Restless Legs Syndrome/ Willis Ekbom Disease

Long-Term Consequences and Management

Mauro Manconi
Diego García-Borreguero
Editors

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The editors dedicate this book to Profs. Pasquale Montagna and Ralf Kohnen, two supreme experts of RLS who prematurely passed away in recent years, after leaving with us important pieces of knowledge on crucial aspects of the syndrome.

Pasquale Montagna served as professor at the University of Bologna (Italy) for 18 years (1992–2010). Sincerely beloved by his students for whom was always available and helpful and by his colleagues who highly respected his refined intelligence, intellectual honesty, and vast knowledge of all areas of neurology and sleep medicine, the latter discipline that he inherited from the Italian fathers of the modern hypnology and that he skillfully cultivated.

Ralf Kohnen was a Professor of Clinical Psychology who worked at Universities of Erlangen-Nürnberg, Hamburg, and Würzburg in Germany. Over 30 years he also became Director of the Institute for Medical Research Management and Biometrics GmbH (IMEREM). Prof. Kohnen provided key contributions for the development of rating scales and other end-points for the measurement of symptom severity and quality of life in RLS. Furthermore, he was crucial to the design

and evaluation of long-term clinical trials in the disease. As a person, he was both liked and respected by his colleagues and friends around the world.

Both experts, Profs. Kohnen and Montagna, provided an example of leadership and scientific rigor in the development of this discipline. Our efforts in this book are dedicated to them.

Foreword

Since the recognition of symptoms in the English literature by Willis in 1685 and a masterful description by Ekbom in 1945 of the condition now known as restless legs syndrome (RLS)/Willis Ekbom Disease (WED), we have made great strides in advancing our understanding of RLS/WED. This is the most common movement disorder but still remains undiagnosed or underdiagnosed. The next milestone is the serendipitous discovery by Akpinar in 1982 of the effectiveness of l-dopa in relieving the symptoms of RLS/WED, and since then dopaminergic medication remained the mainstay of treatment for this condition until recently. Soon, however, it was found that all was not well. Researchers from the Johns Hopkins University led by Richard Allen in 1996 found out about the undesirable long-term iatrogenic side effects of dopaminergic medications causing worsening of RLS symptoms, which they called "augmentation." This remains the most common significant vexing long-term consequence of dopaminergic treatment, besides other long-term consequences, some of which are disease related. Although a large percentage of patients (up to 73%) on l-dopa treatment developed augmentation, it was also noted with dopaminergic agonist treatment but to a lesser extent. It is important to be aware of these consequences as these can be managed, minimized, or prevented by following appropriate principles of treatment. Long-term consequence of RLS include both disease-related and RLS medication-related issues. These long-term consequences of dopaminergic treatment provided impetus for research to find alternative treatments as well as to look for other long-term consequences including the long-term course (natural history) of RLS/WED. All these have been published in various journals in a scattered manner but no one put all these together in one place in a comprehensive manner for easy reading. Time is now ripe to do just this. Mauro Manconi and Diego García-Borreguero, two outstanding and innovative investigators contributing many original and critical articles advancing the scientific field of RLS/WED, have now compiled these vexing undesirable long-term consequences of RLS/WED in a single edited volume addressing also the management issues. They picked up their contributors thoughtfully and carefully from a world cast of characters in the field. These two editors and, of course, all the other contributors deserve our hearty congratulations for putting together an impressive piece of work. The most controversial and hotly debated issue amongst all the long-term consequences is the question of an association between RLS/WED and

cardio-cerebovascular diseases. Although some cross-sectional studies suggested such an association, causality is not proven, and at present there is no convincing and compelling evidence for RLS/WED being responsible for cardiovascular catastrophe or stroke. This book addresses both the positive and negative aspects of this controversy. Much of the long-term consequences may be related to sleep disruption; this hypothesis remains to be proven. The other important issue is the knowledge about the natural history of RLS/WED. Is it a chronic progressive disease or does it ever remit? There are limited studies showing remission in up to 40–50% cases but this question remains controversial.

The book is divided into two parts. Part I deals with long-term health consequences of RLS/WED. Part II deals with long-term management of RLS/WED. The book is intended for a multidisciplinary field of sleep clinicians taking care of patients with RLS/WED, and therefore, should be useful to neurologists, pulmonologists and other internists including those specializing in cardiovascular, gastrointestinal, renal and endocrine medicine, as well as family physicians, psychiatrists, psychologists, pediatricians, and OBGYN specialists who may have to take care of pregnant women suffering from RLS/WED. The book should also be useful to others who may have an interest in advancing their knowledge in RLS/WED, such as the fellows, residents, medical students and even patients suffering from the burden of this disease. The next decade will bring new ideas in understanding the pathophysiology of RLS/WED along with new advances in treatment. The best treatment for RLS is yet to come. Stay tuned.

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Preface

The present book follows from an idea of Prof. Richard Allen, one of the most worldwide recognized prominent experts in restless legs syndrome (RLS) working at Johns Hopkins University, in Baltimore, MD (USA). After the efforts made in the last decade of the past century in spreading out the knowledge of the disease to the large audience of non-sleep specialists, the time was now ready to focus the attention of the readers on one of the most relevant clinical aspect of the syndrome: its chronicity.

Despite few cases of partial or complete remission, idiopathic RLS is usually a chronic long-term condition with a longer duration for patients with an early onset of symptoms. This feature often leaves the patients hopeless and worried about possible long-term consequences of the disease and about the efficacy and possible complications of a prolonged pharmacological treatment. On the other hand, the chronicity of the disease represents a major challenge for physicians, who have to be aware that once an effective drug is started, it will be difficult to be withdrawn in the future. Scientific data on the long-term efficacy and tolerability of most of the medication used in RLS are poor. This should be taken in high consideration by sleep specialists, who need to carefully calibrate their pharmacological intervention without focusing only on the immediate efficacy of drugs but thinking with a long prospective view. Behind the enthusiastic short-term efficacy of dopamine-agonists, more than few insidious long-term complications are hidden such as tolerability, loss of efficacy and mainly augmentation, which is a paradoxical pharmacologically induced increase in the overall severity of RLS, and it has probably become the main challenge in the long-term clinical management of RLS. Augmentation has been reported so far on all dopaminergic treatments.

Nevertheless, some kind of treatment is necessary because, besides a significant detriment of life quality, if symptoms persist, other harmful long-term consequences might upsurge. RLS patients are more prone to develop depression, anxiety, chronic sleep deprivation, nocturnal eating or smoking, other sleep disorders, and maybe cardiovascular pathologies. All of the above-described phenomena

brought our attention to the experts in the field, who kindly contributed to this book, providing the readers with the best knowledge available on the chronic aspect of RLS, with precise answers to important questions such as when and how a pharmacological treatment should be started and how possible future and challenging complications can be managed.

Lugano, Switzerland — Mauro Manconi
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RLS/WED: Criteria, Differential Diagnosis and Prevalence of Occurrence

1

Luigi Ferini-Strambi

Diagnostic Criteria: Historical Aspects

Restless legs syndrome (RLS), also known as Willis–Ekbom disease (WED), is a common neurosensorimotor disorder. The clinical importance of RLS/WED is underlined by epidemiological studies showing that one in 100 people may experience RLS/WED symptoms which seriously impact quality of life [1]. The diagnosis is based primarily on patient self-report and history. However, a number of diseases have symptoms that are often confused with those of RLS/WED, and other conditions are associated with higher rates of RLS/WED [2].

The formal diagnostic criteria for the Restless Legs Syndrome (RLS) start with the seminal monograph *Restless Legs* by Karl-Axel Ekbom in 1945 [3]. In 1960, he offered the following diagnostic guidance:

> The following criteria should be born 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 [4].

In 1990, the American Sleep Disorder Association published the International Classification of Sleep Disorders (ICSD) [5] and described the first official operational diagnostic criteria for RLS/WED. The ICSD classified 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 causes an almost irresistible urge to move the legs" (Table 1.1).

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Table 1.1 Diagnostic criteria for restless legs syndrome/Willis–Ekbom disease (RLS/WED): evolution from 1990 to 2003

1990 ICSD Diagnostic Criteria for RLS	1995 IRLSSG "Minimal" Criteria for Diagnosis of RLS (1 + 2 + 3 + 4)	2003 NIH/IRLSSG "Essential" Criteria for Diagnosis of RLS
A. A complaint of an unpleasant sensations 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	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	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)

RLS Restless Legs Syndrome; *WED* Willis–Ekbom disease; *ICSD* International Classification of Sleep Disorders; *IRLSSG* International Restless Legs Syndrome Study Group; *NIH* National Institutes of Health

In 1995, the founding members of the International Restless Legs Syndrome Study Group (IRLSSG) developed the first diagnostic criteria based on a broad international consensus of clinical RLS/WED experts [6]. They established the "four minimal criteria" for RLS/WED that remain even now in the core of RLS/WED diagnosis (Table 1.1). This provided a fundamental basis that enabled a considerable increase in RLS/WED research, but the clinical research accumulated

in the following years has highlighted the limitations of these initial IRLSSG diagnostic criteria.

In 2002, the IRLSSG, WED Foundation and the National Institute on Aging, in partnership with other branches of National Institute of Health, supported an RLS/WED diagnosis and epidemiology workshop to revise the 1995 IRLSSG criteria. During the workshop, the 1995 IRLSSG criteria were updated and the new criteria were published in 2003 and are usually referred to as the "NIH/IRLSSG criteria" for RLS/WED diagnosis [7]. The "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. The "relief of symptoms by movement and exacerbation of symptoms by inactivity" became separate criteria to highlight the need for clear ascertainment of these features of RLS/WED. The workshop also addressed new diagnostic criteria for two special populations—children and the cognitively impaired elderly—and even diagnostic criteria for the treatment-related problem of augmentation.

However, the fast progress in the field of RLS/WED over the past years showed some limitations of the 2003 NIH/IRLSSG diagnostic criteria. In the epidemiological studies, the 3- or 4-item questionnaires covering the 2003 criteria, intended to screen for RLS/WED, led sometimes to excessively high prevalence estimates. Moreover, these questionnaires for RLS/WED screening became increasingly and erroneously used in the primary care setting for diagnostic purposes, without considering the aspects of clinical relevance and differential diagnosis. The need to define "clinically significant" RLS/WED appeared related to another nontrivial point: the marketing-oriented strategy by the pharmaceutical companies avoided to adequately discriminate milder from more severe forms of RLS/WED, with consequent accusations of "disease-mongering" within the medical field and popular media.

Moreover, the 2003 NIH/IRLSSG criteria based on the four essential criteria raised concerns about validity of diagnosis, particularly on its specificity. Recently, some studies have showed that the 4-item questionnaires lead to low positive predictability of RLS/WED (e.g., 50–60%) [8–10]. The lack of consideration of differential diagnosis during the diagnostic evaluation may explain the "false-positives". Indeed, typical symptoms of RLS/WED such as restlessness and sensory misperception in the extremities may also occur in some neurological diseases. Other common conditions may closely "mimic" RLS symptoms requiring particular attention to differential diagnosis [11].

Obviously, the inclusion of "false positive" RLS/WED in pathophysiological studies might lead to erroneous study findings with consequent obstacle in the understanding of the disease.

All these aspects have been considered in the 2012 IRLSSG consensus diagnostic criteria.

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 address the issues of "clinical significance" and "'clinical course" in order to emphasize the severity range and the heterogeneity of RLS/WED manifestations.

2012 IRLSSG Consensus Diagnostic Criteria

RLS/WED is diagnosed by ascertaining symptom patterns that meet all five essential criteria adding clinical specifiers where appropriate (Table 1.2). No biological assay is available for the diagnosis of RLS/WED. Clinical diagnosis of RLS/WED is based on clinician-patient interaction and assessment by the clinician of the patient's subjective reports in comparison to the essential features of RLS/WED.

The five Essential Diagnostic Criteria are the following:

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 that remains the key diagnostic feature of RLS/WED, includes three separate components: urge to move (or akathisia), legs, and sensations (dysesthesias). Some patients will not be able to separate symptomatically or temporally the urge to move and the accompanying sensory symptoms. However,

Table 1.2 2012-IRLSSG revised criteria for restless legs syndrome/Willis–Ekbom disease (RLS/WED)

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
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
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
5.	The occurrence of the above features are 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)
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
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	

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patients affected by a clinically significant RLS/WED may often clearly delineate them. In 30–50% of patients, the uncomfortable sensations may be described as painful, but isolated pain without an urge to move does not represent RLS/WED [12–14].

RLS/WED may also involve the arms or other body parts. Arm involvement is reported in up to 50% of cases [15] and when RLS/WED symptoms are more severe, they may spread to other body parts, including the face [16]. However, the legs are typically affected first and more severely than are other body parts.

RLS/WED usually involves symptoms in both legs but not always at the same time or symmetrically [15]. Unilateral RLS is not rare and it has been recently reported [17] that although similar to bilateral RLS in clinical features, this entity may more often be secondary and less often associated with a positive family history.

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.

In criterion 2, the most important improvement is the coupling of the "urge to move" and "unpleasant sensations." This criterion has been validated by some pioneering studies based on the suggested immobilization test (SIT), paradigm that evaluated the effects of immobility on RLS/WED [18]. More recent studies [19, 20] confirmed that patients with RLS/WED, compared to controls, exhibit pronounced sensory symptoms in the legs and periodic leg movements while resting and awake that increase with the duration of rest.

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.

Three important features of this criterion should be underlined: relief versus resolution, immediacy, and persistence. RLS/WED patients, when asked about the effect of activity on RLS/WED, can confuse relief with resolution of symptoms. It is important to note that response to movement for this criterion is fulfilled by temporary relief, not necessarily complete resolution of the symptoms. Patients with very severe RLS/WED may, however, report minimal or no relief of symptoms even after a prolonged period of activity such as walking, bending, or moving. These very severe cases are deemed to meet criterion 3 if they report either some very minimal transitory relief or if they were able to have relief with movement earlier in the course of their syndrome with milder symptoms.

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 night.

Morning appears to be a relatively "protected period" for RLS/WED symptoms. Even if afternoon symptoms are not uncommon, particularly when the patient has long periods of inactivity [21], the symptoms are most pronounced in the evening and night with relative improvements late in the sleep period or early morning.

Studies validating the criterion 4 have clearly showed that the circadian variation in symptoms occurs independently of activity, sleep deprivation, or sleep–wake state [22–24]. This circadian pattern has been confirmed by suggested immobilization tests performed across the day [25, 26]. However, patients with very severe RLS/WED may have symptoms persisting throughout the day and night without any clear circadian variation. In these cases, they meet the criterion if circadian variation of their symptoms was present earlier in the course of their syndrome, in presence of milder symptoms.

5. The occurrences of the above features are 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).

This criterion is a new addition to the revised IRLSSG criteria for RLS/WED. A diagnosis of RLS/WED is made after complete evaluation of differential diagnoses for excluding possible mimicking conditions [11, 12, 27]. These mimics produce symptoms that meet (or at least come very close to meeting) criteria 1–4. It has been reported that adding differential diagnosis to the diagnostic criteria in diagnostic questionnaires or scales produces much improved agreement with clinical expert diagnosis that exceeds 90% [8, 9, 28].

Patients with RLS/WED can, however, have one or more of these other conditions in addition to RLS/WED, e.g., RLS/WED and peripheral neuropathy [11].

In the 2012 IRLSSG Consensus Diagnostic Criteria, specifiers for clinical course and clinical significance have been added in order to more completely characterize RLS/WED. Specifiers for Clinical Course of RLS/WED will be discussed in the section dedicated to the "Prevalence of Occurrence" in the current chapter.

Concerning the specifiers for Clinical Significance of RLS/WED, it is known that the symptoms of RLS/WED may cause significant distress or impairment in social, occupational, educational areas by their impact on sleep, energy/vitality, daily activities, behavior, cognition or mood. Several functional domains have been provided to the clinician for evaluation of clinical significance, but no consensus was reached in terms of the specific frequency and duration of RLS/WED to specify "clinical significance." However, using standard health-related quality of life (HRQoL) measures, physical and mental health scores have been reported lower for individuals with RLS/WED [29–31]. Some studies showed that HRQoL impairments are strongly associated with RLS/WED severity. These HRQoL impairments are strongly associated with RLS/WED severity [29, 32] and an improvement with treatment of RLS/WED has been observed [33, 34].

Table 1.3 Clinical features supporting the diagnosis of restless legs syndrome/Willis–Ekbom disease (RLS/WED), according to 2012-IRLSSG revised criteria

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

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The 2012 IRLSSG Consensus Diagnostic Criteria also reported both a motor sign and several common clinical patterns that can support a diagnosis, particularly when there is some lack of diagnostic certainty (Table 1.3).

