History of Restless Legs Syndrome, Recently Named Willis–Ekbom Disease

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Richard P. Allen

Willis–Ekbom disease (WED) classically known as restless legs syndrome (RLS) has a remarkable history demonstrating interlocking relations between biology and treatment of a medical disorder. WED had little effective treatment or recognition until the later part of the twentieth century when critical advances occurred in understanding the biology of the disorder and treatment options. Prior to these developments, thousands suffered from a tortuous inability to remain at rest in the evening or night. This was well described by Thomas Willis in 1685 [1] as

> leapings and contractions of tendons and so great the restlessness and tossing of their members (arms and legs) ensure, that the diseased are no more able to sleep than if they were in the place of greatest torture.

The actual number with such extreme suffering is somewhat uncertain even today, but the most conservative estimate would be about 0.2–0.8% of the adults in Western Europe and North America (USA and Canada) [2, 3] or more than two million adults. These individuals suffered torturous nights without effective treatment or even recognition of their disorder. The history of WED provides an excellent example of how scientifically based medical developments significantly reduce human suffering.

The history of the WED divides into two phases, i.e., early clinical descriptions of a syndrome and disease conceptualization. Features of the disease conceptualization develop simultaneously along various separate tracks representing developments in diagnosis, patient advocacy, epidemiology, biology, and treatment. This small section can only provide a general overview of this remarkable history and thus focuses on the developments in each area most related to advances in treatment and diagnosis.

Early Reports of WED

Thomas Willis provided the first known medical description of WED in his Latin discourses in 1672 [4] and translated into English in a posthumously published collection of his writings in 1685 [1]. There are scattered limited descriptions of WED after that, mostly from the nineteenth and early twentieth century. The nineteenth-century descriptions were mostly similar to that of Wittmaack who in 1861 referred to WED symptoms as *anxietas tibiarum* [5]. Beard similarly in 1880 refers to WED in relation to "nervous exhaustion" [6]. The nineteenth-century terms used to describe WED at that time indicated a clinical condition without a well-defined biological basis, but these were later read as indicating WED was a psychiatric disorder associated with neuroses and anxiety. This unfortunate linguistic distortion produced a general neglect of WED as a neurological disease.

Diagnosis

It was not until the seminal work by Ekbom in the 1940s [7,8] that WED was restored to consideration as a neurological disease. Others, at about this time, also described the disorder as medical not psychiatric condition, e.g., Mussio-Fournier and Rawak in 1940 refer to inherited familial disease worsening during pregnancy [9], and Allison in 1943 describes "leg jitters" as "a combination of voluntary and involuntary jerks" disturbing sleep [10]. None before Ekbom produced a systematic case series nor a careful description of a large clinical sample. Ekbom's monograph translated into English from Swedish in 1945 [8] provides the first definitive description of the disease and the basis for its current view as neurological disorder. He emphasized both the urge to move and the sensory discomfort with the disorder and named it "restless legs." He clearly identified this as a chronic condition, which he saw as having exclusively or mainly subjective symptoms that "embitter but do not endanger the patient's life."

R. P. Allen (✉)
Department of Neurology, Johns Hopkins University, Baltimore, MD, USA
e-mail: rallen6@jhmi.edu

S. Chokroverty, M. Billiard (eds.), *Sleep Medicine,* DOI 10.1007/978-1-4939-2089-1_30,

After Ekbom, the development of attention to physiological recordings of sleep produced a discovery in 1953 of periodic leg movements during sleep (PLMS) [11], which were found to be very common among WED patients [12]. Thus, the sleep field added to the RLS diagnosis the motor signs of PLMS that were found to be fairly specific [13] but not sensitive for diagnosis of WED [14], largely because they occur at high rates in healthy adults over age 45 [15]. Unfortunately, the sleep medicine field when establishing their initial diagnostic criteria for sleep-related disorders distorted the characteristics of WED over emphasizing nighttime symptoms and the sleep disturbance and also PLMS as closely associated with the sleep disruption [16]. This produced considerable confusion about the relation of PLMS to WED that has persisted to some extent. Studies have since clearly demonstrated that the sleep disturbance of WED does not relate to the commonly occurring PLMS but reflects a separate aspect of the disease [13, 17].

