among RLS/WED clinicians and researchers. The current revision of diagnostic criteria was undertaken with respect and appreciation for the earlier work by the pioneers in the field of RLS/WED and aims to avoid arbitrary alteration of current clinical practice and research without available supporting empirical evidence. The newly revised criteria add the fifth criterion for differential diagnosis that was implicit but not required in the previous 2003 IRLSSG/NIH criteria. The specifiers for clinical course and significance have been added in order to provide flexibility in defining the target population for future RLS/WED research that intends to elucidate etiopathogenesis and develop better prevention and treatment strategies for specific groups of RLS/WED sufferers.

Future ascertainment of correct diagnosis in a clinical or research setting should include documentation that all five diagnostic criteria are considered. A validated diagnostic method (e.g. RLS-DI, Benes et al. [68]) and/or a structured diagnostic interview (e.g. Hopkins Telephone Diagnostic Interview/HTDI [67]) covering all five diagnostic criteria should be adopted for future clinical and research studies in order to standardize case ascertainment, increase accuracy, and allow replications and comparisons among studies. However, whereas a few validated diagnostic tools are available, they remain in a nascent stage of development. Clearly, more work is needed in order to develop new tools to improve case ascertainment and diagnostic validity and to increase instrumental options for future researchers.

Future efforts to develop diagnostic and case ascertainment instruments should be accompanied by a search for objective, reliable biomarkers for RLS/WED. The ongoing advances in research on the biology of RLS/WED indicate possible underlying biological and genetic features that alone or combined in some mosaic with clinical symptoms may provide the basis for the next advance in the RLS/WED diagnostic criteria.

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Conflict of interest

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References

[1] Allen RP, Walters AS, Montplaisir J, Hening W, Myers A, Bell TJ, et al. Restless legs syndrome prevalence and impact: REST general population study. Archs Intern Med 2005;165:1286–92.
[2] Winkelman JW, Redline S, Baldwin CM, Resnick HE, Newman AB, Gottlieb DJ. Polysomnographic and health-related quality of life correlates of restless legs syndrome in the Sleep Heart Health Study. Sleep 2009;32:772–8.
[3] Earley CJ, Silber MH. Restless legs syndrome: understanding its consequences and the need for better treatment. Sleep Med 2010;11:807–15.
[4] Allen RP, Picchietti D, Hening WA, Trenkwalder C, Walters AS, Montplaisir J. 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.
[5] International Restless Legs Study Group. IRLSSG diagnostic criteria for RLS (2012). Available at: www.irlssg.org.
[6] Willis T. The London practice of physick. London: Basset & Crook; 1685.
[7] Ekbom KA. Restless legs. Acta Med Scand 1945; 158(Suppl.):1–123.
[8] Ekbom KA. Restless legs syndrome. Neurology 1960;10:868–73.
[9] Diagnostic classification of sleep and arousal disorders 1979 first edition. Association of Sleep Disorders Centers and the Association for the Psychophysiological Study of Sleep. Sleep 1979;2:1–154.
[10] Bassetti CL, Mauerhofer D, Gugger M, Mathis J, Hess CW. Restless legs syndrome: a clinical study of 55 patients. Eur Neurol 2001;45:67–74.
[11] Gamaldo C, Benbrook AR, Allen RP, Oguntimein O, Earley CJ. Evaluating daytime alertness in individuals with restless legs syndrome (RLS) compared to sleep restricted controls. Sleep Med 2009;10:134–8.
[12] Allen RP, Barker PB, Horska A, Earley CJ. Thalamic glutamate/glutamine in restless legs syndrome: increased and related to disturbed sleep. Neurology 2013;80:2028–34.
[13] American Sleep Disorders Association. Diagnostic classification steering committee. The international classification of sleep disorders: diagnostic and coding manual. Rochester, MN: ASDA; 1990.
[14] Walters AS. Toward a better definition of the restless legs syndrome. The International Restless Legs Syndrome Study Group. Mov Disord 1995;10:634–42.
[15] Ohayon MM, O'Hara R, Vitiello MV. Epidemiology of restless legs syndrome: a synthesis of the literature. Sleep Med Rev 2012;16:283–95.
[16] Hening WA, Allen RP, Earley CJ, Picchietti DL, Silber MH. An update on the dopaminergic treatment of restless legs syndrome and periodic limb movement disorder. Sleep 2004;27:560–83.
[17] Garcia-Borreguero D, Ferini-Strambi L, Kohnen R, O'Keeffe S, Trenkwalder C, Hogl B, et al. European guidelines on management of restless legs syndrome: report of a joint task force by the European Federation of Neurological Societies, the European Neurological Society and the European Sleep Research Society. Eur J Neurol 2012;19:1385–96.
[18] Aurora RN, Kristo DA, Bista SR, Rowley JA, Zak RS, Casey KR, et al. The treatment of restless legs syndrome and periodic limb movement disorder in adults – an update for 2012: practice parameters with an evidence-based systematic review and meta-analyses. Sleep 2012;35:1039–62.
[19] Connor JR, Boyer PJ, Menzies SL, Dellinger B, Allen RP, Ondo WG, et al. Neuropathological examination suggests impaired brain iron acquisition in restless legs syndrome. Neurology 2003;61:304–9.