RLS/WED has one identified sign, periodic leg movements (PLMs). PLMs can occur in sleep (PLMS) or wakefulness (PLMW). The amount of PLMS but not PLMW during the sleep period relate well to RLS/WED severity [35]. Recent studies have documented a bimodal distribution of the intermovement intervals for PLMs that divide into short (<10 s) and long (10–90 s) intermovement intervals [36], with the second interval range being representative of the typical periodic activity. In RLS/WED patients, PLMW during the sleep period have mostly short intermovement intervals (<10 s), while the PLMS have mostly long intermovement intervals (10–90 s) [37].

PLMS occur with significant transient changes in EEG, heart rate, and blood pressure [38], that may reflect a process producing the increased risk of cardiovascular disease observed with RLS/WED in several but not all studies [38].

Moreover, the amount of PLMS, although fairly sensitive for RLS/WED, is not very specific since it has been found to be high in several other medical conditions, with several medications, and commonly among adults over age 45 [39–43].

Most RLS/WED patients show at least some initial clinical benefit of fast-acting dopaminergic medications, e.g., levodopa and dopamine agonists. A small clinical trial using levodopa treatment showed 100% sensitivity but only 80% specificity for ascertaining RLS/WED [44]. Larger clinical trials showed a good clinical response to dopamine agonist treatment in only about a 60–75% [44–46]. Thus, in the clinical practice, a failure to ever respond to a dopaminergic treatment should raise some concern about the accuracy of diagnosis, without precluding a RLS/WED diagnosis.

RLS/WED has been observed to occur commonly in families indicating significant genetic or shared environmental factors for the disease. Some authors found that 20% of consecutive RLS/WED patients in two clinical settings reported RLS/WED among their first-degree relatives [47]. Moreover, twin studies have shown high concordance for RLS/WED [48, 49]. Thus, the presence of RLS/WED among first-degree relatives is supportive of the diagnosis.

Individuals with moderate-to-severe RLS/WED have chronic short sleep duration but usually they do not report a level of daytime sleepiness that would be expected on the basis of the sleep loss degree [50, 51]. Patients may report other consequences of sleep deprivation such as fatigue, reduced vigilance, and depression, but do not usually nap. Daytime sleepiness may be found in severe cases of RLS/WED, but should usually alert the clinician to other possible etiologies, such as sleep apnea or narcolepsy.

The 2012 IRLSSG Consensus Diagnostic Criteria also reported some clinical features that are particularly important for completing a full diagnostic assessment of RLS/WED status.

Concerning the gender, RLS/WED occurs in adults over 35 about twice as often for women as men [52] and this may be in part secondary to pregnancy [53].

Concerning the age of onset of RLS/WED, the later appearance in life and the more rapid onset are usually associated with another medical condition, such as iron deficiency, neuropathy, and renal disease [54]. History of the course of the disease seems to be important for indicating the future course. In particular, 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 [54].

Sleep disturbance is a frequent and distressing aspect of RLS/WED [1, 10, 52]. Epidemiological studies showed that about 75% of RLS/WED patients have difficulties in falling asleep and/or in maintaining sleep. It has been reported that patients with moderate-to-severe RLS/WED have chronic sleep loss with total sleep times of 4.5–6 h a night [10, 52, 55]. Interestingly, the sleep disturbance correlates with RLS/WED severity and the sleep disturbance itself is a primary source of the health impact of the syndrome [56, 57]. Moreover, sleep disturbance may be minimal or not present at all in milder RLS/WED cases.

Daily pattern of symptoms and activity levels are important. Documenting the usual time each day of symptom onset and duration may help in treatment planning, as well as in evaluating for the progression of the disease and side effects of treatment. It is known that onset of RLS/WED occurs earlier in the day for more severe RLS/WED and may appear earlier in the day with the natural progression and the development of augmentation [58, 59]. Lack of activity may increase the symptoms, thus the daily activity level and lifestyle of the subject should be related to onset time of RLS/WED symptoms [18].

Since history of pregnancy increases the risk of RLS/WED in later life about twofold and transient RLS/WED during pregnancy confers an approximate fourfold

increased risk of developing chronic RLS/WED within 7 years [60–62], a woman's history of pregnancy and RLS/WED status during pregnancy should be noted.

It is known that an increased possibility of recurring or persisting iron deficiency may impact RLS/WED symptoms. Thus, evaluation of iron status and possible iron treatments should be considered in patients with a past history of iron deficiency [63].

International Classification of Sleep Disorders, Third Edition (Icsd-3) Diagnostic Criteria for Rls/Wed

The recently released ICSD-3 [64] diagnostic criteria for RLS/WED are analogous to the 2012 IRLSSG Revised Criteria. The five essential criteria of the IRLSSG are required for ICSD-3 diagnosis of RLS/WED (Table 1.4).

Criteria A1-3 specify the necessary characteristics of the RLS sensations: worse at rest, better with movement, and predominant occurrence in the evening or night. The separation of worsening at rest (criterion A1) from worsening in the evening/night (criterion A3) is based on circadian rhythm studies that show an increase at night, independently from the activity level. According to the criterion B, RLS must be differentiated from other conditions that can mimic RLS. Clinically

Table 1.4 ICSD-3 diagnostic criteria for RLS/WED

A.	An urge to move the legs, usually accompanied by or felt to be caused by uncomfortable and unpleasant sensations in the legs.[a,b] These symptoms must:
	1. Begin or worsen during periods of rest or inactivity such as lying down or sitting
	2. Be partially or totally relieved by movement, such as walking or stretching, at least as long as the activity continues[c] and
	3. Occur exclusively or predominantly in the evening or night rather than during the day[d]
B.	The above features are not solely accounted for as symptoms of another medical or a behavioral condition (e.g., leg cramps, positional discomfort, myalgia, venous stasis, leg edema, arthritis, habitual foot tapping)
C.	The symptoms of RLS cause concern, distress, sleep disturbance, or impairment in mental, physical, social, occupational, educational, behavioral, or other important areas of functioning[e]

[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]As a result of severity, treatment intervention or treatment-induced augmentation, the worsening in the evening or night may not be noticeable but must have been previously present
[e]For certain research applications, such as genetic or epidemiological studies, it may be appropriate to omit criterion C. If so, this should be clearly stated in the research report

significant RLS is defined by RLS symptoms causing substantial distress, sleep disturbance, or impairment of function (criterion C).

An important difference between the ICSD-3 and 2012 IRLSSG Revised Criteria is the evaluation of the issue of clinical significance. In ICSD-3 this criterion "must be met" for the diagnosis of RLS/WED, with the possible 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.

ICSD-3 also includes a part dedicated to the "associated features". It has been underlined that sleep onset and maintenance complaints in RLS are notably higher than in controls, with odds ratios (OR) between 1.7 and 3.5. Daytime fatigue and daytime sleepiness are also common complaints; however, the sleepiness is not as severe as expected for the degree of sleep disruption, implying hyperarousal in RLS. Moreover, some patients with RLS may choose to work at night, thereby shifting quiet activities and their sleep schedule away from the circadian peak of their RLS symptoms.

ICSD-3 considers that PLMs, a family history of RLS, and response to dopaminergic therapy are supportive of the diagnosis. Multiple clinic-based and population-based studies have shown an increased prevalence of depressive and anxiety disorders in individuals with RLS. Most controlled studies using validated assessments have shown significantly increased odds ratios for moderately or highly elevated depressive symptoms (OR 1.95 and 3.67), major depression (OR 2.6), major depressive disorder (OR 2.57 and 4.7), generalized anxiety disorder (OR 3.5), panic disorder (OR 4.7, 12.9, and 18.9), and posttraumatic stress disorder (OR 3.76). Moreover, a positive correlation has been found between the severity of RLS and depression/anxiety symptoms. Relevant to the RLS–depression relationship is the emerging evidence that treatment of RLS improves depressive symptoms.

Diagnostic Statistical Manual of Mental Disorders, Fifth Edition (Dsm-5) Diagnostic Criteria for Rls/Wed

In the previous DSM-4, RLS/WED was not listed and was subsumed under the diagnostic category of Dyssomnia Not Otherwise Specified. In the recent fifth edition of DSM [65], RLS/WED has been included as a separate diagnostic entity based on the general population prevalence of the disease, scientific progress made by RLS/WED researchers, and the necessity of identifying a clinically significant condition that is easily encountered in clinical psychiatric practice.

Diagnostic criteria can be found in the *Diagnostic and Statistical Manual*, fifth edition. The novelty, in comparison to other diagnostic criteria, is the DSM-5 requirement for frequency (at least three times per week) and duration (at least 3 months) of symptoms. While arbitrary cutoffs 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 minimizes the possible clinical significance of the intermittent subtype of the disease, as well as of the recent mild forms.

Moreover, in comparison to the 2012-IRLSSG Revised Criteria that define a full spectrum of RLS/WED, the DSM-5 criteria 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., different works in terms of physical activity) as well as the syndrome severity.

Differential Diagnosis

The differentiation of RLS/WED from other conditions that may have similar characteristics is essential, since about 40% of individuals without RLS/WED will report some urge or need to move the legs while at rest [64]. The most important "mimics" of RLS are leg cramps, positional discomfort, arthralgias/arthritis, myalgias, leg edema, peripheral neuropathy, radiculopathy, and habitual foot tapping. In particular, leg cramps, positional discomfort, peripheral neuropathy, and radiculopathy may more likely to fulfill all of IRLSSG criteria 1–4.

Like RLS/WED, sleep-related leg cramps are worse at night and are relieved by movement. However, leg cramps always involve a specific muscle and usually require stretching of the muscle more than moving of the leg to relieve symptoms. Moreover, residual pain or sensitivity after the event helps to differentiate leg cramps from RLS/WED [11].

Positional discomfort may occur from pressure that compresses nerves, limits blood flow, or stretches body tissue. The symptomatology is resolved by changing body position without requiring any repetitive movement. Unlike RLS/WED, the discomfort does not include an urge to move the legs [11].

It is true that in RLS/WED the location of symptoms in the legs may vary considerably both between patients and over time for a patient. However, the middle portions of the calves and thighs are affected most commonly with RLS/WED [3, 15]. Involvement of feet or joints is not prominent in contrast to the distal, "stocking" pattern with polyneuropathy and the joint predominant pattern with arthritis. Moreover, a feature that differentiates RLS/WED from polyneuropathy is the lack of the classic distal to proximal progression [3].

About one-half of RLS/WED patients report the symptoms as painful not just uncomfortable [13]. However, they usually describe the symptoms as more of an ache rather than a sharp pain [66]. RLS/WED symptoms differ from those of neuropathy by not typically including superficial numbness or burning.

While it is important that RLS symptoms not be attributable solely to another medical or behavioural condition, it should also be appreciated that any of these mimics can occur in an individual who also has RLS. For example, some subjects may have both RLS and leg cramps. When the diagnosis of RLS is not certain, evaluation for the supportive features such as the presence of PLMS or a family history of RLS may be helpful.

Concerning the link between RLS and neuropathy, it seems that at least some subtypes of polyneuropathy may be significantly associated with RLS, and in particular those with prominent dysesthesic/painful symptoms [67]. It can be supposed that hypothetical spinal RLS generators are activated not only by impaired descending dopaminergic control, as suggested for primary RLS, but also by peripherally disrupted sensory modulation, mainly affecting small fibers [68].

Less common conditions to be differentiated from RLS include neuroleptic-induced akathisia, myelopathy, peripheral artery disease (intermittent claudication), painful legs/moving toes, and anxiety-induced restlessness.

Neuroleptic-induced akathisia is motor restlessness, induced by dopamine receptor antipsychotic compounds, that differs from RLS/WED in the generalized nature of the need to move the body and in the lack of the typical circadian pattern. Iatrogenic akathisia is not associated with prominent paresthesia and, interestingly, levodopa does not suppress the disturbance as it does RLS/WED symptoms [11].

Concerning myelopathy, the pain related to the narrow spinal canal could be misdiagnosed as RLS/WED. In this case, when lying in bed, pain is usually more pronounced in the supine position compared to a lateral position with bended knees. The frequent combination with back pain, as well as with clinical signs of a myelopathy (i.e., paraparesis, bowel or bladder sphincter dysfunction) that is usually found in the narrow spinal canal may help in the differential diagnosis.

Intermittent claudication consists of a complexity of symptoms characterized by (a) absence of pain or discomfort in a limb when at rest; (b) intensification of the condition until walking becomes impossible; and (c) the disappearance of the symptoms after a period of rest. In the vascular form of intermittent claudication, the lower legs and feet become red, warm, and swollen. The condition intensifies, and a feeling of tension and weakness occurs after walking until it becomes painful, the legs become weak and the person must stop to rest. In contrast with RLS/WED, intermittent claudication symptoms disappear with the rest.

Painful legs and moving toes syndrome is characterized by severe pain in one or both feet, usually with a sensation of burning and associated with frequent, repetitive movements of the toes. Unlike RLS/WED, pain is not necessarily increased at night or relieved by movement.

Prevalence of Occurrence

Clinical course is generally judged to be an important distinction among RLS/WED patients. Some have sporadic and infrequent episodes of RLS/WED symptoms while others have them regularly. The latter are more likely to seek treatment and represent those seen most often in clinical practice. However, population-based surveys show 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 a 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 [69]. This last group is often referred to as RLS/WED sufferers.

A recent study was performed in order to assess prevalence, disease burden, and costs of primary RLS in the US [70]. In 2007, 313.000 subjects from a representative US panel completed an online "global opinions" survey identifying respondents reporting all four diagnostic features of RLS. 4.484 met all criteria, and 1.400 were randomly selected to complete a questionnaire to exclude those with diagnoses indicating possible secondary RLS. Those that did not have diagnoses associated with secondary RLS were asked to complete the Cambridge–Hopkins RLS questionnaire to exclude RLS mimics. Prevalence was estimated for the following groups: (1) RLS symptomatic, (2) primary RLS, and (3) primary RLS sufferers (symptoms $\geq$2/wk with moderate-to-severe distress). The validated diagnostic tools and exclusion of medical conditions likely to cause RLS provide a very conservative estimate of US census-weighted prevalence of 2.4% for primary RLS and 1.5% for primary RLS 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.

The 2012-IRLSSG Revised Criteria include the following 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.

There is a dimensionality of RLS/WED, from mild, rare episodes to severe, chronic-persistent RLS/WED. Together with the specifier for clinical significance, the 2012-IRLSSG Revised Criteria provide to clinicians flexibility to prescribe individualized treatment in RLS/WED patients [71].

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 syndrome with milder and rare symptom episodes. Restricting RLS/WED diagnosis to the more frequent form of RLS/WED may be of clinical utility, but would restrict research only to the more severe forms of the disease. Moreover, 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-hour day–night cycle is 0.031. This was accepted as a minimal number of lifetime events required to make the diagnosis of RLS/WED.

Very recently, a study evaluated individual variations of RLS severity over a short, i.e., 7-day, and a long, i.e., 36-month time period and to analyze the impact of these variations on self-perceived quality of life, sleep quality, and depressive symptoms in a cohort of German and Swiss RLS patients [72]. The Course of RLS Study (COR-S) was started in fall 2007 and was conducted by mailed questionnaires. All 4385 members of the RLS support group in Germany and the 633 members of the Swiss RLS Patient Association were once contacted by mail, and invited to participate in the study. In the study, mean RLS/WED severity was rather stable over the course of 3 years, indicating "little change", despite considerable changes in individual RLS/WED medications. A worsening in RLS severity caused small to moderate negative effects on quality of life, depressive symptoms, and sleep quality. No evidence was found to support the hypothesis that age is a determinant of progression of RLS beyond 55 years.

References

1. Earley CJ, Silber MH. Restless legs syndrome: understanding its consequences and the need for better treatment. Sleep Med. 2010;11:807–15.
2. Ondo WG. Common comorbidities and differential diagnosis of restless legs syndrome. J Clin Psychiatry. 2014;75(3):e06.
3. Ekbom KA. Restless legs. Acta Med Scand. 1945;Suppl 158:1–123.
4. Ekbom KA. Restless legs syndrome. Neurology. 1960;10:868–73.
5. American Sleep Disorders Association. Diagnostic Classification Steering Committee. The International classification of sleep disorders: diagnostic and coding manual. Rochester, MN, U.S.A.: ASDA; 1990.
6. Walters AS. Toward a better definition of the restless legs syndrome. The International Restless Legs Syndrome Study Group. Mov Disord. 1995;10:634–42.
7. 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.

8. 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.
9. 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.
10. 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.
11. Ferini-Strambi L. RLS-like symptoms: differential diagnosis by history and clinical assessment. Sleep Med. 2007:S3–6.
12. 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.
13. 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.
14. Winkelman J, Gagnon A, Clai AG. Sensory symptoms in restless legs syndrome: the enigma of pain. Sleep Med. 2013;14:934–42.
15. Karroum EG, Leu-Semenescu S, Arnulf I. Topography of the sensations in primary restless legs syndrome. J Neurol Sci. 2012;320:26–31.
16. Buchfuhrer MJ. Restless legs syndrome (RLS) with expansion of symptoms to the face. Sleep Med. 2008;9:188–90.
17. Shukla G, Gupta A, Pandey RM, Kalaivani M, Goyal V, Srivastava A, Behari M. What features differentiate unilateral from bilateral restless legs syndrome? A comparative observational study of 195 patients. Sleep Med. 2014;15(6):714–9.
18. 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.
19. 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.
20. 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.
21. 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.
22. 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.
23. 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.
24. 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.
25. 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.
26. 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.
27. 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.