At about the same time as the development of sleep medicine interest in WED, three movement disorder experts also "discovered" WED. Arthur Walters and Wayne Hening under the supervision of Sudhansu Chokroverty noted pronounced WED symptoms in a small series of patients and reported for the first time the periodic limb movements during resting wake state [18]. This important work emphasized the need for a diagnostic criteria for WED established not by experts in other fields, but by those working with the disorder. Walters with support from Hening formed the International RLS Study Group (IRLSSG) comprised of 28 WED experts from North American and Europe. Based on their shared clinical experiences, they were able to reach unanimous consensus on a set of four essential diagnostic criteria defining WED [19]. These four criteria emphasize the sensory urge to move (or akathisia) the legs as primary with sensory discomfort common but not always present. The criteria note rest or inactivity engender, and movement relieves the symptoms. Finally, there is a strong circadian component with symptoms exclusive or worse in the evening or night than in the morning. Thus, the patient can remain at rest longer without symptoms in the morning than in the evening.

The initial formulation of the four basic WED diagnostic criteria confounded rest engendering with activity relieving the symptoms, and included a concept of restless feelings that turned out to be confusing. These technical problems were corrected in a 2002 major consensus conference of the IRLSSG held at the National Institute of Health in Washington D.C., USA, chaired by Richard Allen. This led to the definitive four essential diagnostic criteria for WED that have provided the basis for recent major advances in epidemiology, biology, and treatment of WED. This 2002 conference also identified the treatment emergent problem of WED augmentation and noted the special diagnostic considerations for children and cognitively impaired adults [20].

Further clinical experience documented that conditions can "mimic" WED symptoms requiring attention to differential diagnosis to exclude these conditions. The "mimics" produce symptoms that are sometimes hard to discriminate from those defining WED, except the "mimics" are usually closely tied to another condition and the symptoms of the "mimics" almost but not totally match the full extent of the WED symptoms [21]. This pointed out the need for adding a fifth essential diagnostic criterion requiring exclusion of the "mimics." A 4-year process to update the RLS diagnostic criteria started with a 2008 clinical conference sponsored by the IRLSSG at Johns Hopkins in Baltimore, MD, USA. These were approved in 2012 after review at an annual meeting of members followed by a web-based review by all members and are available on www.irlssg.org website [21a]. (See Table 30.1.)

The IRLSSG diagnostic criteria reflect the view that WED is a neurological disease. Two other disciplines have defined WED as either a sleep-related disorder or a psychiatric disorder and in the process have unfortunately distorted the diagnosis to fit their particular discipline ignoring the neurological basis for this disease. So there is one correct set of diagnostic criteria (Table 30.1) and unfortunately two that err particularly in each having a totally arbitrary and different criterion not supported by data for frequency of symptoms required before the diagnosis can be made. RLS diagnosed independently by two neurologists experienced with RLS with 100 % agreement included 19 % who did not have symptoms at least twice a week (required by the sleep medicine diagnostic criteria) and 33 % who did not have symptoms at least three times a week [21b].

Patient Advocacy

Since there had been little professional help available for treatment of WED, the patients themselves organized self-help groups and national organizations around the world to advocate for better recognition, treatment, and eventually a cure for the disease. The experience in the USA started with kitchen table meetings of three RLS patients: Pickett Guthrie, Virginia Wilson, and Robert Balkam. This developed into the current WED foundation with several thousand members and a regular "nightwalkers" publication. Early in this development another WED sufferer, Robert H Yoakum, a well-known humanist and author wrote an article on WED for Modern Maturity. This article produced more reader response as compared to others. More than 40,000 letters were sent to the magazine from older adults reporting relief that someone had identified the cause of their nighttime tortures. Thus, the WED foundation began its continuing campaign for recognition and acceptance of WED in the medical es-

tablishment. Today, there are active patient advocacy groups not only in the USA but also in most western European countries. They hold in conjunction with the IRLSSG an annual WED awareness day on Ekbom's birthday.