[20] Connor JR, Ponnuru P, Wang XS, Patton SM, Allen RP, Earley CJ. Profile of altered brain iron acquisition in restless legs syndrome. Brain 2011;134:959–68.
[21] Mizuno S, Mihara T, Miyaoka T, Inagaki T, Horiguchi J. CSF iron, ferritin and transferrin levels in restless legs syndrome. J Sleep Res 2005;14:43–7.
[22] Earley CJ, Connor JR, Beard JL, Malecki EA, Epstein DK, Allen RP. Abnormalities in CSF concentrations of ferritin and transferrin in restless legs syndrome. Neurology 2000;54:1698–700.
[23] Earley CJ, Barker PB, Horska A, Allen RP. MRI-determined regional brain iron concentrations in early- and late-onset restless legs syndrome. Sleep Med 2006;7:458–61.
[24] Allen RP, Barker PB, Wehrl F, Song HK, Earley CJ. MRI measurement of brain iron in patients with restless legs syndrome. Neurology 2001;56:263–5.
[25] Sun ER, Chen CA, Ho G, Earley CJ, Allen RP. Iron and the restless legs syndrome. Sleep 1998;21:371–7.
[26] Frauscher B, Gschliesser V, Brandauer E, El-Demerdash E, Kaneider M, Rucker L, et al. The severity range of restless legs syndrome (RLS) and augmentation in a prospective patient cohort: association with ferritin levels. Sleep Med 2009;10:611–5.
[27] Konofal E, Cortese S, Marchand M, Mouren MC, Arnulf I, Lecendreux M. Impact of restless legs syndrome and iron deficiency on attention-deficit/hyperactivity disorder in children. Sleep Med 2007;8:711–5.
[28] Allen R. Dopamine and iron in the pathophysiology of restless legs syndrome (RLS). Sleep Med 2004;5:385–91.
[29] Stiasny-Kolster K, Magerl W, Oertel WH, Moller JC, Treede RD. Static mechanical hyperalgesia without dynamic tactile allodynia in patients with restless legs syndrome. Brain 2004;127:773–82.
[30] Bachmann CG, Rolke R, Scheidt U, Stadelmann C, Sommer M, Pavlakovic G, et al. Thermal hypoaesthesia differentiates secondary restless legs syndrome associated with small fibre neuropathy from primary restless legs syndrome. Brain 2010;133:762–70.
[31] Stiasny-Kolster K, Haeske H, Tergau F, Muller HH, Braune HJ, Oertel WH. Cortical silent period is shortened in restless legs syndrome independently from circadian rhythm. Suppl Clin Neurophysiol 2003;56:381–9.
[32] Larsson BW, Kadi F, Ulfberg J, Aulin KP. Skeletal muscle morphology in patients with restless legs syndrome. Eur Neurol 2007;58:133–7.
[33] Patton SM, Ponnuru P, Snyder AM, Podskalny GD, Connor JR. Hypoxia-inducible factor pathway activation in restless legs syndrome patients. Eur J Neurol 2011;18:1329–35.
[34] Wahlin-Larsson B, Ulfberg J, Aulin KP, Kadi F. The expression of vascular endothelial growth factor in skeletal muscle of patients with sleep disorders. Muscle Nerve 2009;40:556–61.
[35] Stefansson H, Rye DB, Hicks A, Petursson H, Ingason A, Thorgeirsson TE, et al. A genetic risk factor for periodic limb movements in sleep. N Engl J Med 2007;357:639–47.
[36] Schormair B, Plag J, Kaffe M, Gross N, Czamara D, Samtleben W, et al. MEIS1 and BTBD9: genetic association with restless leg syndrome in end stage renal disease. J Med Genet 2011;48:462–6.
[37] Winkelmann J, Lichtner P, Putz B, Trenkwalder C, Hauk S, Meitinger T, et al. Evidence for further genetic locus heterogeneity and confirmation of RLS-1 in restless legs syndrome. Mov Disord 2006;21:28–33.
[38] Winkelmann J, Lichtner P, Schormair B, Uhr M, Hauk S, Stiasny-Kolster K, et al. Variants in the neuronal nitric oxide synthase (nNOS, NOS1) gene are associated with restless legs syndrome. Mov Disord 2008;23:350–8.
[39] Winkelmann J, Schormair B, Lichtner P, Ripke S, Xiong L, Jalilzadeh S, et al. Genome-wide association study of restless legs syndrome identifies common variants in three genomic regions. Nat Genet 2007;39:1000–6.
[40] Xiong L, Catoire H, Dion P, Gaspar C, LaFreiniere RG, Girard SL, et al. MEIS1 intronic risk haplotype associated with restless legs syndrome affects its mRNA and protein expression levels. Hum Mol Genet 2009;18:1065–74.
[41] Xiong L, Dion P, Montplaisir J, Levchenko A, Thibodeau P, Karemera L, et al. Molecular genetic studies of DMT1 on 12q in French-Canadian restless legs syndrome patients and families. Am J Med Genet B Neuropsychiatr Genet 2007;144B:911–7.
[42] Xiong L, Jang K, Montplaisir J, Levchenko A, Thibodeau P, Gaspar C, et al. Canadian restless legs syndrome twin study. Neurology 2007;68:1631–3.