28. 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.
29. 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.
30. 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.
31. 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.
32. 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.
33. 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.
34. 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.
35. 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.
36. 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.
37. 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.
38. Ferini-Strambi L, Walters AS, Sica D. The relationship among restless legs syndrome (Willis-Ekbom Disease), hypertension, cardiovascular disease, and cerebrovascular disease. J Neurol. 2014;261(6):1051–68.
39. 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.
40. 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.
41. 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.
42. Hoque R, Chesson AL Jr. 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.
43. 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.
44. 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.
45. 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.
46. 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.

47. Allen RP, La Buda MC, Becker P, Earley CJ. Family history study of the restless legs syndrome. Sleep Med. 2002;3(Suppl):S3–7.
48. Ondo WG, Vuong KD, Wang Q. Restless legs syndrome in monozygotic twins: clinical correlates. Neurology. 2000;55:1404–6.
49. 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.
50. 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.
51. 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.
52. 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.
53. 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.
54. Allen RP, Earley CJ. Defining the phenotype of the restless legs syndrome (RLS) using age-of-symptom-onset. Sleep Med. 2000;1:11–9.
55. 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.
56. 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.
57. 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.
58. Allen RP, Earley CJ. Validation of the Johns Hopkins restless legs severity scale. Sleep Med. 2001;2:239–42.
59. 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.
60. 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.
61. 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.
62. 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.
63. 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.
64. American Academy of Sleep Medicine. International classification of sleep disorders. 3rd ed. Darien, IL: American Academy of Sleep Medicine; 2014.
65. American Psychiatric Association. Diagnostic and statistical manual of mental disorders. 5th ed. Arlington, VA: American Psychiatric Association; 2013.
66. Kerr S, McKinon W, Bentley A. Descriptors of restless legs syndrome sensations. Sleep Med. 2012;13:409–13.
67. Gemignani F, Vitetta F, Brindani F, Contini M, Negrotti A. Painful polyneuropathy associated with restless legs syndrome. Clinical features and sensory profile. Sleep Med. 2013;14(1):79–84. doi:10.1016/j.sleep.2012.08.013.

68. 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.
69. 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.
70. 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.
71. Silber MH, Becker PM, Earley C, Garcia-Borreguero D, Ondo WG, Willis-Ekbom Dis F. Willis-Ekbom disease foundation revised consensus statement on the management of restless legs syndrome. Mayo Clin Proc. 2013;88:977–86.
72. Fuhs A, Dunya Bentama D, Antkowiak R, Mathis J, Trenkwalder C, Berger K. Effects of short- and long-term variations in RLS severity on perceived health status—the COR-study. PLoS ONE. 2014;9(4):e94821.
73. Picchietti DL, Bruni O, de Weerd AI, et al. Pediatric restless legs syndrome diagnostic criteria: an update by the International Restless Legs Syndrome Study Group. Sleep Med. 2013;14(12):1253–1259.

Part I
Long Term Health Consequences of Restless Legs Syndrome/Willis-Ekbom Disease

Mental Health Disorders Associated with RLS

2

Mark A. Oldham and Hochang B. Lee

In the middle of the nineteenth century, Wittmaack reported on the co-occurrence of restless legs and psychiatric symptoms including depression and anxiety, coining the term *anxietas tibiarum* to describe this clinical co-occurrence [1]. Because the pathophysiology of restless leg syndrome (RLS) was not understood at the time and RLS was commonly comorbid with depression and anxiety, he considered that it may be a form of hysteria or neurasthenia [2]. Since its early descriptions, RLS has often been limited to reports in neurology, though the co-occurrence of mood symptoms was not entirely overlooked [3]. Early psychiatrists rarely appreciated the significance of RLS in mental health treatment prior to the twenty-first century. It is notable that the Swedish neurologist Karl Ekbom is credited with having described the psychiatric condition delusional parasitosis in 1937 [4] and subsequently RLS in 1945 [5].

Epidemiological studies among patients with RLS have revealed high rates of psychiatric comorbidity. The odds of a patient with RLS having clinically significant depression or anxiety are two to five times that of the general population [6]. Despite the fact that descriptions of RLS have identified co-occurring depression, anxiety, and somatic distress date back to the nineteenth century, only in 2013 was RLS defined as an independent psychiatric diagnosis in the Fifth Edition of the Diagnostic and Statistical Manual of Mental Disorders (DSM-5) [7]. Previously, RLS had been subsumed under Dyssomnia Not Otherwise Specified. Several reasons underlie the need to conceptualize RLS a unique clinical diagnosis. Most pressing among these is the prevalence and suffering associated with syndromal

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RLS in the population [8, 9]. Specifically, RLS symptoms are often encountered in patients with mental illness and in patients taking psychotropic medications. Implicit in recognizing RLS as an independent diagnosis is that RLS demands clinical attention including screening, clinical and laboratory evaluation, physical examination, and treatment. One anticipates that adding RLS to DSM-5 will encourage enhanced awareness of this condition, particularly among psychiatric populations but also in primary care settings.

In this chapter, we explore the ways in which RLS and mental health interface. We begin by reviewing psychiatric conditions in which RLS is often comorbid. After reviewing the epidemiological data for these conditions, we consider the potential for bidirectional effects between RLS and these conditions it frequently accompanies. Next, we discuss the relationship between RLS and psychopharmacology. Several classes of psychotropic medications are known to influence RLS or induce RLS-like symptoms such as akathisia. Finally, because the agents used to treat RLS have psychotropic effects, we review of the mental health considerations related to RLS pharmacology.

Epidemiology of RLS and Mental Health

Depression and Anxiety in RLS Patients

Depression and anxiety, along with their common feature sleep disruption, are common among RLS patients. Overall, patients with RLS are more impaired functionally, experience higher levels of somatic distress, and have impaired sleep. In fact, patients with RLS may have lower quality of life than patients with other medical conditions such as hypertension, congestive heart failure, history of myocardial infarction in the past year, patients with angina, or even diabetes [10]. Patients with RLS also tend to have numerous somatic symptoms, which appears to be mediated, at least in part, by greater burden of stress and anxiety [11].

RLS and mood disorders share several epidemiological features. RLS and major depressive disorder (MDD) have similar prevalence rates in the community: 2–7% of the general population has RLS symptoms of varying severity [12, 13], and the annual prevalence of depression has been reported to be similar (e.g., 6.7% in the National Epidemiological Survey on Alcoholism and Related Conditions [14]). The mean age of onset for both conditions is in the 30s with a wide distribution [15], and each demonstrates a female preponderance of 2:1 [16, 17]. Additionally, genetic predisposition accounts for a large portion of developing each of these conditions [18, 19].

RLS is a Sleep–Wake Disorder that exhibits disrupted sleep—as demonstrated on nocturnal electroencephalography [20]—and excessive daytime sleepiness with decreased quality of life [21, 22]. On this basis alone one would expect higher rates of depression and anxiety among patients with RLS than among those without [6].

However, the chronic distress caused by internal restlessness may be interpreted as anxiety and over time serve as a stressor that precipitates irritability or dysphoria.

Several cross-sectional, community-based epidemiological studies have found higher rates of self-reported depression and anxiety symptoms as well as self-reported psychotropic use among patients with RLS than among those without RLS [23–33]; however, these population-based studies tend to rely on depression and anxiety screens rather than validated diagnostic evaluations. Nevertheless, these data are internationally consistent and include findings from the UK, Germany, Italy, Portugal, and Spain [23]; the US [24, 25]; Sweden [26–28]; Norway and Denmark [29]; Korea [30]; Japan [32]; Turkey [31]; and France [33].

Using a structured psychiatric interview called the Munich-Composite International Diagnostic Interview for DSM-IV, Winkelmann et al. evaluated a clinical population of 130 patients with RLS for psychiatric disorders, and these data were compared with a population of 2265 residents who participated in a community-based study [34]. Using formal diagnostic criteria for psychiatric disorders (unlike the international cross-sectional surveys above), they found a significantly elevated 12-month prevalence of panic disorder (PD) (OR 4.7; 95% CI = 2.1–10.1), generalized anxiety disorder (GAD) (OR = 3.5; 95% CI = 1.7–7.1), and major depression (OR = 2.6; 95% CI = 1.5–4.4) in RLS patients when compared with a nationally representative sample of community respondents [34]. Given that this study employed a clinical sample, study patients may be expected to have a greater RLS symptom burden than community samples by way of referral bias.

Using the validated Center for Epidemiologic Studies Depression Scale (CES-D) to screen for clinical depression and the International RLS Study Group (IRLSSG) criteria for RLS, Rothdach and colleagues surveyed 369 geriatric community patients in Germany [35]. Using face-to-face interviews, these researchers found higher average rates of depression among study participants with RLS than among those without RLS (CES-D scores of 11.6 vs. 7.8; $p = 0.01$). Stratifying for gender revealed that this association was limited to male subjects. A door-to-door study in Turkey identified 103 subjects positive for RLS per IRLSSG criteria out of 3234 community subjects screened [36]. Those with RLS had significantly higher Hamilton Anxiety Rating Scale and Hamilton Depression Rating Scale scores than those without RLS.

Two population-based epidemiological studies using validated diagnostic criteria for RLS and screening instruments for psychiatric diagnosis have demonstrated significantly higher rates of depression and anxiety among patients with RLS relative to those without [37, 38]. In the first of these, Lee and associates examined data from the Baltimore site of the Epidemiologic Catchment Area (ECA) program, a multi-site initiative supported by the National Institute of Mental Health [37]. In this epidemiological study, 1024 participants completed the seven-item RLS Questionnaire and Diagnostic Interview Schedule. After adjusting for demographics, overall health, and antidepressant use, Lee et al. found that patients with RLS had a greater 12-month prevalence of depression (OR = 4.7; 95% CI = 1.2–18.3), PD (OR = 12.9; 95% CI = 3.6–46), and obsessive-compulsive disorder (OCD) (OR = 5.6; 95% CI = 1.4–21.9) than patients without RLS [37]. These data

were replicated in a community sample of 6509 Korean adults [38]. In this replication study, face-to-face interviews included a Korean translation of the IRLSSG criteria and the Korean version of Composite International Diagnostic Interview. Relative to matched participants without RLS, those with RLS had higher lifetime rates of major depression (OR = 2.57; 95% CI = 1.33–4.96), PD (OR = 18.9; 95% CI = 4.72–75.9), and posttraumatic stress disorder (PTSD) (OR = 3.76; 95% CI = 1.32–10.7). Additionally, RLS participants endorsed a lower quality of life based on EuroQol scores than those without RLS [38].

Three recent prospective studies have evaluated whether RLS predicts clinically significant depression or vice versa [39, 40]. In the first of these, 56,399 women were screened for depression and RLS at baseline (based on self-report of physician-based diagnosis), and they were followed for six years [39]. Self-report of physician-diagnosed RLS at baseline increased the risk of developing clinically significant depression as defined as regular use of an antidepressant and physician-diagnosed depression (RR 1.5; 95% CI = 1.1–2.1) as well as higher scores on the CES-D and the 15-item Geriatric Depression Scale. The second report includes two population-based prospective studies [40]: the first cohort comprised 1312 subjects who were followed for a mean of 2 years; the second cohort 4308 subjects who were followed a mean of 5 years. Clinically significant depressive symptoms (CSDS) at baseline, as defined by a CES-D score of 16 or greater or positive screen on the Munich-Composite International Diagnostic Screener, were a risk factor for developing new-onset RLS in both cohorts (ORs 1.94 and 2.37, respectively) after appropriate adjustments. Conversely, RLS per IRLSSG criteria at baseline increased the risk of incident CSDS on follow-up in the second of these cohorts.

Taken together, data from community and clinic-based epidemiological studies suggest that patients with RLS should be screened for major depression and anxiety disorders given the higher rates of these conditions found among this patient population. Moreover, in view of recent prospective studies, it may be prudent to screen patients with RLS regularly for incident depression as well.

RLS in Mental Health Cohorts

The question of whether RLS is higher among patients with mental illness has been much less evaluated in epidemiological studies, and data are inconsistent. For instance, in a geriatric outpatient mental health clinic in Spain, researchers documented an 11% prevalence of definite RLS with an additional 10% prevalence of possible RLS among a cohort of non-demented patients for RLS using the Revised IRLSSG criteria [41]. Even higher rates of RLS and RLS symptoms were found in a cohort of 182 hospitalized patients with schizophrenia receiving antipsychotics [42]. Using the IRLSSG criteria, 21.4% of these patients were diagnosed with RLS, and 47.8% met at least one criterion. The prevalence of RLS was over twice as common among patients treated for schizophrenia as compared with an age- and sex-matched cohort without schizophrenia (21.4% vs. 9.3%; $p = 0.009$). A third study, though, found only one case of RLS out of 100 patients

taking neuroleptics [43]. The findings from this third study are difficult to interpret given that this rate of 1% is *lower* than in the general population and is consternating because dopamine antagonism is expected to cause or exacerbate movement disorders.

The preponderance of the evidence would suggest that patients with mental illness are at an elevated risk of developing RLS than the general population regardless of whether this is because they share neurobiological features or psychotropic-induced (see below) [40]. Perhaps the high prevalence of RLS in the first two studies above could be attributed, in part, to the older population included in these studies. Several psychotropic agents may also contribute to RLS symptom burden as well. Additionally, as described below, the RLS and mental illness may share overlapping neuropathology accounting for a portion of the elevated incidence of RLS among psychiatric cohorts.

Explaining the Comorbidity Between RLS and Mental Illness

Depression and Anxiety

Several of the diagnostic criteria of major depression are common in RLS including insomnia, psychomotor slowing, daytime fatigue, and impaired concentration, and this may contribute to the clinical overlap between these two syndromes. However, as seen in epidemiological studies, patients with RLS have a higher incidence of syndromal major depression as well [37, 38]. In fact, the close association between RLS and major depression suggest that this relationship is more than epiphenomenal. The majority of patients with RLS experience sleep disruption due to the crepuscular predilection of symptoms in RLS [7], and reduced sleep not only contributes to depressive symptoms but may also precipitate major depressive episodes [44]. Beyond its effects on sleep, RLS causes unsettled sensations that may serve as an independent stressor thereby contributing to depression [45].

Dopamine is likely involved in the neurobiological convergence of RLS and MDD. The most consistently characterized neurotransmitter abnormality in RLS is decreased dopaminergic activity in the striatum and substantia nigra [46, 47]. Depression, on the other hand, is associated with alterations in dopamine activity, though this abnormality is most prominent in the prefrontal cortex [48].

The clinical co-occurrence of RLS and anxiety disorders deserves particular consideration for several reasons [38]. One would expect patients with RLS, which experience an internal restless sensation, would be more likely to develop state anxiety. Thus, the association between RLS and GAD requires little imagination; however, RLS has been associated with OCD, PD, and PTSD—each of which has a distinct neurobiological signature. Functional neuroimaging has revealed that dysfunction in the cortico–striatral–thalamo–cortical circuit, which involves dopamine, glutamate, and γ-aminobutyric acid (GABA), is integral to OCD [49].

This may, in part, explain the reason for elevated incidence of OCD among patients with RLS, which also involves reduced dopamine activity in the striatum. PD and PTSD, on the other hand, are much more closely aligned with fear responses. It remains unclear how the "fear network," which includes the amygdala, insula, and anterior cingulate cortex, may overlap with neurological findings in RLS. Nevertheless, positron emission tomography and single-photon emission computed tomography studies of compulsive and anxiety disorders including PD and PTSD have revealed decreased striatal D2 receptor binding, which may account for the higher incidence of these disorders with RLS [50].

RLS and Neurocognitive Impairment

Studies suggest that RLS may be associated with mild impairment in cognition; however, the results of the few studies remain inconsistent limiting the scope of conclusions that can be drawn. Several authors have proposed that RLS may be associated with neurocognitive impairment in large part due to fragmented sleep [33, 51–53]. In the earliest of these studies, Pearson et al. compared 16 RLS subjects off RLS treatment for at least two weeks with 15 age and gender-matched controls [51]. Patients with RLS were found to have significant deficits on tasks of prefrontal cortical function relative to controls—deficits roughly consistent with those seen after a night of sleep deprivation. Similarly, cognitive testing of 23 unmedicated RLS subjects compared with 23 age, sex, and education-matched controls revealed subtle deficits in short-term attention and verbal fluency, but no differences were found in working memory, memory, learning, cognitive flexibility, and abstract reasoning [52]. To test whether sleep-restricted controls without RLS would demonstrate deficits comparable to RLS subjects, Gamaldo and colleagues subjected 13 healthy controls to a 14-day partial sleep-restriction protocol prior to comparing their neurocognitive function against 16 RLS subjects [53]. Unexpectedly, RLS subjects performed *better* than sleep-restricted controls on letter and category fluency, two tests that are particularly sensitive to sleep impairment. In discussing their results, the authors propose that patients with RLS may adapt partially to chronic sleep loss.