Severity Assessment

Early in the development of WED evaluations, it became clear that a clinical scale was needed to assess WED severity. A scale called the IRLS, developed and validated in 2002 by the IRLSSG, has since provided a standard unifying clinical WED studies. This ten-item scale has scores ranging from 0 to 40, excellent psychometric properties [22, 23] and two subscales, i.e., symptoms and impact [23]. The scale has been translated into 32 or more languages and is available from Messaging Application Programming Interface (MAPI) Research Trust Patient-Reported Outcome & Quality of Life Instruments Database (Proqolid) at http://www.proqolid.org.

Epidemiology

The initial efforts to determine prevalence of WED used questionnaires asking patients about critical diagnostic symptoms. Efforts before the development of the full diagnostic criteria had a very limited set of questions missing some of the essential features of the diagnosis and produced surprisingly high prevalence, e.g., 15 % of French Canadians [24]. Subsequent better studies relied upon questions covering the four essential diagnostic criteria of IRLSSG and often added some assessment to identify clinically significant RLS. Among the best of these, the RLS epidemiology, symptoms, and treatment (REST) studies have served to define out the understanding of RLS prevalence in Europe and USA. The REST general population study documented a 7 % prevalence for RLS symptoms occurring in the past year and more significantly a 2.7 % prevalence for RLS sufferers, i.e., those with symptoms occurring in the past year usually at least twice a week with moderate to severe distress when occurring [25]. The REST study documents characteristics of the RLS sufferers including the increasing prevalence with

Table 30.1 2013 diagnostic criteria for restless legs syndrome/Willis–Ekbom disease. The preferred diagnostic criteria published by the International Restless Legs Syndrome Study Group). (From Allen, R. P., et al., 2014)

IRLSSG Consensus Diagnostic Criteria for RLS (2012)
Restless legs syndrome (RLS), 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 the severity varies from mildly annoying to disabling. Symptoms may also remit for various periods of time. RLS 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[f]
A. Chronic-persistent RLS: Symptoms when not treated would occur on average at least twice weekly for the past year
B. Intermittent RLS: Symptoms when not treated occured on an average of less than twice per week for the past year, with at least five lifetime events
Specifier for Clinical Significance of RLS
The symptoms of RLS cause significant distress or impairment in social, occupational, educational, or other important areas of functioning by the 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 mimics," have been commonly confused with RLS 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 may also occur with any of these conditions, but the RLS 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 such as pregnancy or drug induced RLS where the frequency may be high but limited to duration of the provocative condition

age and a 2:1 female: male ratio. It is often misunderstood that these characteristics were not determined for all RLS but only RLS sufferers.

The developing understanding of WED mimics indicated that the questionnaire approach without any effort to correct for mimics would likely produce a low false positive rate. The 4-item questionnaire diagnosis compared in one large international study with trained physician diagnosis had, indeed, only a 58% positive predictive value for identification of RLS sufferers [2]. In another study questions asking about the four diagnostic criteria compared to a validated questionnaire excluding mimics had only a 50% positive predictive value [3]. It takes a very high specificity with reasonable sensitivity to obtain a reasonable positive predictive value for identification of a condition with about a 5% prevalence. A questionnaire was then developed in a collaborative study involving Cambridge University and Johns Hopkins that included questions designed to exclude common "mimics." The validation compared to a clinical interview found for ascertainment of WED in a population of blood donors a positive predictive value of 86% [26]. This questionnaire has since been used in other studies and as expected showed that using questions covering only the four-diagnostic criteria has a low positive-predictive value of about 50% [26]. Moreover, among those determined to have RLS by the Cambridge–Hopkins questionnaire about 8% had very severe, 38% severe, and 12% mild WED as defined by the IRLS.

Thus, the estimated prevalence for WED in Europe and North America is about half that reported in most prior questionnaire survey studies, e.g., about 3–5% for WED symptoms in the past year, 1–2% for current clinically significant WED, and about 0.2–0.8% for very severe WED. The studies conducted in Asia including India have produced conflicting results related to population and methods, but overall indicate lower prevalence than in Europe or the USA.