[43] Allen RP, Burchell BJ, MacDonald B, Hening WA, Earley CJ. Validation of the self-completed Cambridge–Hopkins questionnaire (CH-RLSq) for ascertainment of restless legs syndrome (RLS) in a population survey. Sleep Med 2009;10:1097–100.
[44] Popat RA, Van Den Eeden SK, Tanner CM, Kushida CA, Rama AN, Black JE, et al. Reliability and validity of two self-administered questionnaires for screening restless legs syndrome in population-based studies. Sleep Med 2010;11:154–60.
[45] Allen RP, Stillman P, Myers AJ. Physician-diagnosed restless legs syndrome in a large sample of primary medical care patients in Western Europe: prevalence and characteristics. Sleep Med 2010;11:31–7.
[46] Hening WA, Allen RP, Washburn M, Lesage SR, Earley CJ. The four diagnostic criteria for restless legs syndrome are unable to exclude confounding conditions ("mimics"). Sleep Med 2009;10:976–81.
[47] Winkelmann J, Wetter TC, Collado-Seidel V, Gasser T, Dichgans M, Yassouridis A, et al. Clinical characteristics and frequency of the hereditary restless legs syndrome in a population of 300 patients. Sleep 2000;23:597–602.

[48] Holmes R, Tluk S, Metta V, Patel P, Rao R, Williams A, et al. Nature and variants of idiopathic restless legs syndrome: observations from 152 patients referred to secondary care in the UK. J Neural Transm 2007;114:929–34.
[49] Picchietti DL, Bruni O, de Weerd A, Durmer JS, Kotagal S, Owens JA, et al. Pediatric restless legs syndrome diagnostic criteria: an update by the International Restless Legs Syndrome Study Group. Sleep Med 2013;14:1253–9.
[50] Michaud M, Chabli A, Lavigne G, Montplaisir J. Arm restlessness in patients with restless legs syndrome. Mov Disord 2000;15:289–93.
[51] Karroum EG, Leu-Semenescu S, Arnulf I. Topography of the sensations in primary restless legs syndrome. J Neurol Sci 2012;320:26–31.
[52] Buchfuhrer MJ. Restless legs syndrome (RLS) with expansion of symptoms to the face. Sleep Med 2008;9:188–90.
[53] Ruppert E, Cretin B, Meyer C, Kilic-Huck U, Bourgin P. Characterization of periodic upper limb movement disorder in a patient with restless arms syndrome. Mov Disord 2012;27:1459–61.
[54] Horvath J, Landis T, Burkhard PR. Restless arms. Lancet 2008;371:530.
[55] Michaud M, Lavigne G, Desautels A, Poirier G, Montplaisir J. Effects of immobility on sensory and motor symptoms of restless legs syndrome. Mov Disord 2002;17:112–5.
[56] Birinyi PV, Allen RP, Lesage S, Dean T, Earley CJ. Investigation into the correlation between sensation and leg movement in restless legs syndrome. Mov Disord 2005;20:1097–103.
[57] Garcia-Borreguero D, Kohnen R, Boothby L, Tzonova D, Larrosa O, Dunkl E. Validation of the multiple suggested immobilization test: a test for the assessment of severity of restless legs syndrome (Willis–Ekbom disease). Sleep 2013;36:1101–9.
[58] Duffy JF, Lowe ASW, Silva EJ, Winkelman JW. Periodic limb movements in sleep exhibit a circadian rhythm that is maximal in the late evening/early night. Sleep Med 2011;12:83–8.
[59] Hening WA, Walters AS, Wagner M, Rosen R, Chen V, Kim S, et al. Circadian rhythm of motor restlessness and sensory symptoms in the idiopathic restless legs syndrome. Sleep 1999;22:901–12.
[60] Michaud M, Dumont M, Selmaoui B, Paquet J, Fantini ML, Montplaisir J. Circadian rhythm of restless legs syndrome: relationship with biological markers. Ann Neurol 2004;55:372–80.
[61] Trenkwalder C, Walters A, Hening W, et al. Circadian rhythm of patients with the idiopathic restless legs syndrome. Sleep Res 1995;24:360.
[62] Trenkwalder C, Hening WA, Walters AS, Campbell SS, Rahman K, Chokroverty S. Circadian rhythm of periodic limb movements and sensory symptoms of restless legs syndrome. Mov Disord 1999;14:102–10.
[63] Michaud M, Dumont M, Paquet J, Desautels A, Fantini ML, Montplaisir J. Circadian variation of the effects of immobility on symptoms of restless legs syndrome. Sleep 2005;28:843–6.
[64] Allen RP, Dean T, Earley CJ. Effects of rest-duration, time-of-day and their interaction on periodic leg movements while awake in restless legs syndrome. Sleep Med 2005;6:429–34.
[65] Tzonova D, Larrosa O, Calvo E, Granizo JJ, Williams AM, de la Llave Y, et al. Breakthrough symptoms during the daytime in patients with restless legs syndrome (Willis–Ekbom disease). Sleep Med 2012;13:151–5.
[66] Moller C, Wetter TC, Koster J, Stiasny-Kolster K. Differential diagnosis of unpleasant sensations in the legs: prevalence of restless legs syndrome in a primary care population. Sleep Med 2010;11:161–6.