At most, population-based studies demonstrate only mild impairment in select neurocognitive domains among those with RLS. A French study evaluated a community sample of 318 subjects for RLS using the IRLSSG criteria and found a prevalence of 24% [33]. Subjects with RLS performed slightly worse on the Stroop interference task and verbal fluency than subjects without RLS—a finding that remained statistically significant even after accounting for the greater rates of hypnotic and antidepressant use as well as higher depression and anxiety scores. A subsequent study of patients included a community research database identified subjects with RLS for at least one year and subjects without RLS, and despite a neurocognitive battery consisting of 36 independent tests, only those related to forward digit span were statistically impaired among patients with RLS [54]. A similar study conducted on the RLS in the Baltimore site of the Epidemiological

Catchment Area (RiBECA) study identified 91 subjects based on RLS status (37 without RLS; 23 untreated RLS subjects; 31 treated RLS subjects) revealed only minimal impairment in clock draw and clock copy despite conducting a neurocognitive battery of 19 unique tests [55].

In summary, it appears that patients with RLS may exhibit very mild clinical deficits relative to healthy controls, but the degree to which these findings are clinically significant or simply related to chronic sleep restriction remains unclear. Evaluations of Mini-Mental State Examination have failed to demonstrate a statistically significant difference between elders with and without RLS [33, 35, 54], and even when excluding patients with dementia only very slight differences have been identified among patients with RLS [54, 55].

RLS and Attention-Deficit/Hyperactivity Disorder

Growing evidence supports an association between attention-deficit/hyperactivity disorder (ADHD) and RLS [56]. RLS and PLMS appear to be common in children and adults with ADHD [57, 58]. For instance, a 2005 review estimated that RLS or RLS symptoms are found in 44% of subjects with ADHD whereas ADHD or ADHD symptoms are found in 26% of those with RLS. These data should be interpreted cautiously given the very significant risk of sampling or referral bias in the studies included in this review, which almost certainly inflate the true cross-prevalence of these conditions.

Similar to the discussion in the **Cognition** section above, ADHD-like symptoms such as inattention or restlessness may be due to disrupted sleep. Conversely, the motoric features of restlessness or hyperactivity found in ADHD may also be misinterpreted as akathisia, particularly in children who have greater difficulty articulating their experience verbally. ADHD *symptoms* appear to be more common in adults with RLS relative to adults with insomnia without RLS or no sleep disorder [59]; however, whether these symptoms represent a formal diagnosis of ADHD remains unclear. Dopamine agonists may be effective for RLS or PLMD in children with ADHD, but a small study was unable to demonstrate that L-dopa improves ADHD symptoms [60].

RLS and Personality

Two features of personality closely aligned with depression and anxiety are high neuroticism and introversion [61], and it has been proposed that personality traits may account for a portion of the comorbidity between RLS. In the RiBECA study, 42 RLS subjects and 982 subjects without RLS completed a personality assessment based on the 240-item NEO Personality Inventory [62]. RLS subjects had higher neuroticism even after adjusting for depression or PD. Steinig and colleagues performed a small-scale replication study and obtained similar results [63]. They enrolled 30 de novo RLS patients and 30 age- and gender-matched healthy controls,

and participants completed the 60-item NEO Five-Factor Inventory. RLS participants had higher rates of neuroticism. RLS patients have higher levels of neuroticism than the general population, which may create a vulnerability to stress and increase the propensity of these patients to develop clinical depression or anxiety. This second study also found RLS patients to score lower on openness to experience. This is notable because openness to experience has been associated with incident coronary artery disease in the community and RLS has been associated with coronary artery and cerebrovascular disease [64]. These personality traits specific to RLS may explain some of the well-established association between RLS and mood disorder or RLS and cardiovascular disease.

Psychotropics and RLS

Serotonergic Antidepressants and RLS

Several lines of evidence have found an association between RLS and antidepressants [selective serotonin reuptake inhibitors (SSRIs), serotonin-norepinephrine reuptake inhibitors (SNRIs), tricyclic antidepressants (TCAs), and serotonin 1A agonists (e.g., buspirone)]. Some population-based studies have found increased rates of antidepressant use among subjects with RLS [23, 33] while others have not [37, 38]. Nevertheless, a French pharmacovigilance study of mandatorily reported adverse drug reactions revealed that antidepressants and neuroleptics were more commonly imputed as the cause of RLS than other agents reported in association with RLS [65].

Despite the central role of serotonin in the pharmacological management of depression, dopamine activity is also altered in major depression [66]. The effect of serotonin and dopamine activity on one another appears to be specific to brain region and receptor-subtype. As pertains to RLS, activation of serotonin 1A receptors may stimulate dopamine release in the prefrontal cortex and nucleus accumbens but may inhibit dopamine release in the striatum [66]. This distinction provides a potential mechanistic rationale for why serotonergic antidepressants improve symptoms of anergia and anhedonia while also inducing movement disturbances such as RLS, akathisia, or even periodic limb movements in sleep (PLMS) [67–70].

However, no prospective, controlled studies have documented a link between pro-serotonergic antidepressants and the worsening of RLS symptoms. Numerous case reports and case series of SSRI-induced RLS symptoms have been published [71–77], which may be a result of their propensity to dampen dopamine activity [78]. A recent case report of RLS associated with the serotonin-norepinephrine reuptake inhibitor (SNRI) duloxetine was also reported [79]. A combination of venlafaxine and quetiapine has been reported to induce RLS [80], and monotherapy venlafaxine has been reported to worsen PLMS [69]. No reports of TCA-induced RLS have been published though one report documented worsening of PLMS with TCA [68], and TCAs such as desipramine [81] and imipramine [82] are known to affect dopamine activity in the nucleus accumbens and striatrum. The relative

frequency of these reports are consistent with the premise that serotonin selectivity as seen in SSRIs and more with venlafaxine than either duloxetine or TCAs increases the risk of RLS symptoms more than a more balanced serotonin-to-norepinephrine profile. As such, one may wonder whether the greater norepinephrine selectivity of secondary amine TCAs or levomilnacipran may offer a clinical advantage in treating depression among patients with RLS [83].

Despite these sparse case reports, retrospective studies have reported that patients experienced *improvement* in RLS symptoms when starting treatment with SSRIs [84] or were unable to identify an association between SSRI use and RLS symptoms [85]. In the first of these reports, 113 consecutive patients receiving SSRIs attending a hospital-based clinic were screened for RLS symptoms, and 43 of 66 returned responses (65% of respondents) endorsed symptoms of RLS [84]. Twenty-five respondents (58%) reported improvements in RLS symptoms after starting SSRI, five (12%) experienced abolition of RLS symptoms, and another five (12%) experienced worsening of symptoms. The remainder experienced no change in RLS symptoms. Two of 23 patients without RLS prior to SSRI developed RLS symptoms upon starting SSRI. A subsequent study that evaluated 200 consecutive patients presenting for sleep initiation insomnia at a sleep disorders clinic did not find a statistical association between antidepressant use and RLS, though only half of the patients were on either an SSRI or an SNRI with the remainder on TCAs, trazodone, bupropion, or other common antidepressants [85]. These studies are limited by being retrospective, unblinded, and self-report. Importantly, neither study used a validated screening tool for RLS diagnosis.

No data were found on an association between buspirone and RLS symptoms; however, a report of two cases suggested that tandospirone (a serotonin 1A agonist available in East Asia) improved RLS symptoms [86]. As described above, serotonin 1A receptors may specifically augment dopamine activity though this effect appears to be specific to the frontal lobes. With this site specificity in mind, one would expect serotonin 1A agonism rather to contribute to RLS symptoms.

The question of whether pro-serotonergic agents influence RLS remains unsettled, particularly in view of contradictory evidence. Either way, the clinical notion that these agents are uniformly associated with worsening of RLS symptoms is not supported by current data. The balance of the evidence suggests that pro-serotonergic agents are liable to induce secondary RLS and perhaps even improve primary RLS. Prospective randomized trials will be needed to clarify the nature of this association.

Other Antidepressants

The effect of mirtazapine, a heterocyclic antidepressant with antagonism at serotonin 2A, 2C, and 3 receptors, on RLS symptoms remains unclear as well. Mirtazapine's use is considered often when treating depressed patients with insomnia due to its sedating antihistaminic properties. Despite its being used to improve sleep, case reports suggest that it may actually worsen RLS symptoms [87–91]. To study the association between mirtazapine and RLS, Kim et al. conducted a

retrospective chart review of 181 patients on mirtazapine to identify clinical features associated with developing RLS per IRLSSG criteria [91]. Eight percent of patients on mirtazapine developed RLS, and most RLS cases occurred within days of starting mirtazapine. Use of tramadol and neuroleptics was more common among mirtazapine patients who developed RLS than among those who did not.

In contrast, bupropion generally *improves* RLS symptoms [92–96]. In addition to several case reports of bupropion improving RLS symptoms, a randomized, double-blind, placebo-controlled trial of bupropion that enrolled 60 patients with moderate to severe RLS revealed clinical benefit [92]. After three weeks, patients receiving 150 mg bupropion sustained release daily had statistically improved RLS symptoms (IRLSSG improvements of 10.8 vs. 6.0, $p = 0.016$). At six weeks, subjects receiving bupropion continued to have lower IRLSSG scores relative to the placebo group, but this was no longer statistically significant (IRLSSG improvements of 10.4 vs. 7.6, $p = 0.108$). Given that it shares dopamine-enhancing activity with standard treatments for RLS [97], bupropion may be considered to treat depression with comorbid RLS provided it is not contraindicated. Limited evidence suggests that trazodone may also have a favorable profile regarding RLS [98]. No data were found suggesting that related compounds vilazodone or nefazodone are associated with RLS symptoms.

Sedative-Hypnotics

Insomnia is common among psychiatric illness—either included in the diagnostic criteria of mood and anxiety disorders or as an associated clinical feature. Although behavioral management should always be included in insomnia treatment, sedative-hypnotic agents such as benzodiazepines and non-benzodiazepine benzodiazepine receptor agonists (BRAs; more commonly known as the Z-drugs) are commonly used. These agents are likely to be either neutral or therapeutic for RLS and PLMS. Clonazepam has long been used to treat RLS clinically, particularly because it improves sleep [99], and is generally preferred to other benzodiazepines due to its longer half-life. In some instances, benzodiazepines may improve sleep without specifically improving PLMS [99]. Additionally, a report of eight patients treated with open-label zolpidem revealed significant improvement in RLS symptoms all patients within a week [100]. Antihistamines are also commonly taken by patients for sleep problems. Whereas diphenhydramine may exacerbate PLMS and RLS [101], hydroxyzine may not be as RLS-averse [102].

Neuroleptic Agents

Typical and atypical neuroleptics, traditionally known as antipsychotics, are commonly used to treat a range of psychiatric illness including schizophrenia, bipolar disorder, and treatment-resistant depression. Neuroleptic-induced movement disorders are common with the use of these agents. In fact, historically, they were

Table 2.1 Differentiating RLS from the more common psychotropic-induced akathisia[a]

	RLS (DSM-5 criteria)	Psychotropic-induced Akathisia
Location	Legs principally or exclusively involved (A)	Generalized, including upper extremities as well
Dysesthesias	Very common (A)	Rare
Relation to movement	Worse during inactivity or rest (A1)	Typically continuous
Response to movement	Partially or totally relieved by rest (A2)	Unaffected by movement
Diurnal variation	Worse in evening or night (A3)	Limited circadian variation
Psychotropic exposure	Independent of psychotropic exposure	Neuroleptics most common though also described with various antidepressants

From Benes et al. [152], with permission

[a]Akathisia is derived from the Greek *a* ("without") and *kathizein* ("seated"), and akathisia is a core feature of RLS. In fact, in movement-disorder terms, RLS has been described as a "movement-responsive quiescegenic nocturnal focal akathisia usually with dysesthesias."

titrated to the "neuroleptic dose," or the dose that led to mild parkinsonism (the term neuroleptic is derived from the Greek roots *neuron*, "sinew," and *lepsis*, "to seize"). Their propensity to induce movement disorders is due to dopamine antagonism in the nigrostriatal pathway. The neuroleptic-induced movement disorder most closely associated with RLS is akathisia, which is characterized by an internal, generalized restlessness or urge to move. Akathisia may be difficult to differentiate from RLS proper (Table 2.1). Clinicians should also bear in mind that several anti-emetics are also typical neuroleptics (e.g., metoclopramide, promethazine, and prochlorperazine). In general, second-generation or atypical neuroleptics less commonly cause movement disorders, which is thought to be because their additional serotonin 2A attenuates dopamine antagonism in the striatum.

Numerous cases of neuroleptics causing RLS symptoms have been reported including those for haloperidol [103], risperidone [104], and olanzapine [105–107]. Even the two neuroleptics with least D2 receptor antagonism and, consequently, the least risk of causing akathisia or other movement disorders—quetiapine [77, 80, 108–111] and clozapine [112]—have been reported to induce RLS symptoms. Although ropinirole was effective in managing a case of quetiapine-induced RLS, this practice cannot be uniformly recommended [109] given the potential for dopamine agonists to precipitate psychiatric destabilization (e.g., psychosis among patients with psychotic illness or mood elevation and impulsivity among patients with bipolar disorder). Studies suggest that certain dopamine receptor and monoamine oxidase alleles may increase a person's vulnerability to neuroleptic-induced RLS [113–116] though the clinical utility of genotyping in the clinic remains limited.

The absence of randomized clinical trials supporting an association between neuroleptics and RLS notwithstanding, the fact that neuroleptics cause akathisia and other movement disorders makes their propensity to cause RLS not only plausible

but quite likely. In general, one may expect atypical neuroleptics to be more benign than typicals with regard to RLS, and quetiapine and clozapine may be the safest options in RLS based on their preferential use in Parkinson's disease and other alpha synucleinopathies. Aripiprazole, given its unique pharmacodynamics as a partial agonist/antagonist of D2 receptors, may offer a more favorable profile regarding RLS. Most reports suggest that aripiprazole does not cause RLS and may improve these symptoms [117–120], but a case report of aripiprazole-related RLS has been reported [121]. Clinicians, however, should note that roughly a third of patients on aripiprazole will experience akathisia. In many clinical situations, no adequate alternative to neuroleptics exists, and it may safest to treat RLS with an adjunctive $\alpha_2\delta$ ligand such as gabapentin [122] or gabapentin enacarbil.

Mood Stabilizers

Bipolar disorder and, at times, major depression are managed with mood stabilizers, which include lithium and several anticonvulsants (e.g., valproic acid, carbamazepine, lamotrigine, or oxcarbazepine). Anticonvulsants that improve neuropathic pain may improve RLS symptoms, and in particular carbamazepine and gabapentin (which is not a traditional mood stabilizer) have long been considered second-line agents for RLS on the basis of randomized clinical trials supporting their efficacy in RLS [123, 124]. Valproic acid [125] and lamotrigine [126] may also improve RLS symptoms. Lithium, however, may worsen RLS symptoms in select patients based on a few case reports [127–129]. Therefore, anticonvulsants may be preferred over lithium in the management of mood disorders with comorbid RLS. Clinicians should be extremely cautious in discontinuing lithium in patients who are euthymic even if RLS symptoms emerge. Lithium remains the gold-standard mood stabilizer and is highly effective. Discontinuation of lithium risks destabilizing bipolar disorder and should not be undertaken lightly.

Psychiatric Considerations of RLS Treatment

The two medication classes approved for RLS—dopamine agonists and $\alpha_2\delta$ ligands—have psychoactive properties that must be considered as well. Although uncommon, dopaminergics are well-documented to cause impulse-control syndromes in a minority of patients. Examples of impulse-control syndromes include pathological gambling [130–132], hypersexuality [130], hoarding [133] and other compulsive [134] behavior, punding [135], and nocturnal eating syndrome [136]. Patients should be monitored closely for these destructive behavioral consequences of treatment, and in virtually all cases the offending agent should be discontinued as rapidly as feasible. Although rare, abrupt discontinuation of dopamine agonists can precipitate a potentially lethal syndrome known as parkinsonism-hyperpyrexia syndrome, which is thought to be akin to neuroleptic malignant syndrome [137].

Agonists of $\alpha_2\delta$ may cause sedation and are often accompanied by anxiolysis. Although not approved for psychiatric use in the US pregabalin is efficacious for the management of general anxiety disorder [138, 139] and approved internationally for this purpose. Also, the potential for misuse of pregabalin and other agents should not be overlooked [140].