Biology

There have been two major historic developments in understanding the biology of WED involving iron and genetics. Iron deficiency had long been associated with increased risk of WED and oral iron treatments reversed or reduced WED symptoms [27, 28]. Most RLS patients, however, have normal blood levels of iron and iron-related proteins. This puzzle was resolved by a major breakthrough in understanding WED when magnetic resonance imaging (MRI) studies showed decreased brain iron in the substantia nigra for patients with normal peripheral iron [29] (see Fig. 30.1). This seminal work from Hopkins has since been confirmed by several other studies based on MRI [30], ultrasound [31–34], and autopsy. [35]. The biological basis for the brain iron loss remains to be determined but may reflect a metabolic disorder affecting iron transport to the brain or the distribution and maintenance of iron in the brain. An active body of research on iron metabolic disturbances and WED has been produced by Earley and Allen at Johns Hopkins in collaboration with James Conner at Penn State School of medicine. The important historic factor is that these documented a biological basis for WED involving the brain and thus WED is a neurological disease.

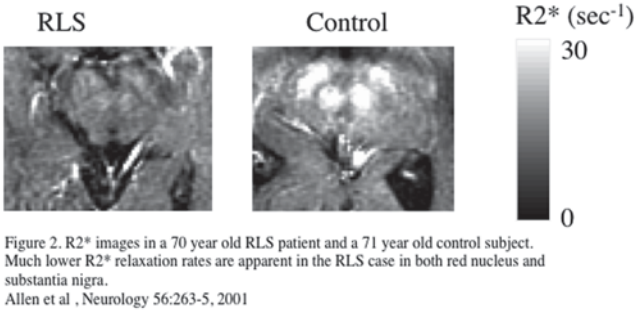

Figure 2. R2* images in a 70 year old RLS patient and a 71 year old control subject. Much lower R2* relaxation rates are apparent in the RLS case in both red nucleus and substantia nigra.
Allen et al , Neurology 56:263-5, 2001

Fig. 30.1 MRI R2* images in a 70-year-old RLS patient and a 71-year-old control subject. Much lower R2* relaxation rates are apparent in the RLS case in both substantia nigra and red nucleus

The second major biological advance came from genetic studies. The family prevalence of RLS has been known since the early cases reported by Ekbom [8]. Genetic linkage studies from large families failed to produce a genetic basis for any of WED. When genome wide association studies became available and were tried with RLS, they provided clear genetic risk factors for RLS. This was demonstrated in two primary studies published at the same time: Stefansson, Rye, and others working with an Icelandic population found a major allele on the BTBD9 gene that increased risk of RLS and also was associated with peripheral iron status [35a]. Winkelmann and colleagues at the Max Plank found allelic variations increasing the risk of RLS on three genes including BDBT9 [36]. These seminal studies have provided the basis for continuing genetic studies of WED. Presumably, the genetics, environmental factors (iron deficiency, pregnancy, age), and iron biology will coalesce into a better understanding of WED biology. That work is ongoing.

The one major area of disappointment from biological studies remains the failure to date to find any conclusive dopamine abnormalities in RLS, despite the efficacy of dopamine treatment.

Treatment

Success leading to a major disappointment marks the history of WED treatment. The earliest treatments with opioids by among others Willis in the seventeenth century [1] produced good but mixed results [37] and treatment with hypnotics promoted sleep but had limited other benefits for PLMS [38] or other WED symptoms [39]. In contrast, Akpinar reported dramatic benefit from levodopa treatment of WED [40] that

was subsequently confirmed in blinded comparator trial between levodopa, propoxyphene, and placebo [41, 42]. At this time, dopamine agonists were being introduced for the treatment of Parkinson's disease. The first of these, pergolide, was shown in initial studies at Johns Hopkins to produce dramatic relief from WED symptoms [43]. This was later also documented for the dopamine agonists pramipexole [44] and ropinirole [45]. Pergolide has since been withdrawn from the market owing to adverse cardiac effects but both ropinirole and pramipexole received wide regulatory approval for treatment of WED and became the drugs of first choice for WED treatment. Patients who had not slept more than 4–6 h a night with these treatments could sleep through most of the night. It seemed a miracle "cure" for WED. But a major disappointment lurked behind the initial success.