[67] Hening WA, Allen RP, Washburn M, Lesage S, Earley CJ. Validation of the Hopkins telephone diagnostic interview for restless legs syndrome. Sleep Med 2008;9:283–9.
[68] Benes H, Kohnen R. Validation of an algorithm for the diagnosis of restless legs syndrome: the Restless Legs Syndrome – Diagnostic Index (RLS-DI). Sleep Med 2009;10:515–23.
[69] Montplaisir J, Boucher S, Poirier G, Lavigne G, Lapierre O, Lesperance P. Clinical, polysomnographic, and genetic characteristics of restless legs syndrome: a study of 133 patients diagnosed with new standard criteria. Mov Disord 1997;12:61–5.
[70] Hening W, Walters AS, Allen RP, Montplaisir J, Myers A, Ferini-Strambi L. Impact, diagnosis and treatment of restless legs syndrome (RLS) in a primary care population: the REST (RLS epidemiology, symptoms, and treatment) primary care study. Sleep Med 2004;5:237–46.
[71] Bjorvatn B, Leissner L, Ulfberg J, Gyring J, Karlsborg M, Regeur L, et al. Prevalence, severity and risk factors of restless legs syndrome in the general adult population in two Scandinavian countries. Sleep Med 2005;6:307–12.
[72] Ulfberg J, Bjorvatn B, Leissner L, Gyring J, Karlsborg M, Regeur L, et al. Comorbidity in restless legs syndrome among a sample of Swedish adults. Sleep Med 2007;8:768–72.
[73] Phillips B, Hening W, Britz P, Mannino D. Prevalence and correlates of restless legs syndrome: results from the 2005 National Sleep Foundation Poll. Chest 2006;129:76–80.
[74] Broman JE, Mallon L, Hetta J. Restless legs syndrome and its relationship with insomnia symptoms and daytime distress: epidemiological survey in Sweden. Psychiatry Clin Neurosci 2008;62:472–5.
[75] Winkelman JW, Finn L, Young T. Prevalence and correlates of restless legs syndrome symptoms in the Wisconsin Sleep Cohort. Sleep Med 2006;7:545–52.
[76] Hornyak M, Feige B, Voderholzer U, Philipsen A, Riemann D. Polysomnography findings in patients with restless legs syndrome and in healthy controls: a comparative observational study. Sleep 2007;30:861–5.
[77] Allen R, Becker PM, Bogan R, Schmidt M, Kushida CA, Fry JM, et al. Ropinirole decreases periodic leg movements and improves sleep parameters in patients with restless legs syndrome. Sleep 2004;27:907–14.
[78] McCrink L, Allen RP, Wolowacz S, Sherrill B, Connolly M, Kirsch J. Predictors of health-related quality of life in sufferers with restless legs syndrome: a multi-national study. Sleep Med 2007;8:73–83.
[79] Kushida C, Martin M, Nikam P, Blaisdell B, Wallenstein G, Ferini-Strambi L, et al. Burden of restless legs syndrome on health-related quality of life. Qual Life Res 2007;16:617–24.
[80] Happe S, Reese JP, Stiasny-Kolster K, Peglau I, Mayer G, Klotsche J, et al. Assessing health-related quality of life in patients with restless legs syndrome. Sleep Med 2009;10:295–305.
[81] Wesstrom J, Nilsson S, Sundstrom-Poromaa I, Ulfberg J. Health-related quality of life and restless legs syndrome among women in Sweden. Psychiatry Clin Neurosci 2010;64:574–9.
[82] Berger K, Luedemann J, Trenkwalder C, John U, Kessler C. Sex and the risk of restless legs syndrome in the general population. Archs Intern Med 2004;164:196–202.
[83] Atkinson MJ, Allen RP, DuChane J, Murray C, Kushida C, Roth T. 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.
[84] Abetz L, Arbuckle R, Allen RP, Mavraki E, Kirsch J. The reliability, validity and responsiveness of the Restless Legs Syndrome Quality of Life questionnaire (RLSQoL) in a trial population. Health Qual Life Outcomes 2005;3:79.
[85] Abetz L, Allen R, Follet A, Washburn T, Earley C, Kirsch J, et al. Evaluating the quality of life of patients with restless legs syndrome. Clin Ther 2004;26:925–35.
[86] Gerhard R, Bosse A, Uzun D, Orth M, Kotterba S. Quality of life in restless legs syndrome. Influence of daytime sleepiness and fatigue. Med Klin (Munich) 2005;100:704–9.
[87] Rothdach AJ, Trenkwalder C, Haberstock J, Keil U, Berger K. Prevalence and risk factors of RLS in an elderly population: the MEMO study. Memory and morbidity in Augsburg elderly. Neurology 2000;54:1064–8.
[88] Cho SJ, Hong JP, Hahm BJ, Jeon HJ, Chang SM, Cho MJ, et al. Restless legs syndrome in a community sample of Korean adults: prevalence, impact on quality of life, and association with DSM-IV psychiatric disorders. Sleep 2009;32:1069–76.
[89] Nomura T, Inoue Y, Kusumi M, Uemura Y, Nakashima K. Prevalence of restless legs syndrome in a rural community in Japan. Mov Disord 2008;23:2363–9.