Treatment Implications

Balancing the management of psychiatric disorders with RLS and the potential for psychotropics to induce or worsen RLS presents many clinical challenges. Patients with RLS should be screened for major depression and anxiety disorders. Patients on dopamine agonists should be monitored closely for impulse-control syndromes and patients on $\alpha_2\delta$ ligands for medication misuse. On the other hand, patients with psychiatric illness should be actively screened for RLS given the high comorbidity. In either case, the comorbidity of RLS and mental illness may influence pharmacological selection.

In patients with RLS and comorbid depression, dopamine agonists are first-line as recommended by the International RLS Task Force [141]. If RLS is prominent and depression is mild, dopamine agonists may be preferable for RLS, which may improve depression as well [142–144]. The use of dopaminergics on depressive symptoms melds biological plausibility (dopamine activity is disrupted in depression) with the knowledge that enhancing sleep also improves mood (mitigating RLS symptoms is likely to improve sleep quality) [145]. If major depression is moderate to severe, bupropion may be considered before pro-serotonergic agents provided it is not contraindicated due to seizures or eating disorders that involve purging. If pro-serotonergic agents are considered, agents with a more balanced serotonin-to-norepinephrine reuptake profile may be less likely to worsen RLS. It should also be kept in mind that mild to moderate major depression may be adequately treated with cognitive behavioral therapy, interpersonal therapy, or psychodynamic psychotherapy per the American Psychiatric Association's treatment guidelines for MDD. For severe major depression, electroconvulsive therapy also remains a viable clinical option.

For patients with RLS and comorbid GAD, $\alpha_2\delta$ ligands are preferred over dopamine agonists for the management of RLS symptoms [141]. As noted above, several randomized, controlled trials have demonstrated efficacy of pregabalin for GAD. Although it is approved in several countries throughout Europe for GAD [139], its use for GAD in the US remains off-label. Benzodiazepines may also be considered for the management of GAD in patients with comorbid RLS. Similarly, the pharmacological management of PD may involve benzodiazepines, but attempts at starting a pro-serotonergic agent could still be considered given their efficacy in preventing future panic attacks. The first-line pharmacological treatment of OCD and PTSD include pro-serotonergic agents, which may make clinical management with comorbid RLS particularly difficult. Psychotherapy should be given strong

consideration for OCD or PTSD when comorbid with RLS because data on comparative efficacy of medications versus CBT in these disorders remain equivocal.

Anticonvulsants should be considered for managing bipolar disorder in the context of RLS as they may actually improve RLS symptoms as well. In general, valproic acid may be a reasonable first-line agent with consideration of carbamazepine as well. The use of lamotrigine for bipolar disorder is generally limited to managing bipolar II disorder given its dearth of anti-manic activity. Lithium may worsen RLS symptoms; though, again, clinicians should be well-advised not to discontinue this without compelling reason in patients who are affectively stable. Treating RLS in bipolar disorder is critical particularly because insomnia may precipitate mood episodes in bipolar disorder. It seems reasonable to consider $\alpha_2\delta$ ligands over dopaminergic agents. The fact that two patients with bipolar disorder tolerated ropinirole without manic switch [109] does not outweigh the potential for this disastrous clinical outcome [146].

For patients with comorbid RLS and schizophrenia, $\alpha_2\delta$ ligands are preferred to dopamine agonists due to the concern that dopamine agonism could pharmacologically work against antipsychotics. The data in support of pramipexole [147] or ropinirole [148] as adjuncts to neuroleptics in schizophrenia is far too meager to support their use in this population. No adequate alternative to neuroleptic agents exists for psychotic disorders. Therefore, patients with schizophrenia and RLS should be treated with antipsychotics with very few exceptions. Atypical neuroleptics are less likely to affect RLS symptoms than typicals, and quetiapine and clozapine may pose the least risk of neuroleptic-induced RLS symptoms based on their comparatively limited D2 receptor binding at therapeutic doses. Nevertheless, the emergence of RLS during neuroleptic use should be treated symptomatically unless these symptoms are severe or threaten patient non-adherence. Additionally, benzodiazepines such as clonazepam are commonly used as adjuncts in schizophrenia and could be considered as second line for RLS symptoms in this population.

Psychiatrists who diagnosis RLS should be well-aware of RLS mimics and consider a broad differential for symptoms consistent with RLS, particularly because such symptoms may be a harbinger of serious medical illness [149, 150]. For instance, misdiagnosis of peripheral neuropathy could risk overlooking type 2 diabetes mellitus. Claudication or pseudoclaudication should alert the clinician to heart disease or spinal cord compression, respectively. Uremia may present with RLS symptoms as may iron deficiency anemia, which could be the presenting symptom of colon cancer. In the same way that psychiatrists diagnose major depression after medical conditions such as hypothyroidism have been ruled out, RLS remains a clinical diagnosis of exclusion. Moreover, clinicians should not rely on the core clinical features of RLS (i.e., DSM-5 Criterion A or the IRLSSG essential criteria 1–4) to rule out conditions other than "true" RLS given the potential for false positives [149].

A differential diagnosis of RLS should be broad, and mental health professionals considering a diagnosis should familiarize themselves with other conditions that may present with RLS symptoms. A differential diagnosis for RLS should include

metabolic (iron deficiency anemia, uremia, dehydration), obstetric (pregnancy), behavioral (positional discomfort or volitional movements ["foot tapping" or "leg rocking"]), sleep–wake-disorder-related (sleep starts, periodic movements in sleep disorder), musculoskeletal/nociceptive (muscle cramping, pain, myalgia, positional discomfort, arthritis, myxedema), vascular (claudication/peripheral vascular disease, peripheral venous insufficiency, hypotensive akathisia, congestive heart failure/peripheral edema), neurological (sciatica, peripheral neuropathy/radiculopathy/myelopathy, pseudoclaudication, painful [or painless] legs-moving toes, reflex sympathetic dystrophy), or medication-induced (akathisia) conditions [151, 152].

Conclusions

RLS is a common disorder that may share a bidirectional association with depression and anxiety. It was elevated to a unique diagnosis in DSM-5 because it is operationally valid, significantly impairs quality of life, and may be effectively treated with a several pharmacologic agents. Patients with RLS or with mental illness should be screened for the other in an ongoing fashion. The treatment of mental illness in RLS patients demands careful consideration of treatment planning including the decision to pursue medication versus therapy and, if using psychotropics, which psychotropic to use. Often, medications will need to be used and RLS symptoms managed in parallel with ongoing psychotropics. Prospective, randomized, controlled studies are needed to define the role of psychotropics in patients with RLS as well as the effects of RLS pharmacology on mental illness.

References

1. Wittmaack T. Pathologie und Therapie der Sensibilitäs Neurosens. Leipzig: E Schäfer; 1861.
2. Oppenheim H. Lehrbuch der Nervenkrankheiten. 7th ed. Berlin: Karger; 1923.
3. Gorman C, Dyck P, Pearson J. Symptom of restless legs. Arch Intern Med. 1965;115:155–60.
4. Ekbom K. The pre-senile delusion of infestation (classic text no. 54). Hist Psychiatry. 2003;14:229–56.
5. Ekbom K. Restless legs: a clinical study. Acta Med Scand. 1945;158:1–123.
6. Picchietti D, Winkelman JW. Restless legs syndrome, periodic limb movements in sleep, and depression. Sleep. 2005;28(7):891–8.
7. American Psychiatric Association. Diagnostic and statistical manual for mental disorders. 5th ed. Arlington, VA: American Psychiatric Publishing, Inc.; 2013.
8. Scholz H, Benes H, Happe S, Bengel J, Kohnen R, Hornyak M. Psychological distress of patients suffering from restless legs syndrome: a cross-sectional study. Health Qual Life Outcomes. 2011;9:73.
9. Salas RE, Kwan AB. The real burden of restless legs syndrome: clinical and economic outcomes. Am J Managed Care. 2012;18(9 Suppl):S207–12.
10. 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(6):925–35.

11. Kim JB, Koo YS, Eun MY, Park KW, Jung KY. Psychosomatic symptom profiles in patients with restless legs syndrome. Sleep Breathing = Schlaf & Atmung. 2013;17(3):1055–61.
12. 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(11):1286–92.
13. Ohayon MM, O'Hara R, Vitiello MV. Epidemiology of restless legs syndrome: a synthesis of the literature. Sleep Med Rev. 2012;16(4):283–95.
14. Hasin DS, Goodwin RD, Stinson FS, Grant BF. Epidemiology of major depressive disorder: results from the National Epidemiologic Survey on Alcoholism and Related Conditions. Arch Gen Psychiatry. 2005;62(10):1097–106.
15. Allen RP, Picchietti D, Hening WA, Trenkwalder C, Walters AS, Montplaisi J, et al. Restless legs syndrome: diagnostic criteria, special considerations, and epidemiology. A report from the restless legs syndrome diagnosis and epidemiology workshop at the National Institutes of Health. Sleep Med. 2003;4(2):101–19.
16. Robins LN, Helzer JE, Weissman MM, Orvaschel H, Gruenberg E, Burke JD Jr, et al. Lifetime prevalence of specific psychiatric disorders in three sites. Arch Gen Psychiatry. 1984;41(10):949–58.
17. Berger K, Luedemann J, Trenkwalder C, John U, Kessler C. Sex and the risk of restless legs syndrome in the general population. Arch Intern Med. 2004;164(2):196–202.
18. Winkelmann J, Muller-Myhsok B, Wittchen HU, Hock B, Prager M, Pfister H, et al. Complex segregation analysis of restless legs syndrome provides evidence for an autosomal dominant mode of inheritance in early age at onset families. Ann Neurol. 2002;52(3): 297–302.
19. Kendler KS. The dappled nature of causes of psychiatric illness: replacing the organic-functional/hardware-software dichotomy with empirically based pluralism. Mol Psychiatry. 2012;17(4):377–88.
20. Brand S, Lehtinen A, Hatzinger M, Holsboer-Trachsler E. Comparison of sleep EEG profiles of patients suffering from restless legs syndrome, restless legs syndrome and depressive symptoms, and major depressive disorders. Neuropsychobiology. 2010;61(1):41–8.
21. 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(4):472–5.
22. 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(9):1387–92.
23. Ohayon MM, Roth T. Prevalence of restless legs syndrome and periodic limb movement disorder in the general population. J Psychosom Res. 2002;53(1):547–54.
24. Phillips B, Young T, Finn L, Asher K, Hening WA, Purvis C. Epidemiology of restless legs symptoms in adults. Arch Intern Med. 2000;160(14):2137–41.
25. Winkelman JW, Finn L, Young T. Prevalence and correlates of restless legs syndrome symptoms in the Wisconsin Sleep Cohort. Sleep Med. 2006;7(7):545–52.
26. 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(7–8):768–72.
27. Ulfberg J, Nystrom B, Carter N, Edling C. Prevalence of restless legs syndrome among men aged 18 to 64 years: an association with somatic disease and neuropsychiatric symptoms. Mov Disord (Official Journal Movement Disorder Society). 2001;16(6):1159–63.
28. Wesstrom J, Nilsson S, Sundstrom-Poromaa I, Ulfberg J. Restless legs syndrome among women: prevalence, co-morbidity and possible relationship to menopause. Climacteric: J Int Menopause Soc. 2008;11(5):422–8.
29. 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(4):307–12.

30. Kim KW, Yoon IY, Chung S, Shin YK, Lee SB, Choi EA, et al. Prevalence, comorbidities and risk factors of restless legs syndrome in the Korean elderly population—results from the Korean Longitudinal Study on Health and Aging. J Sleep Res. 2010;19(1 Pt 1):87–92.
31. Sevim S, Dogu O, Camdeviren H, Bugdayci R, Sasmaz T, Kaleagasi H, et al. Unexpectedly low prevalence and unusual characteristics of RLS in Mersin, Turkey. Neurology. 2003;61 (11):1562–9.
32. Nomura T, Inoue Y, Kusumi M, Uemura Y, Nakashima K. Prevalence of restless legs syndrome in a rural community in Japan. Mov Disord (Official Journal Movement Disorder Society). 2008;23(16):2363–9.
33. Celle S, Roche F, Kerleroux J, Thomas-Anterion C, Laurent B, Rouch I, et al. Prevalence and clinical correlates of restless legs syndrome in an elderly French population: the synapse study. J Gerontol Ser A, Biol Sci Med Sci. 2010;65(2):167–73.
34. 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(1):67–71.
35. 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(5):1064–8.
36. 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(2):226–30.
37. 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(1):101–5.
38. 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(8):1069–76.
39. 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 (4):279–88.
40. Szentkiralyi A, Volzke H, Hoffmann W, Baune BT, Berger K. The relationship between depressive symptoms and restless legs syndrome in two prospective cohort studies. Psychosom Med. 2013;75(4):359–65.
41. Aguera-Ortiz L, Perez MI, Osorio RS, Sacks H, Palomo T. Prevalence and clinical correlates of restless legs syndrome among psychogeriatric patients. Int J Geriatr Psychiatry. 2011;26 (12):1252–9.
42. Kang SG, Lee HJ, Jung SW, Cho SN, Han C, Kim YK, et al. Characteristics and clinical correlates of restless legs syndrome in schizophrenia. Prog Neuropsychopharmacol Biol Psychiatry. 2007;31(5):1078–83.
43. Jagota P, Asawavichienjinda T, Bhidayasiri R. Prevalence of neuroleptic-induced restless legs syndrome in patients taking neuroleptic drugs. J Neurol Sci. 2012;314(1–2):158–60.
44. van Mill JG, Vogelzangs N, van Someren EJ, Hoogendijk WJ, Penninx BW. Sleep duration, but not insomnia, predicts the 2-year course of depressive and anxiety disorders. J Clin Psychiatry. 2014;75(2):119–26.
45. Paykel ES. Basic concepts of depression. Dialogues Clin Neurosci. 2008;10(3):279–89.
46. Connor JR, Wang XS, Allen RP, Beard JL, Wiesinger JA, Felt BT, et al. Altered dopaminergic profile in the putamen and substantia nigra in restless leg syndrome. Brain: J Neurol. 2009;132(Pt 9):2403–12.
47. Cervenka S, Palhagen SE, Comley RA, Panagiotidis G, Cselenyi Z, Matthews JC, et al. Support for dopaminergic hypoactivity in restless legs syndrome: a PET study on D2-receptor binding. Brain: J Neurol. 2006;129(Pt 8):2017–28.

48. Bennabi D, Vandel P, Papaxanthis C, Pozzo T, Haffen E. Psychomotor retardation in depression: a systematic review of diagnostic, pathophysiologic, and therapeutic implications. BioMed Res Int. 2013;2013:158746.
49. Brennan BP, Rauch SL, Jensen JE, Pope HG Jr. A critical review of magnetic resonance spectroscopy studies of obsessive-compulsive disorder. Biol Psychiatry. 2013;73(1):24–31.
50. Nikolaus S, Antke C, Beu M, Muller HW. Cortical GABA, striatal dopamine and midbrain serotonin as the key players in compulsive and anxiety disorders-results from in vivo imaging studies. Rev Neurosci. 2010;21(2):119–39.
51. Pearson VE, Allen RP, Dean T, Gamaldo CE, Lesage SR, Earley CJ. Cognitive deficits associated with restless legs syndrome (RLS). Sleep Med. 2006;7(1):25–30.
52. Fulda S, Beitinger ME, Reppermund S, Winkelmann J, Wetter TC. Short-term attention and verbal fluency is decreased in restless legs syndrome patients. Mov Disord (Official Journal Movement Disorder Society). 2010;25(15):2641–8.
53. Gamaldo CE, Benbrook AR, Allen RP, Oguntimein O, Earley CJ. A further evaluation of the cognitive deficits associated with restless legs syndrome (RLS). Sleep Med. 2008;9(5):500–5.
54. Driver-Dunckley E, Connor D, Hentz J. No evidence for cognitive dysfunction or depression in patients with mild restless legs syndrome. Mov Disord (Official Journal Movement Disorder Society). 2009;24:1843–7.
55. Lee HB, Ramsey CM, Spira AP, Vachon J, Allen R, Munro CA. Comparison of cognitive functioning among individuals with treated restless legs syndrome (RLS), untreated RLS, and no RLS. J Neuropsychiatry Clin Neurosci. 2014;26(1):87–91.
56. Cortese S, Konofal E, Lecendreux M, Arnulf I, Mouren MC, Darra F, et al. Restless legs syndrome and attention-deficit/hyperactivity disorder: a review of the literature. Sleep. 2005;28(8):1007–13.
57. Chervin R, Archbold K, Dillon J, Pituch K, Panahi P, Dahl R, et al. Associations between symptoms of inattention, hyperactivity, restlessness legs, and periodic leg movements. Sleep. 2002;25(2):213–8.
58. 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(2):253–66.
59. Wagner ML, Walters AS, Fisher BC. Symptoms of attention-deficit/hyperactivity disorder in adults with restless legs syndrome. Sleep. 2004;27(8):1499–504.
60. England SJ, Picchietti DL, Couvadelli BV, Fisher BC, Siddiqui F, Wagner ML, et al. L-dopa improves restless legs syndrome and periodic limb movements in sleep but not attention-deficit-hyperactivity disorder in a double-blind trial in children. Sleep Med. 2011;12(5):471–7.
61. Bienvenu OJ, Samuels JF, Costa PT, Reti IM, Eaton WW, Nestadt G. Anxiety and depressive disorders and the five-factor model of personality: a higher- and lower-order personality trait investigation in a community sample. Depress Anxiety. 2004;20(2):92–7.
62. Kalaydjian A, Bienvenu OJ, Hening WA, Allen RP, Eaton WW, Lee HB. Restless legs syndrome and the five-factor model of personality: results from a community sample. Sleep Med. 2009;10(6):672–5.
63. Steinig J, Reess G, Klösch C, Sauter J, Zeitlhofer, Happe S. Personality traits in patients with restless legs syndrome. Somnologie-Schlafforschung und Schlafmedizin. 2013;17(4):281–3.
64. Ferini-Strambi L, Walters AS, Sica D. The relationship among restless legs syndrome (Willis-Ekbom Disease), hypertension, cardiovascular disease, and cerebrovascular disease. J Neurol. 2013.
65. Perez-Lloret S, Rey MV, Bondon-Guitton E, Rascol O, Montastruc AJ. French Association of Regional Pharmacovigilance C. Drugs associated with restless legs syndrome: a case/noncase study in the French Pharmacovigilance Database. J Clin Psychopharmacol. 2012;32(6):824–7.