Treatment longer than the usual 3-month study revealed disquieting evidence that the dopaminergic medications were making the underlying WED disease worse. This iatrogenic WED augmentation was initially reported and defined by Allen and Earley at Johns Hopkins [46] and later confirmed for other dopaminergic medications [47, 48]. The worsening of WED (augmentation) necessitated increasing the dopaminergic dose. Symptom intensity, amount of the body involved, and amount of the day with symptoms increased for WED. In severe cases patients with initial leg symptoms at night now had leg and arm symptoms 24 h a day, somewhat controlled at night by high doses of dopamine agonists. Adverse effects of compulsiveness and sleepiness became more of a problem. Thus, what started so promising has ended hurting patients. This major problem in WED treatment has led to a reappraisal of treatment approaches.

Fortunately, new studies have documented that the new alpha-2-delta ligand anticonvulsants also provide dramatic benefit for WED that in one study was slightly better than treatment with the dopamine agonists pramipexole. One of these medications, gabapentin enacarbil (Horizant), has been extensively tested [49–51] and is now approved by the Food and Drug Administration (FDA) for WED treatment. There are also indications that high-potency opioid treatment is effective for patients who do not respond to dopaminergic medications [52]. A committee of the IRLSSG met in Madrid in 2012 and under the direction of Diego Garcia Borreguero produced an evidence based and expert consensus on long-term treatment of WED. This emphasizes avoiding dopaminergic augmentation by either keeping the dopaminergic dose low or starting with a very long acting dopamine agonist or an alpha-2-delta ligand as the first medication.

However, perhaps the most interesting treatment development has been the logical development of iron treatment of RLS. The biological studies indicated that increasing peripheral iron to higher levels could produce some increase in brain iron [53] that at least, theoretically, could reduce WED symptoms. IV iron provides one method to produce high peripheral iron status and had been tried with considerable success by Nordlander [54, 55] in the middle of the twentieth century. A recent animal study has indicated that IV iron in mice with experimentally induced decreased iron in the substantia nigra will normalize the iron in that brain area without producing iron overload in other areas [56]. The problem is determining the correct iron formulation and IV dose. The limited data available indicate this may be a promising treatment for 25–50 % of the WED patients producing in one treatment a long lasting relief of more than a year from their symptoms. This treatment development stems from the consideration of the biology of RLS and is supported by preclinical animal studies. More work like that is needed to advance RLS treatments

References

1. Willis T. The London practice of physick. London: Bassett and Crooke; 1685.
2. 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.
3. 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.
4. Willis T. De Animae Brutorum. London: Wells and Scott; 1672.
5. Wittmaack T. Pathologie und Therapie der Sensibilitäts neurosen. Liepzig: Schäfer; 1861.
6. Beard G. A practical treatis on nervous exhaustion. New York: William Wood; 1880.
7. Ekbom KA. Asthenia crurum paraesthetica ("irritable legs"). Acta Medica Scandinavica. 1944;118(1–3):197–209.
8. Ekbom KA. Restless legs. Stockholm: Ivar Haeggströms; 1945.
9. Mussio-Fournier JC, Rawak F. Familiäres Auftreten von Pruritus, Utikaria und parästhetischer Hyperkinese der unteren Extremitäten. Confinia Neurol. 1940;3:110–4.
10. Allison FG. Obscure pains in the chest, back or limbs. Can Med Assoc J. 1943;48:36–9.
11. Symonds CP. Nocturnal myoclonus. J Neurol Neurosurg Psychiatr. 1953;16:166.
12. Lugaresi E, Coccagna G, Berti Ceroni G, Ambrosetto C. Restless legs syndrome and nocturnal myoclonus. In: Gastaut H, Lugaresi E, Berti Ceroni G, editors. The abnormalites of sleep in man. Bologna: Aulo Gaggi Editore; 1968. 285–94.
13. 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.
14. Montplaisir J, Michaud M, Denesle R, Gosselin A. Periodic leg movements are not more prevalent in insomnia or hypersomnia but are specifically associated with sleep disorders involving a dopaminergic impairment. Sleep Med. 2000;1:163–7.
15. 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.
16. ASDA. International classification of sleep disorders, revised: Diagnostic and coding manual. Rochester, Minnesota: American Sleep Disorders Association; 1997.
17. 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.