[90] Cuellar NG, Strumpf NE, Ratcliffe SJ. Symptoms of restless legs syndrome in older adults: outcomes on sleep quality, sleepiness, fatigue, depression, and quality of life. J Am Geriatr Soc 2007;55:1387–92.
[91] Trenkwalder C, Garcia-Borreguero D, Montagna P, Lainey E, de Weerd AW, Tidswell P, et al. Ropinirole in the treatment of restless legs syndrome: results from the TREAT RLS 1 study, a 12 week, randomised, placebo controlled study in 10 European countries. J Neurol Neurosurg Psychiatry 2004;75:92–7.
[92] Walters AS, Ondo WG, Dreykluft T, Grunstein R, Lee D, Sethi K. Ropinirole is effective in the treatment of restless legs syndrome. TREAT RLS 2: a 12-week, double-blind, randomized, parallel-group, placebo-controlled study. Mov Disord 2004;19:1414–23.
[93] Winkelman JW, Sethi KD, Kushida CA, Becker PM, Koester J, Cappola JJ, et al. Efficacy and safety of pramipexole in restless legs syndrome. Neurology 2006;67:1034–9.
[94] Oertel WH, Benes H, Garcia-Borreguero D, Hogl B, Poewe W, Montagna P, et al. Rotigotine transdermal patch in moderate to severe idiopathic restless legs syndrome: a randomized, placebo-controlled polysomnographic study. Sleep Med 2010;11:848–56.
[95] Winkelmann J, Prager M, Lieb R, Pfister H, Spiegel B, Wittchen HU, et al. "Anxietas Tibiarum" depression and anxiety disorders in patients with restless legs syndrome. J Neurol 2005;252:67–71.
[96] Lee HB, Hening WA, Allen RP, Kalaydjian AE, Earley CJ, Eaton WW, et al. Restless legs syndrome is associated with DSM-IV major depressive disorder and panic disorder in the community. J Neuropsychiatry Clin Neurosci 2008;20:101–5.
[97] Sevim S, Dogu O, Kaleagasi H, Aral M, Metin O, Camdeviren H. Correlation of anxiety and depression symptoms in patients with restless legs syndrome: a population based survey. J Neurol Neurosurg Psychiatry 2004;75:226–30.
[98] Hornyak M, Benes H, Kohnen R, Banik N, Schoen S, Bergmann L. Ropinirole improves depressive symptoms and core RLS symptoms in patients with moderate to severe idiopathic RLS: a multicentre, randomised, placebo-controlled study in Germany. Eur J Neurol 2009;16:517.
[99] Montagna P, Hornyak M, Ulfberg J, Hong SB, Koester J, Crespi G, et al. Randomized trial of pramipexole for patients with restless legs syndrome (RLS) and RLS-related impairment of mood. Sleep Med 2011;12:34–40.
[100] Coccagna G, Lugaresi E. Restless legs syndrome and nocturnal myoclonus. Int J Neurol 1981;15:77–87.
[101] Montplaisir J, Boucher S, Nicolas A, Lesperance P, Gosselin A, Rompre P, et al. Immobilization tests and periodic leg movements in sleep for the diagnosis of restless leg syndrome. Mov Disord 1998;13:324–9.
[102] Ferri R, Zucconi M, Manconi M, Bruni O, Ferini-Strambi L, Vandi S, et al. Different periodicity and time structure of leg movements during sleep in narcolepsy/cataplexy and restless legs syndrome. Sleep 2006;29:1587–94.
[103] Ferri R, Manconi M, Plazzi G, Bruni O, Cosentino FII, Ferini-Strambi L, et al. Leg movements during wakefulness in restless legs syndrome: time structure

and relationships with periodic leg movements during sleep. Sleep Med 2012;13:529–35.
[104] Sforza E, Juony C, Ibanez V. Time-dependent variation in cerebral and autonomic activity during periodic leg movements in sleep: implications for arousal mechanisms. Clin Neurophysiol 2002;113:883–91.
[105] Sforza E, Jouny C, Ibanez V. Time course of arousal response during periodic leg movements in patients with periodic leg movements and restless legs syndrome. Clin Neurophysiol 2003;114:1116–24.
[106] Fantini ML, Michaud M, Gosselin N, Lavigne G, Montplaisir J. Periodic leg movements in REM sleep behavior disorder and related autonomic and EEG activation. Neurology 2002;59:1889–94.
[107] Ferri R, Zucconi M, Rundo F, Spruyt K, Manconi M, Ferini-Strambi L. Heart rate and spectral EEG changes accompanying periodic and non-periodic leg movements during sleep. Clin Neurophysiol 2007;118:438–48.
[108] Sforza E, Pichot V, Cervena K, Barthelemy JC, Roche F. Cardiac variability and heart-rate increment as a marker of sleep fragmentation in patients with a sleep disorder: a preliminary study. Sleep 2007;30:43–51.
[109] Winkelman JW. The evoked heart rate response to periodic leg movements of sleep. Sleep 1999;22:575–80.
[110] Pennestri MH, Montplaisir J, Colombo R, Lavigne G, Lanfranchi PA. Nocturnal blood pressure changes in patients with restless legs syndrome. Neurology 2007;68:1213–8.