66. Dunlop BW, Nemeroff CB. The role of dopamine in the pathophysiology of depression. Arch Gen Psychiatry. 2007;64(3):327–37.
67. Montplaisir J, Lorrain D, Godbout R. Restless legs syndrome and periodic leg movements in sleep: the primary role of dopaminergic mechanism. Eur Neurol. 1991;31(1):41–3.
68. Garvey MJ, Tollefson GD. Occurrence of myoclonus in patients treated with cyclic antidepressants. Arch Gen Psychiatry. 1987;44(3):269–72.
69. Yang C, White DP, Winkelman JW. Antidepressants and periodic leg movements of sleep. Biol Psychiatry. 2005;58(6):510–4.
70. Winkelman JW, James L. Serotonergic antidepressants are associated with REM sleep without atonia. Sleep. 2004;27(2):317–21.
71. Bakshi R. Fluoxetine and restless legs syndrome. J Neurol Sci. 1996;142(1–2):151–2.
72. Sanz-Fuentenebro FJ, Huidobro A, Tejadas-Rivas A. Restless legs syndrome and paroxetine. Acta Psychiatr Scand. 1996;94(6):482–4.
73. Perroud N, Lazignac C, Baleydier B, Cicotti A, Maris S, Damsa C. Restless legs syndrome induced by citalopram: a psychiatric emergency? Gen Hosp Psychiatry. 2007;29(1):72–4.
74. Hargrave R, Beckley DJ. Restless leg syndrome exacerbated by sertraline. Psychosomatics. 1998;39(2):177–8.
75. Salin-Pascual RJ, Galicia-Polo L, Drucker-Colin R. Sleep changes after 4 consecutive days of venlafaxine administration in normal volunteers. J Clin Psychiatry. 1997;58(8):348–50.
76. Page RL 2nd, Ruscin JM, Bainbridge JL, Brieke AA. Restless legs syndrome induced by escitalopram: case report and review of the literature. Pharmacotherapy. 2008;28(2):271–80.
77. Chou KJ, Chen PY, Huang MC. Restless legs syndrome following the combined use of quetiapine and paroxetine. Prog Neuropsychopharmacol Biol Psychiatry. 2010;34(6): 1139–40.
78. Damsa C, Bumb A, Bianchi-Demicheli F, Vidailhet P, Sterck R, Andreoli A, et al. "Dopamine-dependent" side effects of selective serotonin reuptake inhibitors: a clinical review. J Clin Psychiatry. 2004;65(8):1064–8.
79. Belli H, Akbudak M, Ural C. Duloxetine-related galactorrhea and restless legs syndrome: a case report. Psychiatria Danubina. 2013;25(3):266–7.
80. Michopoulos I, Ferentinos P, Oulis P, Gournellis R. Restless legs syndrome associated with the combined use of quetiapine and venlafaxine. J Clin Psychopharmacol. 2014;34(1): 159–61.
81. Brown EE, Nomikos GG, Wilson C, Fibiger HC. Chronic desipramine enhances the effect of locally applied amphetamine on interstitial concentrations of dopamine in the nucleus accumbens. Eur J Pharmacol. 1991;202(1):125–7.
82. Scavone C, Aizenstein ML, Planeta Cda S, De Lucia R. Long-term effects of imipramine on striatal dopamine autoreceptor function: involvement of both noradrenergic and serotonergic systems. Gen Pharmacol. 1992;23(3):397–401.
83. Mago R, Mahajan R, Thase ME. Levomilnacipran: a newly approved drug for treatment of major depressive disorder. Expert Rev Clin Pharmacol. 2014;7(2):137–45.
84. Dimmitt SB, Riley GJ. Selective serotonin receptor uptake inhibitors can reduce restless legs symptoms. Arch Intern Med. 2000;160(5):712.
85. Brown LK, Dedrick DL, Doggett JW, Guido PS. Antidepressant medication use and restless legs syndrome in patients presenting with insomnia. Sleep Med. 2005;6(5):443–50.
86. Shioda K, Nisijima K, Yamauchi Y, Ohtuka K, Kato S. Use of a serotonin 1A receptor agonist to treat restless legs syndrome. J Clin Psychopharmacol. 2006;26(6):673–5.
87. Bahk WM, Pae CU, Chae JH, Jun TY, Kim KS. Mirtazapine may have the propensity for developing a restless legs syndrome? A case report. Psychiatry Clin Neurosci. 2002;56 (2):209–10.
88. Teive HA, de Quadros A, Barros FC, Werneck LC. Worsening of autosomal dominant restless legs syndrome after use of mirtazapine: case report. Arq Neuropsiquiatr. 2002;60 (4):1025–9.

89. Agargun MY, Kara H, Ozbek H, Tombul T, Ozer OA. Restless legs syndrome induced by mirtazapine. Journal Clin Psychiatry. 2002;63(12):1179.
90. Bonin B, Vandel P, Kantelip JP. Mirtazapine and restless leg syndrome: a case report. Therapie. 2000;55(5):655–6.
91. Kim SW, Shin IS, Kim JM, Park KH, Youn T, Yoon JS. Factors potentiating the risk of mirtazapine-associated restless legs syndrome. Hum Psychopharmacol. 2008;23(7):615–20.
92. Bayard M, Bailey B, Acharya D, Ambreen F, Duggal S, Kaur T, et al. Bupropion and restless legs syndrome: a randomized controlled trial. J Am Board Family Med: JABFM. 2011;24(4):422–8.
93. Park YM, Lee HJ, Kang SG, Cho JH, Kim L. Resolution of pregabalin and mirtazapine associated restless legs syndrome by bupropion in a patient with major depressive disorder. Psychiatry Inv. 2009;6(4):313–5.
94. Lee JJ, Erdos J, Wilkosz MF, LaPlante R, Wagoner B. Bupropion as a possible treatment option for restless legs syndrome. Ann Pharmacother. 2009;43(2):370–4.
95. Kim SW, Shin IS, Kim JM, Yang SJ, Shin HY, Yoon JS. Bupropion may improve restless legs syndrome: a report of three cases. Clin Neuropharmacol. 2005;28(6):298–301.
96. Nofzinger EA, Fasiczka A, Berman S, Thase ME. Bupropion SR reduces periodic limb movements associated with arousals from sleep in depressed patients with periodic limb movement disorder. J Clin Psychiatry. 2000;61(11):858–62.
97. Feighner JP, Meredith CH, Stern WC, Hendrickson G, Miller LL. A double-blind study of bupropion and placebo in depression. Am J Psychiatry. 1984;141(4):525–9.
98. Saletu-Zyhlarz GM, Abu-Bakr MH, Anderer P, Gruber G, Mandl M, Strobl R, et al. Insomnia in depression: differences in objective and subjective sleep and awakening quality to normal controls and acute effects of trazodone. Prog Neuropsychopharmacol Biol Psychiatry. 2002;26(2):249–60.
99. Saletu M, Anderer P, Saletu-Zyhlarz G, Prause W, Semler B, Zoghlami A, et al. Restless legs syndrome (RLS) and periodic limb movement disorder (PLMD): acute placebo-controlled sleep laboratory studies with clonazepam. Eur Neuropsychopharmacol: J Eur Coll Neuropsychopharmacol. 2001;11(2):153–61.
100. Bezerra ML, Martinez JV. Zolpidem in restless legs syndrome. Eur Neurol. 2002;48(3): 180–1.
101. Allen R, Lesage S, Earley C. Anti-histamines and benzodiazepines exacerbate daytime restless legs syndrome symptoms. Sleep. 2005;28:A279.
102. Di Fabio R, Casali C, Vadala R, Pierelli F. Hydroxyzine hydrochloride in familial restless legs syndrome. Can J Neurol Sci Le Journal canadien des sciences neurologiques. 2010;37 (3):406–7.
103. Horiguchi J, Yamashita H, Mizuno S, Kuramoto Y, Kagaya A, Yamawaki S, et al. Nocturnal eating/drinking syndrome and neuroleptic-induced restless legs syndrome. Int Clin Psychopharmacol. 1999;14(1):33–6.
104. Wetter TC, Brunner J, Bronisch T. Restless legs syndrome probably induced by risperidone treatment. Pharmacopsychiatry. 2002;35(3):109–11.
105. Kraus T, Schuld A, Pollmacher T. Periodic leg movements in sleep and restless legs syndrome probably caused by olanzapine. J Clin Psychopharmacol. 1999;19(5):478–9.
106. Kang SG, Lee HJ, Kim L. Restless legs syndrome and periodic limb movements during sleep probably associated with olanzapine. J Psychopharmacol. 2009;23(5):597–601.
107. Khalid I, Rana L, Khalid TJ, Roehrs T. Refractory restless legs syndrome likely caused by olanzapine. J Clin Sleep Med: JCSM (Official Publication of the American Academy of Sleep Medicine). 2009;5(1):68–9.
108. Pinninti NR, Mago R, Townsend J, Doghramji K. Periodic restless legs syndrome associated with quetiapine use: a case report. J Clin Psychopharmacol. 2005;25(6):617–8.
109. Urbano MR, Ware JC. Restless legs syndrome caused by quetiapine successfully treated with ropinirole in 2 patients with bipolar disorder. J Clin Psychopharmacol. 2008;28(6): 704–5.

110. Rittmannsberger H, Werl R. Restless legs syndrome induced by quetiapine: report of seven cases and review of the literature. Int J Neuropsychopharmacol (Official Scientific Journal of the Collegium Internationale Neuropsychopharmacologicum). 2013;16(6):1427–31.
111. Webb J. Co-occurring akathisia and restless legs syndrome likely induced by quetiapine. J Neuropsychiatry Clin Neurosci. 2012;24(2):E46–7.
112. Duggal HS, Mendhekar DN. Clozapine-associated restless legs syndrome. J Clin Psychopharmacol. 2007;27(1):89–90.
113. Desautels A, Turecki G, Montplaisir J, Ftouhi-Paquin N, Michaud M, Chouinard VA, et al. Dopaminergic neurotransmission and restless legs syndrome: a genetic association analysis. Neurology. 2001;57(7):1304–6.
114. Kang SG, Lee HJ, Choi JE, Park YM, Park JH, Han C, et al. Association study between antipsychotics- induced restless legs syndrome and polymorphisms of dopamine D1, D2, D3, and D4 receptor genes in schizophrenia. Neuropsychobiology. 2008;57(1–2):49–54.
115. Kang SG, Park YM, Choi JE, Lim SW, Lee HJ, Lee SH, et al. Association study between antipsychotic-induced restless legs syndrome and polymorphisms of monoamine oxidase genes in schizophrenia. Hum Psychopharmacol. 2010;25(5):397–403.
116. Kang SG, Lee HJ, Park YM, Yang HJ, Song HM, Lee YJ, et al. The BTBD9 gene may be associated with antipsychotic-induced restless legs syndrome in schizophrenia. Hum Psychopharmacol. 2013;28(2):117–23.
117. Raveendranathan D, Shiva L, Venkatasubramanian G, Rao MG, Varambally S, Gangadhar BN. Clozapine-induced restless legs syndrome treated with aripiprazole. J Neuropsychiatry Clin Neurosci. 2013;25(2):E62–3.
118. Virit O, Selek S, Savas HA, Kokacya H. Improvement of restless legs syndrome and trichotillomania with aripiprazole. J Clin Pharm Ther. 2009;34(6):723–5.
119. Kikukawa S. Effectiveness of aripiprazole in treatment of adults with attention deficit disorder and restless legs syndrome. Int J Neuropsychopharmacol (Official Scientific Journal of the Collegium Internationale Neuropsychopharmacologicum). 2008;11(3):439–40.
120. McLean AJ. The use of the dopamine-receptor partial agonist aripiprazole in the treatment of restless legs syndrome. Sleep. 2004;27(5):1022.
121. Bolanos-Vergaray J, Obaya JC, Gonzalez R, Echeverri C, Piquer P. Restless legs syndrome due to aripiprazole. Eur J Clin Pharmacol. 2011;67(5):539–40.
122. Sullivan MA, Wilbur R. Gabapentin pharmacotherapy for antipsychotic-induced akathisia: single-patient experiment and case report. Ther Adv Psychopharmacol. 2014;4(2):100–2.
123. Telstad W, Sorensen O, Larsen S, Lillevold PE, Stensrud P, Nyberg-Hansen R. Treatment of the restless legs syndrome with carbamazepine: a double blind study. Br Med J. 1984;288 (6415):444–6.
124. Garcia-Borreguero D, Larrosa O, de la Llave Y, Verger K, Masramon X, Hernandez G. Treatment of restless legs syndrome with gabapentin: a double-blind, cross-over study. Neurology. 2002;59(10):1573–9.
125. Eisensehr I, Ehrenberg BL, Rogge Solti S, Noachtar S. Treatment of idiopathic restless legs syndrome (RLS) with slow-release valproic acid compared with slow-release levodopa/benserazid. J Neurol. 2004;251(5):579–83.
126. McMeekin H. Treatment of bipolar disorder, restless legs syndrome and parkinsonian symptoms using lamotrigine: a report of seven patients. J South Carolina Med Assoc. 2007;103(3):69–73.
127. Terao T, Terao M, Yoshimura R, Abe K. Restless legs syndrome induced by lithium. Biol Psychiatry. 1991;30(11):1167–70.
128. Evidente VG, Caviness JN. Focal cortical transient preceding myoclonus during lithium and tricyclic antidepressant therapy. Neurology. 1999;52(1):211–3.
129. Heiman EM, Christie M. Lithium-aggravated nocturnal myoclonus and restless legs syndrome. Am J Psychiatry. 1986;143(9):1191–2.

130. Driver-Dunckley ED, Noble BN, Hentz JG, Evidente VG, Caviness JN, Parish J, et al. Gambling and increased sexual desire with dopaminergic medications in restless legs syndrome. Clin Neuropharmacol. 2007;30(5):249–55.
131. Quickfall J, Suchowersky O. Pathological gambling associated with dopamine agonist use in restless legs syndrome. Parkinsonism Related Disord. 2007;13(8):535–6.
132. Tippmann-Peikert M, Park JG, Boeve BF, Shepard JW, Silber MH. Pathologic gambling in patients with restless legs syndrome treated with dopaminergic agonists. Neurology. 2007;68 (4):301–3.
133. Salas RE, Allen RP, Earley CJ, Gamaldo CE. Drug hoarding: a case of atypical dopamine dysregulation syndrome in a RLS patient. Mov Disord (Official Journal of the Movement Disorder Society). 2009;24(4):627–8.
134. Pourcher E, Remillard S, Cohen H. Compulsive habits in restless legs syndrome patients under dopaminergic treatment. J Neurol Sci. 2010;290(1–2):52–6.
135. Evans AH, Stegeman JR. Punding in patients on dopamine agonists for restless leg syndrome. Mov Disord (Official Journal Movement Disorder Society). 2009;24(1):140–1.
136. Provini F, Antelmi E, Vignatelli L, Zaniboni A, Naldi G, Calandra-Buonaura G, et al. Association of restless legs syndrome with nocturnal eating: a case-control study. Mov Disord (Official Journal of the Movement Disorder Society). 2009;24(6):871–7.
137. Arora A, Fletcher P. Parkinsonism hyperpyrexia syndrome caused by abrupt withdrawal of ropinirole. Br J Hosp Med. 2013;74(12):698–9.
138. Wensel TM, Powe KW, Cates ME. Pregabalin for the treatment of generalized anxiety disorder. Ann Pharmacotherapy. 2012;46(3):424–9.
139. Boschen MJ. A meta-analysis of the efficacy of pregabalin in the treatment of generalized anxiety disorder. Can J Psychiatry Revue canadienne de psychiatrie. 2011;56(9):558–66.
140. Gahr M, Freudenmann RW, Hiemke C, Kolle MA, Schonfeldt-Lecuona C. Pregabalin abuse and dependence in Germany: results from a database query. Eur J Clin Pharmacol. 2013;69 (6):1335–42.
141. 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(7):675–84.
142. Benes H, Mattern W, Peglau I, Dreykluft T, Bergmann L, Hansen C, et al. Ropinirole improves depressive symptoms and restless legs syndrome severity in RLS patients: a multicentre, randomized, placebo-controlled study. J Neurol. 2011;258(6):1046–54.
143. 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(1):34–40.
144. Pae CU. Pramipexole augmentation in treatment-resistant major depressive disorder. Expert Rev Neurother. 2014;14(1):5–8.
145. Hornyak M. Depressive disorders in restless legs syndrome: epidemiology, pathophysiology and management. CNS Drugs. 2010;24(2):89–98.
146. Singh A, Althoff R, Martineau RJ, Jacobson J. Pramipexole, ropinirole, and mania in Parkinson's disease. Am J Psychiatry. 2005;162(4):814–5.
147. Kelleher JP, Centorrino F, Huxley NA, Bates JA, Drake JK, Egli S, et al. Pilot randomized, controlled trial of pramipexole to augment antipsychotic treatment. Eur Neuropsychopharmacol (The Journal of the European College of Neuropsychopharmacology). 2012;22 (6):415–8.
148. Michalopoulou PG, Azim A, Tracy D, Shergill SS. Ropinirole as an effective adjunctive treatment for clozapine-resistant negative symptoms in simple schizophrenia: a case report. J Clin Psychopharmacol. 2012;32(5):719–20.
149. 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(9):976–81.