18. Walters AS, Hening WA, Chokroverty S. Frequent occurrence of myoclonus while awake and at rest, body rocking and marching in place in a subpopulation of patients with restless legs syndrome. Acta Neurol Scand. 1988;77:418–21.
19. Walters AS, Aldrich MA, Allen RP, Ancoli-Israel S, Buchholz D, Chockroverty S, et al. Toward a better definition of the restless legs syndrome. Mov Disord. 1995;10:634–42.
20. 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.
21. Hening WA, Allen RP, Washburn M, Lesage S, Earley C. The four diagnostic criteria for the restless legs syndrome are unable to exclude confounding conditions ("mimics"). Sleep Med. 2009;10:976–81.

21a. Cho, Y.W., et al., *Prevalence and clinical characteristics of restless legs syndrome in diabetic peripheral neuropathy: comparison with chronic osteoarthritis*. Sleep Med, 2013; 14: 1387–92

21b. Allen RP, Picchietti DL, Garcia-Borreguero D, Ondo WG, Walter AS, Winkelman JW, et al. Restless legs syndrome/Willis-Ekbom disease diagnostic criteria: updated International Restless Legs Syndrome Study Group (IRLSSG) consensus criteria history, rationale, description, and signifi cance. Sleep Med, 2014;15:860–73.

22. Walters AS, LeBrocq C, Dhar A, Hening W, Rosen R, Allen RP, et al. Validation of the International Restless Legs Syndrome Study Group rating scale for restless legs syndrome. Sleep Med. 2003;4:121–32.
23. Abetz L, Arbuckle R, Allen RP, Garcia-Borreguero D, Hening W, Walters AS, et al. The reliability, validity and responsiveness of the International Restless Legs Syndrome Study Group rating scale and subscales in a clinical-trial setting. Sleep Med. 2006;7:340–9.
24. Lavigne GJ, Montplaisir JY. Restless legs syndrome and sleep bruxism: prevalence and association among Canadians. Sleep. 1994;17:739–43.
25. Allen RP, Walters AS, Montplaisir J, Hening W, Myers A, Bell TJ, et al. Restless legs syndrome prevalence and impact: REST general population study. Arch Intern Med. 2005;165:1286–92.
26. 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.
27. O'Keeffe ST, Gavin K, Lavan JN. Iron status and restless legs syndrome in the elderly. Age Ageing. 1994;23:200–3.
28. O'Keeffe ST, Noel J, Lavan JN. Restless legs syndrome in the elderly. Postgrad Med J. 1993;69:701–3.
29. 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.
30. 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;7:459–61.
31. Schmidauer C, Sojer M, Seppi K, Stockner H, Hogl B, Biedermann B, et al. Transcranial ultrasound shows nigral hypoechogenicity in restless legs syndrome. Ann Neurol. 2005;58:630–4.
32. Godau J, Klose U, Di Santo A, Schweitzer K, Berg D. Multiregional brain iron deficiency in restless legs syndrome. Mov Disord. 2008;23:1184–7.
33. Godau J, Manz A, Wevers AK, Gaenslen A, Berg D. Sonographic substantia nigra hypoechogenicity in polyneuropathy and restless legs syndrome. Mov Disord. 2009;24:133–7.
34. Godau J, Schweitzer KJ, Liepelt I, Gerloff C, Berg D. Substantia nigra hypoechogenicity: definition and findings in restless legs syndrome. Mov Disord. 2007;22:187–92.
35. Connor JR, Boyer PJ, Menzies SL, Dellinger B, Allen RP, Earley CJ. Neuropathological examination suggests impaired brain iron acquisition in restless legs syndrome. Neurology. 2003;61:304–9.

35a. Stefansson H1, Rye DB, Hicks A, et al. A genetic risk factor for periodic limb movements in sleep. N Engl J Med. 2007 Aug 16;357(7):639-47.