[111] Giannaki CD, Zigoulis P, Karatzaferi C, Hadjigeorgiou GM, George KP, Gourgoulianis K, et al. Periodic limb movements in sleep contribute to further cardiac structure abnormalities in hemodialysis patients with restless legs syndrome. J Clin Sleep Med 2013;9:147–53.
[112] Siddiqui F, Strus J, Ming X, Lee IA, Chokroverty S, Walters AS. Rise of blood pressure with periodic limb movements in sleep and wakefulness. Clin Neurophysiol 2007;118:1923–30.
[113] Walters AS, Rye DB. Evidence continues to mount on the relationship of restless legs syndrome/periodic limb movements in sleep to hypertension, cardiovascular disease, and stroke. Sleep 2010;33:287.
[114] Koo BB, Blackwell T, Ancoli-Israel S, Stone KL, Stefanick ML, Redline S. Association of incident cardiovascular disease with periodic limb movements during sleep in older men: outcomes of Sleep Disorders in Older Men (MrOS) Study. Circulation 2011;124:1223–31.
[115] Winkelman JW, Shahar E, Sharief I, Gottlieb DJ. Association of restless legs syndrome and cardiovascular disease in the Sleep Heart Health Study. Neurology 2008;70:35–42.
[116] Benediktsdottir B, Janson C, Lindberg E, Arnardottir ES, Olafsson I, Cook E, et al. Prevalence of restless legs syndrome among adults in Iceland and Sweden: lung function, comorbidity, ferritin, biomarkers and quality of life. Sleep Med 2010;11:1043–8.
[117] Baumann CR, Marti I, Bassetti CL. Restless legs symptoms without periodic limb movements in sleep and without response to dopaminergic agents: a restless legs-like syndrome? Eur J Neurol 2007;14:1369–72.
[118] Bombois S, Derambure P, Pasquier F, Monaca C. Sleep disorders in aging and dementia. J Nutr Health Aging 2010;14:212–7.
[119] Dauvilliers Y, Rompre S, Gagnon JF, Vendette M, Petit D, Montplaisir J. REM sleep characteristics in narcolepsy and REM sleep behavior disorder. Sleep 2007;30:844–9.
[120] Pedroso JL, Braga-Neto P, Felicio AC, Aquino CC, do Prado LB, do Prado GF, et al. Sleep disorders in cerebellar ataxias. Arq Neuropsiquiatr 2011;69:253–7.
[121] Fulda S, Rusakova I, Ferri R, Bassetti CL, Pisarenco I, Colamartino E, et al. P6. Leg movements during sleep in patients with obstructive sleep apnea. Clin Neurophysiol 2012;123:e104.
[122] Winkelman J. High rates of periodic leg movements of sleep in REM-sleep behavior disorder raise more questions about the relationship between sleep-related movement disorders. Article reviewed: M.L. Fantini, M. Michaud, N. Gosselin, G. Lavigne, J. Montplaisir, Periodic leg movements in REM sleep behavior disorder and related autonomic and EEG activation, Neurology 59 (2002) 1889–1894. Sleep Med 2003;4:261–2.
[123] Hoque R, Chesson Jr AL. Pharmacologically induced/exacerbated restless legs syndrome, periodic limb movements of sleep, and REM behavior disorder/REM sleep without atonia: literature review, qualitative scoring, and comparative analysis. J Clin Sleep Med 2010;6:79–83.
[124] Yang C, White DP, Winkelman JW. Antidepressants and periodic leg movements of sleep. Biol Psychiatry 2005;58:510–4.
[125] Pennestri MH, Whittom S, Adam B, Petit D, Carrier J, Montplaisir J. PLMS and PLMW in healthy subjects as a function of age: prevalence and interval distribution. Sleep 2006;29:1183–7.
[126] Claman DM, Redline S, Blackwell T, Ancoli-Israel S, Surovec S, Scott N, et al. Prevalence and correlates of periodic limb movements in older women. J Clin Sleep Med 2006;2:438–45.
[127] Ferri R. The time structure of leg movement activity during sleep: the theory behind the practice. Sleep Med 2012;13:433–41.
[128] Ferri R, Manconi M, Lanuzza B, Cosentino FI, Bruni O, Ferini-Strambi L, et al. Age-related changes in periodic leg movements during sleep in patients with restless legs syndrome. Sleep Med 2008;9:790–8.
[129] Michaud M, Paquet J, Lavigne G, Desautels A, Montplaisir J. Sleep laboratory diagnosis of restless legs syndrome. Eur Neurol 2002;48:108–13.
[130] Stiasny-Kolster K, Kohnen R, Carsten Möller J, Trenkwalder C, Oertel WH. Validation of the "l-DOPA test" for diagnosis of restless legs syndrome. Mov Disord 2006;21:1333–9.
[131] Trenkwalder C, Benes H, Poewe W, Oertel WH, Garcia-Borreguero D, de Weerd AW, et al. Efficacy of rotigotine for treatment of moderate-to-severe restless legs syndrome: a randomised, double-blind, placebo-controlled trial. Lancet Neurol 2008;7:595–604.