150. Ondo WG. Common comorbidities and differential diagnosis of restless legs syndrome. J Clin Psychiatry. 2014;75(3):e06.
151. Ferini-Strambi L. RLS-like symptoms: differential diagnosis by history and clinical assessment. Sleep Med. 2007;8(Suppl 2):S3–6.
152. Benes H, Walters AS, Allen RP, Hening WA, Kohnen R. Definition of restless legs syndrome, how to diagnose it, and how to differentiate it from RLS mimics. Mov Disord (Official Journal of the Movement Disorder Society). 2007;22(Suppl 18):S401–8.

Sleep Impact: Insomnia, Hypersomnia, Sleep Attacks, and Circadian Disorders

3

Maria Turchese Caletti and Federica Provini

Since the first clinical and polygraphic descriptions of restless legs syndrome (RLS) [1, 2] it was clear that sleep disturbance is one of the most common and most impactful of RLS symptoms [3]. Since sleep onset requires a period of rest and motor activity is alerting, the conditions needed to initiate sleep are apt to produce RLS symptoms, and the methods to relieve them are likely to interfere with sleep [4].

RLS patients could experience severe insomnia, characterized by a long sleep latency, due to difficulties in initiating sleep but also in maintaining sleep and waking up several times per night. In more severe cases, RLS symptoms can disrupt rest, also during waking hours, every time the patient tries to relax. Thus, whether awake or asleep, RLS patients could experience few opportunities for the general restorative behaviors necessary for health, resulting in a substantial reduction of the quality of life, higher rates of comorbidities including depression and anxiety, and in a substantial larger healthcare utilization. It is unclear what percentage of RLS patients have a sleep disturbance, but clinical experience shows that virtually all patients seeking treatment reported disordered sleep [4] (Table 3.1). In the REST study, which has investigated the impact of RLS on sleep patterns in five Western industrialized countries (France, Germany, Spain, UK and USA), sleep-related symptoms were the most commonly reported by patients, and were also considered to be the most troublesome [3]. In the REST primary care study, 88.4% of 551 RLS sufferers reported at least one sleep-related symptom, and 43.4% rated a

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Table 3.1 Prevalence of sleep-related symptoms in primary RLS patients, according to the different studies

Authors and year of the study	Population of the study	Instruments used to determine sleep-related symptoms	The most troublesome sleep-related symptoms	% of RLS patients reporting sleep-related symptoms
Montplaisir et al. [8]	133 RLS patients	Questionnaires and polysomnography	Sleep onset insomnia and numerous nocturnal awakenings	94
Allen et al. [17]	26 patients	Polysomnography	Sleep efficiency below 50–35%	20
Hening et al. [5]	551 RLS sufferers	Questionnaire	Taking >30 min to fall asleep, 3 or more awakening times/night	88.4
Allen et al. [6]	416 RLS sufferers	REST general population questionnaire	Disrupted sleep and inability to fall asleep	75.5
Cuellar et al. [9]	39 RLS patients	Pittsburgh sleep quality inventory (PSQI)	Short sleep duration and poor sleep quality	87.2
Happe et al. [59]	519 patients	Medical outcomes study (MOS) sleep scale	Sleep duration <5 h	43.8
Happe et al. [59]	519 patients	Medical outcomes study (MOS) sleep scale	Have a "not optimal sleep"	69.1
Allen et al. [7]	251 RLS patients	Global questions about sleep quality	Not good sleep	62
Fulda and Wetter [24]	4114 participants to 26 studies	Epworth sleepiness scale (ESS)	Daytime sleepiness	29.6
Happe et al. [59]	519 patients	Epworth sleepiness scale (ESS)	Daytime sleepiness	45.6
Budhiraja et al. [15]	535 patients	Epworth sleepiness scale (ESS)	Daytime sleepiness	38.2
Allen et al. [6]	416 RLS sufferers	REST general population questionnaire	Daytime sleepiness	32
Allen et al. [6]	416 RLS sufferers	REST general population questionnaire	Disruption of normal daily activities	40.1

sleep-related symptom as their most troublesome symptom [5]. In the REST general population study, among the 416 RLS sufferers, 75.5% reported sleep-related symptoms [6]. In a subsequent survey, Allen et al. reported that significant sleep disturbance was noted for 62% of the 251 primary RLS patients examined [7]. According to Hening and colleagues, 68.6% of those with moderate or severe RLS

reported insomnia symptoms [5]. Similar results were reported by Montplaisir et al. who studied 133 patients diagnosed with RLS and found that 94% had complained of difficulties falling asleep and/or staying asleep [8]. In a study by Cuellar et al. the entire sample reported poor sleep, as demonstrated by high scores on the Pittsburgh Sleep Quality Inventory (PSQI), taking in consideration subjective sleep quality, sleep latency, sleep duration, habitual sleep efficiency, sleep disturbance, sleep medications, and daytime dysfunction [9]. In all cases, subjects with severe or very severe RLS had significantly worse sleep outcomes than those with mild to moderate RLS, suggesting that sleep quality and sleep duration may vary with the severity of RLS [9].

The sleep disturbances associated with RLS can severely affect patients' daily activities or personal relationships, having a negative effect not only on performance-related functions but also on mood [3, 5, 6]. Especially among elders, severe RLS has been associated with poorer social function and emotional well-being [9]. Some authors suggested that emotional distress observed in RLS patients does not appear to be directly caused by the primary RLS symptoms but it seems moderated by their effects on sleep [10]. One recent study on a small group of RLS patients showed that RLS patients present substantial cognitive deficits similar to those of subjects deprived of sleep for one night, despite assessment at a time when RLS symptoms were not active [11]. Chronic sleep deprivation, in untreated RLS, may also lead to the impairment of sleep-dependent memory consolidation [12].

Insomnia

Many studies demonstrate increased sleep latency, increased number of awakenings, insufficient hours of sleep, and a lower sleep efficiency in RLS patients [5, 6, 13–15] (Fig. 3.1). High percentages of patients with moderate or severe RLS reported taking 30 min or more to fall asleep and waking three or more times per night because of RLS symptoms [5]. Patients with moderate to severe RLS may sleep an average of 3–5 h per night and may chronically have less sleep time than patients with almost any other persistent sleep disorder [16], including insomnia [3]. Budhiraja and colleagues conducted an overnight polysomnographic study demonstrating that participants with RLS symptoms had higher prevalence of insomnia with daytime consequences [15]. Another polysomnographic study documented that the mean sleep efficiency was reduced in RLS patients, approximately at 50%, and was below 35% (<3 h sleep per night) in one-fifth of RLS patients [17]. The authors suggested that the reduced sleep efficiency correlates with the reported clinical severity of RLS [16]; for patients with mild RLS, sleep disturbances may be less of a problem [4].

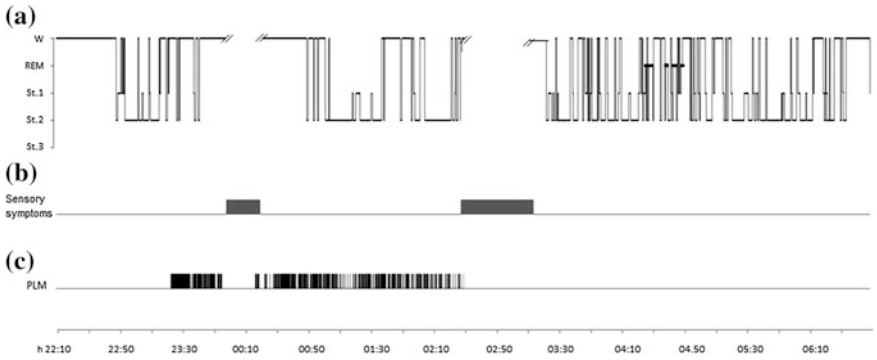

Fig. 3.1 **a** Sleep histogram and representation of sensory and motor symptoms in a patient with severe RLS. The histogram shows a long sleep latency of about 40 min and a marked sleep fragmentation with a reduction of total sleep time. Slow-wave sleep is absent. REM sleep is reached only in the second part of the night with a long latency (about 6 h). **b** Periods of appearance of sensory symptoms during which the patient feels the urge to get out of the bed and move in order to relieve her discomfort. Note that in these periods the patient asks to be disconnected from the cables (interruption of the wake line). **c** A significant number of PLM is observed both during relaxed wakefulness and sleep, in the first part of the night

Hornyak et al. comparing a group of 45 patients with RLS to a group of age- and sex-matched healthy controls reported shorter total sleep times and lower sleep efficiencies in the RLS group [13]. Interestingly, according to the one-epoch criterion, sleep onset latency was comparable in RLS patients and in controls as documented also by Saletu et al. [18]. This finding is surprising, as most patients complain about difficulties in initiating sleep, but the discrepancy might be explained by the clinical observation that some RLS patients fall asleep rapidly but cannot maintain sleep (Fig. 3.2).

Furthermore, RLS patients showed a markedly fragmented sleep with numerous periods of waking with increased arousals represented by an augmented arousal index and a sleep fragmentation index significantly higher in the RLS group compared to controls [13, 19, 20].

Moreover, RLS patients presented an increased number of periodic limb movements per hour of sleep (PLMS index) associated with or shortly followed by arousal (PLMS-arousal index), compared to healthy controls [3, 8, 13]. These either could cause the patient to wake up or prevent he/she from reaching deeper stages of sleep. PLM may also occur during relaxed wakefulness (PLMW), delaying the onset of sleep [21].

More recently, Hornyak and colleagues reported evidence of REM sleep disturbance, with longer REM sleep latency and decreased percentage of REM sleep in the RLS group. It might have occurred as a consequence of sleep interruptions which were in turn due to the nocturnal occurrence of RLS symptoms, or as a consequence of the earlier bedtimes in the sleep laboratory or it could be related to the pathology of RLS itself [13].

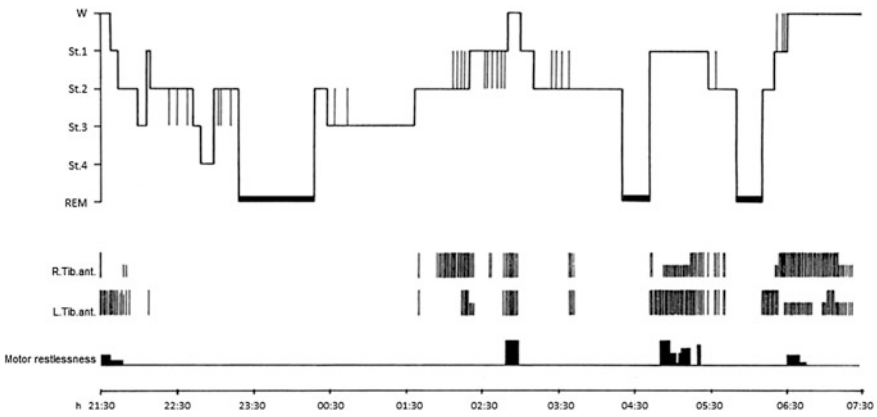

Fig. 3.2 Correlation between sleep histogram and motor symptoms in a RLS patient. The patient presents a normal sleep latency falling asleep rapidly but cannot maintain sleep, awakening in the middle of the night (From Coccagna G, Lugaresi E, et al. La sindrome delle gambe senza riposo (Restless legs). Omnia Med Ther. 1966, with permission.)

Interestingly, modest reductions of sleep time and specific loss of REM sleep, even in healthy normal-sleep subjects, appear to be related to hyperalgesia the following morning [22], an observation which may be especially relevant in RLS patients in light of the mechanical hyperalgesia described in this disorder [23].

Excessive Daytime Sleepiness

As would be expected, chronic sleep loss observed in RLS patients leads inevitably to significant consequences on the daytime function. The consequences of chronic sleep deprivation have been investigated intensively in recent years.

Across studies, there was converging evidence that around 20–25% of subjects with untreated idiopathic RLS are likely to experience increased daytime sleepiness [24].

In the REST general population study, more than half of the RLS cohort reported disturbances in daytime functioning such as exhaustion or fatigue, daytime sleepiness, difficulty in concentrating during the next afternoon and during the next evening [6]. One large epidemiological study found significantly higher complaints of decreased vigor in a population judged to have clinically significant RLS symptoms compared to normal controls [6, 25]. Bassetti et al. reported a significantly high degree of daytime fatigue among their 55 RLS patients [26], a finding consistent with the report that RLS sufferers, due to their daytime fatigue, have more work difficulties and driving impairment [27].

Budhiraja and colleagues, obtaining data from the Tucson Cohort of the Sleep Heart Health Study, including 535 participants who answered questions regarding RLS symptoms, documented that participants with RLS had a higher prevalence of daytime sleepiness (38.2%) [15]. Fulda and Wetter, considering 26 studies reporting ESS scores in untreated idiopathic RLS patients, estimated that 29.6% of RLS subjects had an ESS score >10 and 22.8% had an ESS score >11 [24]. EDS in RLS has been noted in two population-based studies [28, 29] suggesting that patients with more frequent RLS symptoms had more elevated ESS scores [29].

Nevertheless, daytime sleepiness, unlike insomnia, does not occur for most RLS patients, and moreover, when sleepiness occurs, it appears to be less severe than expected for the degree of sleep disruption reported by RLS patients [10, 24]: intriguingly, the relatively modest degree of sleepiness is not concordant with the profound sleep debt and insomnia reported by these patients [24] (Fig. 3.3).

The assessment of daytime sleepiness in RLS patients is complicated by the fact that daytime napping is often impossible especially for those with more severe symptoms, impeding to perform Multiple Sleep Latency Test (MSLT) and Maintenance Wakefulness Test (MWT). Nevertheless, Kallweit et al. examined 27 RLS patients finding that 10 out of 27 patients reported EDS (ESS > 10). The 10 sleepy patients underwent video polysomnography (PSG) and MSLT demonstrating that RLS patients with sleepiness had a higher amount of total sleep time ($p = 0.029$) and a mean pathological sleep latency on MSLT (6.4 min). Under dopaminergic treatment, both RLS severity and ESS improved [30].

Gamaldo and colleagues studied 20 RLS subjects and 13 sleep-restricted controls using morning and evening Suggested Immobilization Test (SIT) which served as a modified MWT. The authors showed that the RLS subjects had a longer sleep latency on the morning and evening SIT than controls [31].