36. 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.
37. Hening WA, Walters A, Kavey N, Gidro-Frank S, Cote L, Fahn S. Dyskinesias while awake and periodic movements in sleep in restless legs syndrome: treatment with opioids. Neurology. 1986;36:1363–6.
38. Mitler MM, Browman CP, Menn SJ, Gujavarty K, Timms RM. Nocturnal myoclonus: Treatment efficacy of clonazepam and temazepam. Sleep. 1986;9:385–92.
39. Boghen D, Lamothe L, Elie R, Godbout R, Montplaisir J. The treatment of the restless legs syndrome with clonazepam: a prospective controlled study. Can J Neurol Sci. 1986;13:245–7.
40. Akpinar S. Treatment of restless legs syndrome with levodopa plus benserazide [letter]. Arch Neurol. 1982;39:739.
41. Kaplan PW, Allen RP, Buchholz DW, Walters JK. A double-blind, placebo-controlled study of the treatment of periodic limb movements in sleep using carbidopa/levodopa and propoxyphene. Sleep. 1993;16:717–23.
42. Allen RP, Kaplan PW, Buchholz DW, Earley CJ, Walters JK. Double-blinded, placebo controlled comparison of high dose propoxyphene and moderate dose carbidopa/levodopa for treatment of periodic limb movements in sleep. Sleep Res. 1992;21:166.
43. Allen R, Early CJ, Hening WA, Walters AS, Wagner MI, Yaffee JB. Double-blind, placebo-controlled, multi-center evaluation of the restless legs syndrome treatment with pergolide (abstract). Sleep. 1998;21:142.
44. Montplaisir J, Nicolas A, Denesle R, Gomez-Mancilla B. Restless legs syndrome improved by pramipexole: a double-blind randomized trial. Neurology. 1999;52:938–43.
45. Freeman A, Rye D, Bliwise DL, Chakravorty S, Krulewicz S, Watts R. Ropinirole fo restless legs syndrome (RLS): an open-label and double-blind placebo-controlled study. Neurology. 2001;56:A5.
46. Allen RP, Earley CJ. Augmentation of the restless legs syndrome with carbidopa/levodopa. Sleep. 1996;19:205–13.
47. Silber MH, Girish M, Izurieta R. Pramipexole in the management of restless legs syndrome: an extended study. Sleep. 2003;26:819–21.
48. Winkelman JW, Johnston L. Augmentation and tolerance with long-term pramipexole treatment of restless legs syndrome (RLS). Sleep Med. 2004;5:9–14.
49. Inoue Y, Uchimura N, Kuroda K, Hirata K, Hattori N. Long-term efficacy and safety of gabapentin enacarbil in Japanese restless legs syndrome patients. Prog Neuropsychopharmacol Biol Psychiatry. 2012;36:251–7.
50. Lee DO, Ziman RB, Perkins AT, Poceta JS, Walters AS, Barrett RW, et al. A randomized, double-blind, placebo-controlled study to assess the efficacy and tolerability of gabapentin enacarbil in subjects with restless legs syndrome. J Clin Sleep Med. 2011;7:282–92.
51. Walters AS, Ondo WG, Kushida CA, Becker PM, Ellenbogen AL, Canafax DM, et al. Gabapentin Enacarbil in Restless Legs Syndrome: A Phase 2b, 2-Week, Randomized, Double-Blind, Placebo-Controlled Trial. Clin Neuropharmacol. 2009; 6:311-20.
52. Ondo WG. Methadone for refractory restless legs syndrome. Mov Disord. 2005;20:345–8.
53. Earley CJ, Connors JR, Allen RP. RLS patients have abnormally reduced CSF ferritin compared to normal controls. Neurology. 1999;52 (suppl 2):A111–A2.
54. Nordlander NB. Therapy in restless legs. Acta Med Scand. 1953;145:453–7.
55. Nordlander NB. Restless legs. Brit J Phys Med. 1954;17:160–2.
56. Unger EL, Earley CJ, Thomsen LL, Jones BC, Allen RP. Effects of IV iron isomaltoside-1000 treatment on regional brain iron status in an iron-deficient animal. Neuroscience. 2013;246:179–85.