[132] Xiong L, Montplaisir J, Desautels A, Barhdadi A, Turecki G, Levchenko A, et al. Family study of restless legs syndrome in Quebec, Canada: clinical characterization of 671 familial cases. Archs Neurol 2010;67:617–22.
[133] Allen RP, La Buda MC, Becker P, Earley CJ. Family history study of the restless legs syndrome. Sleep Med 2002;3(Suppl.):S3–7.
[134] Desai AV, Cherkas LF, Spector TD, Williams AJ. Genetic influences in self-reported symptoms of obstructive sleep apnoea and restless legs: a twin study. Twin Res 2004;7:589–95.
[135] Ondo WG, Vuong KD, Wang Q. Restless legs syndrome in monozygotic twins: clinical correlates. Neurology 2000;55:1404–6.
[136] Saletu B, Anderer P, Saletu M, Hauer C, Lindeck-Pozza L, Saletu-Zyhlarz G. EEG mapping, psychometric, and polysomnographic studies in restless legs syndrome (RLS) and periodic limb movement disorder (PLMD) patients as compared with normal controls. Sleep Med 2002;3(Suppl.):S35–42.
[137] Kallweit U, Khatami R, Pizza F, Mathis J, Bassetti CL. Dopaminergic treatment in idiopathic restless legs syndrome: effects on subjective sleepiness. Clin Neuropharmacol 2010;33:276–8.
[138] Plazzi G, Ferri R, Antelmi E, Bayard S, Franceschini C, Cosentino FI, et al. Restless legs syndrome is frequent in narcolepsy with cataplexy patients. Sleep 2010;33:689–94.
[139] Picchietti D, Allen RP, Walters AS, Davidson JE, Myers A, Ferini-Strambi L. Restless legs syndrome: prevalence and impact in children and adolescents – the Peds REST study. Pediatrics 2007;120:253–66.
[140] Yilmaz K, Kilincaslan A, Aydin N, Kor D. Prevalence and correlates of restless legs syndrome in adolescents. Dev Med Child Neurol 2011;53:40–7.
[141] Pantaleo NP, Hening WA, Allen RP, Earley CJ. Pregnancy accounts for most of the gender difference in prevalence of familial RLS. Sleep Med 2010;11:310–3.
[142] Allen RP, Earley CJ. Defining the phenotype of the restless legs syndrome (RLS) using age-of-symptom-onset. Sleep Med 2000;1:11–9.
[143] Ondo W, Jankovic J. Restless legs syndrome: clinicoetiologic correlates. Neurology 1996;47:1435–41.
[144] Walters AS, Hickey K, Maltzman J, Verrico T, Joseph D, Hening W, et al. A questionnaire study of 138 patients with restless legs syndrome: the 'Night-Walkers' survey. Neurology 1996;46:92–5.
[145] Budhiraja P, Budhiraja R, Goodwin JL, Allen RP, Newman AB, Koo BB, et al. Incidence of restless legs syndrome and its correlates. J Clin Sleep Med 2012;8:119–24.
[146] Kagimura T, Nomura T, Kusumi M, Nakashima K, Inoue Y. Prospective survey on the natural course of restless legs syndrome over two years in a closed cohort. Sleep Med 2011;12:821–6.
[147] Szentkiralyi A, Fendrich K, Hoffmann W, Happe S, Berger K. Incidence of restless legs syndrome in two population-based cohort studies in Germany. Sleep Med 2011;12:815–20.
[148] Garcia-Borreguero D, Kohnen R, Silber MH, Winkelman JW, Earley CJ, Hogl B, et al. The long-term treatment of restless legs syndrome/Willis–Ekbom disease: evidence-based guidelines and clinical consensus best practice guidance: a report from the International Restless Legs Syndrome Study Group. Sleep Med 2013;14:675–84.
[149] Saletu B, Gruber G, Saletu M, Brandstatter N, Hauer C, Prause W, et al. Sleep laboratory studies in restless legs syndrome patients as compared with normals and acute effects of ropinirole. 1. Findings on objective and subjective sleep and awakening quality. Neuropsychobiology 2000;41:181–9.
[150] Garcia-Borreguero D, Larrosa O, Granizo JJ, de la Llave Y, Hening WA. Circadian variation in neuroendocrine response to L-dopa in patients with restless legs syndrome. Sleep 2004;27:669–73.
[151] Mallon L, Broman J-E, Hetta J. Restless legs symptoms with sleepiness in relation to mortality: 20-year follow-up study of a middle-aged Swedish population. Psychiatry Clin Neurosci 2008;62:457–63.
[152] Bentley AJ, Rosman KD, Mitchell D. Can the sensory symptoms of restless legs syndrome be assessed using a qualitative pain questionnaire? Clin J Pain 2007;23:62–6.
[153] Karroum EG, Golmard J-L, Leu-Semenescu S, Arnulf I. Sensations in restless legs syndrome. Sleep Med 2012;13:402–8.
[154] Kerr S, McKinon W, Bentley A. Descriptors of restless legs syndrome sensations. Sleep Med 2012;13:409–13.
[155] Valko PO, Siccoli MM, Bassetti CL. Unilateral RLS with predominantly ipsilateral PLMS and variable response to dopaminergic drugs: a variant of idiopathic RLS? Eur J Neurol 2009;16:430–2.
[156] Allen RP, Earley CJ. Validation of the Johns Hopkins restless legs severity scale. Sleep Med 2001;2:239–42.
[157] Earley CJ, Allen RP. Pergolide and carbidopa/levodopa treatment of the restless legs syndrome and periodic leg movements in sleep in a consecutive series of patients. Sleep 1996;19:801–10.
[158] Allen RP, Earley CJ. Augmentation of the restless legs syndrome with carbidopa/levodopa. Sleep 1996;19:205–13.
[159] Manconi M, Ulfberg J, Berger K, Ghorayeb I, Wesstrom J, Fulda S, et al. When gender matters: restless legs syndrome. Report of the "RLS and woman" workshop endorsed by the European RLS Study Group. Sleep Med Rev 2012;16:297–307.

[160] Neau JP, Marion P, Mathis S, Julian A, Godeneche G, Larrieu D, et al. Restless legs syndrome and pregnancy: follow-up of pregnant women before and after delivery. Eur Neurol 2010;64:361–6.
[161] Cesnik E, Casetta I, Turri M, Govoni V, Granieri E, Strambi LF, et al. Transient RLS during pregnancy is a risk factor for the chronic idiopathic form. Neurology 2010;75:2117–20.
[162] Allen RP, Auerbach S, Bahrain H, Auerbach M, Earley CJ. The prevalence and impact of restless legs syndrome on patients with iron deficiency anemia. Am J Hematol 2013;88:261–4.
[163] Wang J, O'Reilly B, Venkataraman R, Mysliwiec V, Mysliwiec A. Efficacy of oral iron in patients with restless legs syndrome and a low-normal ferritin: a randomized, double-blind, placebo-controlled study. Sleep Med 2009;10:973–5.
[164] Mohri I, Kato-Nishimura K, Kagitani-Shimono K, Kimura-Ohba S, Ozono K, Tachibana N, et al. Evaluation of oral iron treatment in pediatric restless legs syndrome (RLS). Sleep Med 2012;13:429–32.
[165] Oner P, Dirik EB, Taner Y, Caykoylu A, Anlar O. Association between low serum ferritin and restless legs syndrome in patients with attention deficit hyperactivity disorder. Tohoku J Exp Med 2007;213:269–76.
[166] Peirano P, Algarin C, Chamorro R, Manconi M, Lozoff B, Ferri R. Iron deficiency anemia in infancy exerts long-term effects on the tibialis anterior motor activity during sleep in childhood. Sleep Med 2012;13:1006–12.
[167] Picchietti MA, Picchietti DL. Restless legs syndrome and periodic limb movement disorder in children and adolescents. Semin Pediatr Neurol 2008;15:91–9.
[168] O'Keeffe ST, Noel J, Lavan JN. Restless legs syndrome in the elderly. Postgrad Med J 1993;69:701–3.
[169] O'Keeffe ST, Gavin K, Lavan JN. Iron status and restless legs syndrome in the elderly. Age Ageing 1994;23:200–3.
[170] O'Keeffe ST. Iron deficiency with normal ferritin levels in restless legs syndrome. Sleep Med 2005;6:281–2.
[171] O'Keeffe ST. Secondary causes of restless legs syndrome in older people. Age Ageing 2005;34:349–52.
[172] American Psychiatric Association. Diagnostic and statistical manual of mental disorders. 5th ed. Arlington (VA): APA; 2013.
[173] American Academy of Sleep Medicine. International classification of sleep disorders, 3rd ed. Darien, IL: AASM; 2014.
[174] Garcia-Borreguero D, Stillman P, Benes H, Buschmann H, Chaudhuri KR, Gonzalez Rodriguez VM, et al. Algorithms for the diagnosis and treatment of restless legs syndrome in primary care. BMC Neurol 2011;11:28.
[175] Silber MH, Becker PM, Earley C, Garcia-Borreguero D, Ondo WG. Medical Advisory Board of the Willis–Ekbom Disease Foundation. Willis–Ekbom Disease Foundation revised consensus statement on the management of restless legs syndrome. Mayo Clin Proc 2013;88:977–86.
[176] Li Y, Mirzaei F, O'Reilly EJ, Winkelman J, Malhotra A, Okereke OI, et al. Prospective study of restless legs syndrome and risk of depression in women. Am J Epidemiol 2012;176:279–88.
[177] Li Y, Wang W, Winkelman JW, Malhotra A, Ma J, Gao X. Prospective study of restless legs syndrome and mortality among men. Neurology 2013;81:52–9.
[178] Cho YW, Allen RP, Earley CJ. Lower molecular weight intravenous iron dextran for restless legs syndrome. Sleep Med 2013;14:274–7.
[179] Hornyak M, Scholz H, Kiemen A, Kassubek J. Investigating the response to intravenous iron in restless legs syndrome: an observational study. Sleep Med 2012;13:732–5.
[180] Molnar MZ, Novak M, Ambrus C, Szeifert L, Kovacs A, Pap J, et al. Restless legs syndrome in patients after renal transplantation. Am J Kidney Dis 2005;45:388–96.
[181] Allen RP, Bharmal M, Calloway M. Prevalence and disease burden of primary restless legs syndrome: results of a general population survey in the United States. Mov Disord 2011;26:114–20.