Other studies found no significant differences in the degree of sleepiness reported by patients, nor in the ESS scores, between the RLS and controls [18, 26]. Kushida and colleagues reported that RLS patients may present no significant daytime sleepiness, but rather a subtle breakthrough of decreased daytime alertness. It appears that diminished alertness is likely to result from an indirect effect of sleep disruption during the previous nights and it is proportional to the degree of sleep debt [10]. However, failure to observe the profound sleepiness expected from sleep

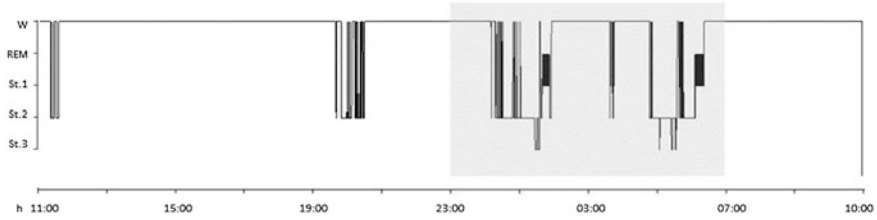

Fig. 3.3 A 24-h sleep–wake recording in a severe RLS patient. Note that despite the short duration of sleep during the nocturnal period (in *grey*), the patient presents only two brief daytime sleep episodes (at around 11 a.m. and 20 p.m.)

disruption could suggest some mechanism among RLS individuals that compensates for daytime sleepiness. Such a compensatory mechanism might be more effective against some of the morbidities associated with sleep loss, such as sleepiness, and less effective in reducing other ones, such as irritability, mood liability, or problems with alertness [10]. An alternative hypothesis is that the RLS-associated discomfort experienced by these patients results in a dissociation between their desire to fall asleep during the day and their reported or objective ability to fall asleep [10].

The study by Gamaldo et al. supports the data that RLS subjects often do not report significant daytime sleepiness, despite chronic sleep loss, but a greater sustained alertness than sleep-restricted controls [31]. Thus, RLS disease state itself appears to enhance alertness in the face of sleep loss, a finding in contrast to that reported in Parkinson's disease, strongly associated with increased daytime sleepiness independent of drug treatments [32, 33]. So, despite the common beneficial response to dopaminergic treatments seen in the two conditions, PD and RLS appear to demonstrate markedly different effects on sleep–wake mechanisms, indicating differences in status of the dopaminergic arousal system in the two disorders [31].

In this point of view, the heightened degree of alertness demonstrated by RLS patients may be in contrast with the perceived impairment in mood, vigor, and vigilance commonly reported in literature [31]. Perhaps the mixed results seen in the studies may be caused by semantic errors, leading subjects to describe the same condition in heterogeneous ways [18, 26]. Drowsiness, vigilance, vigor, and daytime fatigue may all be influenced by the chronic sleep disruption observed in RLS patients; nevertheless they are separated aspects which could be differently affected by sleep deprivation.

Excessive daytime sleepiness and poor sleep quality were reported also in secondary RLS forms, associated with end-stage renal disease (ESRD), diabetes, and pregnancy.

Gigli and colleagues evaluated the prevalence of RLS in a large multicentric series of 601 ESRD patients undergoing dialytic treatment, administering a questionnaire [34]. The percentage of RLS patients was 21.5%. The group of patients suffering from RLS, in comparison with the control group, was significantly more affected by symptoms of insomnia, and had more fragmented and less restful nightly sleep associated with a significant daytime somnolence [34].

In the same way, examining 400 patients on hemodialysis, Araujo and colleagues, found that 21.5% of them presented RLS. Of these RLS patients, 69.8% presented a poorer quality of sleep (PSQI > 5), compared to negative RLS patients, and 38.4% showed excessive daytime sleepiness (ESS > 10) [35].

Sabbatini and colleagues showed that morning patients (patients who underwent dialyses in the morning) were more subjected to insomnia [36], whereas a questionnaire-based study showed that patients on evening hemodialysis had better sleep quality and less daytime symptoms [37]. Even though it is unclear which factors of dialysis are implicated in the development of RLS in uremic patients, considering that sleep-deprived patients are at risk of cardiovascular disease [38],

disordered sleep can be an important factor in reducing the life expectancy of patients with ESRD [39].

Skomro and colleagues examined the prevalence and characteristics of sleep disturbances in a population of 58 adult type 2 diabetic outpatients attending endocrinology clinics [40]. Sleep complaints were common among these patients: over 55% of diabetics complained of daytime sleepiness (ESS > 10), and frequent daytime naps were reported by 25.9% of diabetics and 16.7% of controls. RLS was common in both groups, affecting over 24% of diabetics patients and 12.5% of the nondiabetic controls and even though the differences were not statistically significant, ESS scores were higher in the diabetics with RLS than in non-RLS diabetics.

Lopes and colleagues studied 100 consecutive patients attending a diabetes clinic in order to investigate the presence of RLS and the presence of sleep-related complaints [41]. RLS was found in 27% of patients and in 45% of RLS patients the quality of sleep, assessed by the PSQI, was scored as poor. Excessive daytime sleepiness was found in 26% of cases, according to ESS [41].

RLS is frequent in pregnant women [42] and RLS symptoms may be of important and clinically severe impact on sleep quality [43].

Suzuki and colleagues examined 16,528 pregnant women randomly selected from a sample of women attending 260 Japanese clinical institutions with maternity services [44]. The prevalence of RLS was found to be 19.9%. Women with sleep-related problems such as subjective difficulty initiating or maintaining sleep, early morning awaking, and excessive daytime sleepiness were more likely to have RLS than those without such problems. These data were confirmed by Hubner and colleagues who studied 501 pregnant women in each trimester and 8 weeks postpartum, interviewing them about RLS symptoms and sleep disturbances [45]. RLS was diagnosed in 12; 45% had an International Restless Legs Scale Score (IRLSS) >20 and 100% had a PSQI >5.

Sleep Attacks

Despite the modest degree of daytime sleepiness reported in the RLS population, sleep attacks may pose some problems in RLS patients. Sleep attacks are defined as episodes of sudden sleep onset, which occur without warning. They have been described as attacks in which the patient could fall asleep while drinking a cup of tea and dropping their cup, or as sudden inappropriate cessation of a conversation mid-sentence, at which time the patient is found to be asleep [46]. Nevertheless, in some cases they could also lead to dangerous situations such as car accidents [47]. Sleep attacks were originally described in patients with Parkinson's disease or narcolepsy [48, 49], and in particular they have been described in patients with Parkinson's disease on treatment with dopaminergic agents [49–51]. Recent studies showed that, although with lower frequency, sleep attacks could occur in RLS patients (32.7%) more often than in control subjects (19.8%) [47]. However, the prevalence of sleep attacks in RLS remains still unknown, and it is difficult to

determine whether the disease itself, the dopaminergic medication, or other factors play the most important role in causing this phenomenon [47]. Möller and colleagues (in their questionnaire survey including 156 RLS patients and 126 controls), found that duration and/or severity of disease seemed to be not associated with the presence of sleep attacks and concluded that RLS itself may render the patients more susceptible to the occurrence of sudden onset of sleep episodes [47]. Sleep attacks prevailed in elder male patients (70.8% of all male patients older than 63 years reported sudden onset of sleep), while female patients (21.1%) featured basically the same prevalence of sleep attacks as controls (19.8%).

Few cases of clusters of sleep attacks in RLS patients have been described associated with the use of dopaminergic drugs such as cabergoline (used for 10 weeks at a dose of 0.5–1 mg once daily) or ropinirole (0.25–0.5 mg per day for 8 weeks) which ceased with the suspension of the drugs [46]. On the other hand, Möller and colleagues reported that dopaminergic therapy, in contrast to Parkinson's disease, appeared to have a possible protective effect and lessened the frequency of reported sleep attacks [47].

Therapeutic trials with dopaminergic agonists have produced inconsistent improvements in daytime sleepiness [52–54]. This may reflect either the sedating properties of the drugs counteracting the beneficial effects on daytime alertness, an inadequate therapeutic effect, differences in the instruments assessing daytime sleepiness, or a relative absence of excessive daytime sleepiness in subjects in clinical trials [29].

Considering that dopaminergic medication is one of the choice therapies for RLS, and given the potential danger of the condition, RLS patients, in particular elder and male subjects, should always be assessed for the presence of sleep attacks.

Circadian Disorders

The exact timing of RLS depends on both the basic circadian pattern of expression and the conditions under which it is expressed. Hening and colleagues found that subjective discomfort and motor restlessness increased from a trough in the morning to a maximum at night in the hours following midnight. Peak intensity was found on the falling phase of the core temperature cycle, whose circadian rhythm appeared to be within the normal range for age [55]. Similarly, Trenkwalder et al. [56] recorded sleeping and waking PLMs and waking sensory symptoms in 8 volunteers with RLS showing that both the PLMs and sensory symptoms were worst at night with a maximum for both between midnight and 1:00 AM and a minimum between 9:00 and 11:00 AM. The highest PLM counts occurred on the falling phase of the circadian temperature curve whereas the lowest PLM counts occurred on the rising phase of the curve. These data confirm that the PLM and sensory symptoms in RLS are influenced by a circadian rhythm, and that the "worsening at night" is, at least in part, distinct from the "worsening while lying or sitting" criterion [56].

The onset of symptoms with rest is in fact variable, with patients with milder symptoms having an onset of symptoms only after longer periods of rest. Many patients with mild RLS, therefore, report that the symptoms only really bother them when they must be immobile and awake for a significant period of time, particularly in soporific or movement-restrained conditions, such as during airplane flights or an evening at the theater. Others describe some mild symptoms at sleep onset, which easily resolve with small movements or cease when the patients fall asleep [4]. Thus, a good sleeper or someone with chronic insufficient sleep may fall asleep rapidly enough so that the period of rest before sleep is too short for any significant degree of symptom development [4]. The circadian pattern of RLS symptoms may also vary among patients, leaving some with symptoms mostly in the evening and not at bedtime. It is not known if this represents a real difference in the circadian phase of the RLS symptoms for these milder cases or whether it is a result of the person spending a longer time sitting in the evening than lying in bed before sleep onset [4].

Conclusions

Sleep disorders are very common and affect sleep quality and quantity in almost all RLS patients. They can be present both in primary and secondary RLS. The consequences of RLS on sleep could be very important, leading to increased morbidity in RLS patients.

Sleep-related symptoms are likely to be a major presenting feature when RLS patients consult a physician. Insomnia and excessive daytime sleepiness are the most frequent sleep complaints, and hence RLS should be specifically explored as a possible diagnosis when a patient complains of sleep abnormalities, such as an inability to fall asleep and frequent wakefulness during the night. Since sleep disorders can have serious clinical consequences and a significant impact on patients' quality of life, a correct diagnosis and appropriate management are mandatory [57–59].

References

1. Ekbom KA. Restless legs: clinical study of hitherto overlooked disease in legs characterized by peculiar paresthesia ("Anxietas tibiarum"), pain and weakness, and occurring in two main forms, asthenia crurum paraesthetica and asthenia crurum dolorosa. Acta Med Scand. 1945;158:1–123.
2. Coccagna G, Lugaresi E, Tassinari CA, Ambrosetto C. La sindrome delle gambe senza riposo (restless legs). Omnia Med Ther. 1966;44:619–84.
3. Garcia-Borreguero D. Time to REST: epidemiology and burden. Eur J Neurol. 2006;13: 15–20.
4. Allen RP, Picchietti D, Heninng 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. 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.
6. 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.
7. 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.
8. Montplaisir J, Boucher S, Poirier G, Lavigne G, Lapierre O, Lespérance 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.
9. 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.
10. Kushida CA, Allen RP, Atkinson MJ. Modeling the causal relationships between symptoms associated with restless legs syndrome and the patient-reported impact of RLS. Sleep Med. 2004;5:485–8.
11. Pearson VE, Allen RP, Dean T, Gamaldo CE, Lesage SR, Earley CJ. Cognitive deficits associated with restless legs syndrome (RLS). Sleep Med. 2006;7:25–30.
12. Stickgold R. Sleep-dependent memory consolidation. Nature. 2005;437:1272–8.
13. 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.
14. 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.
15. 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.
16. Allen RP, Earley CJ. Restless legs syndrome: a review of clinical and pathophysiologic features. J Clin Neurophysiol. 2001;18:128–47.
17. Allen RP, Earley CJ. Defining the phenotype of the restless legs syndrome (RLS) using age-of-symptom-onset. Sleep Med. 2000;1:11–9.
18. Saletu M, Anderer P, Saletu B, Lindeck-Pozza L, Hauer C, Saletu-Zyhlarz G. EEG mapping in patients with restless legs syndrome as compared with normal controls. Psychiatry Res. 2002;115:49–61.
19. Morrell MJ, Finn L, Kim H, Peppard PE, Badr MS, Young T. Sleep fragmentation, awake blood pressure, and sleep-disordered breathing in a population-based study. Am J Respir Crit Care Med. 2000;162:2091–6.
20. Haba-Rubio J, Ibanez V, Sforza E. An alternative measure of sleep fragmentation in clinical practice: the sleep fragmentation index. Sleep Med. 2004;5:577–81.
21. Michaud M, Paquet J, Lavigne G, Desautels A, Montplaisir J. Sleep laboratory diagnosis of restless legs syndrome. Eur Neurol. 2002;48:108–13.
22. Roehrs T, Hyde M, Blasdell B, Greenwald M, Roth T. Sleep loss and REM sleep loss are hyperalgesic. Sleep. 2006;29:145–51.
23. Stiasny-Kolster K, Magerl W, Oertel WH, Möller JC, Treede RD. Static mechanical hyperalgesia without dynamic tactile allodynia in patients with restless legs syndrome. Brain. 2004;127:773–82.
24. Fulda S, Wetter TC. Is daytime sleepiness a neglected problem in patients with restless legs syndrome? Mov Disord. 2007;22:409–13.

25. Abetz L, Allen R, Follet A, Washburn T, Early C, Kirsch J, et al. Evaluating the quality of life of patients with restless legs syndrome. Clin Ther. 2004;26:925–35.
26. 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.
27. 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.
28. Ulfberg J, Nyström B, Carter N, Edling C. Restless Legs Syndrome among working-aged women. Eur Neurol. 2001;46:17–9.
29. Winkelman JW, Finn L, Young T. Prevalence and correlated of restless legs syndrome symptoms in the Wisconsin Sleep Cohort. Sleep Med. 2006;7:545–52.
30. Kallweit U, Siccoli MM, Poryazova R, Werth E, Bassetti CL. Excessive daytime sleepiness in idiopathic restless legs syndrome: characteristics and evolution under dopaminergic treatment. Eur Neurol. 2009;62:176–9.
31. 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.
32. Ondo WG, Dat Vuong K, Khan H, Atassi F, Kwak C, Jankovic J. Daytime sleepiness and other sleep disorders in Parkinson's disease. Neurology. 2001;57:1392–6.
33. Dhawan V, Dhoat S, Williams AJ, Dimarco A, Pal S, Forbes A, et al. The range and nature of sleep dysfunction in untreated Parkinson's disease (PD). A comparative controlled clinical study using the Parkinson's disease sleep scale and selective polysomnography. J Neurol Sci. 2006;248:158–62.
34. Gigli GL, Adorati M, Dolso P, Piani A, Valente M, Brotini S, et al. Restless legs syndrome in end-stage renal disease. Sleep Med. 2004;5:309–15.
35. Araujo SM, de Bruin VM, Nepomuceno LA, Maximo ML, Daher Ede F, Correia Ferrer DP, et al. Restless legs syndrome in end-stage renal disease: clinical characteristics and associated comorbidities. Sleep Med. 2010;11:785–90.
36. Sabbatini M, Minale B, Crispo A, Pisani A, Ragosta A, Esposito R, et al. Insomnia in maintenance haemodialysis patients. Nephrol Dial Transplant. 2002;17:852–6.
37. Hsu CY, Lee CT, Lee YJ, Huang TL, Yu CY, Lee LC, et al. Better sleep quality and less daytime symptoms in patients on evening hemodialysis: a questionnaire-based study. Artif Organs. 2008;32:711–6.
38. Nilsson PM, Nilsson A, Hedblad B, Berglund G. Sleep disturbance in association with elevated pulse rate for prediction of mortality-consequences of mental strain? J Int Med. 2001;250:521–9.
39. Winkelman JW, Chertow GM, Lazarus JM. Restless legs syndrome in end-stage renal disease. Am J Kidney Dis. 1996;28:372–8.
40. Skomro RP, Ludwig S, Salamon E, Kryger MH. Sleep complaints and restless legs syndrome in adult type 2 diabetics. Sleep Med. 2001;2:417–22.
41. Lopes LA, Lins Cde M, Adeodato VG, Quental DP, de Bruin PF, Montenegro RM Jr, et al. Restless legs syndrome and quality of sleep in type 2 diabetes. Diab Care. 2005;28(11): 2633–6.
42. Manconi M, Govoni V, De Vito A, Economou NT, Cesnik E, Mollica G, et al. Pregnancy as a risk factor for restless legs syndrome. Sleep Med. 2004;5:305–8.
43. Neau JP, Porcheron A, Mathis S, Julian A, Meurice JC, Paquereau J, et al. Restless legs syndrome and pregnancy: a questionnaire study in the Poitiers District, France. Eur Neurol. 2010;64:268–74.
44. Suzuki K, Ohida T, Sone T, Takemura S, Yokoyama E, Miyake T, et al. The prevalence of restless legs syndrome among pregnant women in Japan and the relationship between restless legs syndrome and sleep problems. Sleep. 2003;26:673–7.
45. Hübner A, Krafft A, Gadient S, Werth E, Zimmermann R, Bassetti CL. Characteristics and determinants of restless legs syndrome in pregnancy: a prospective study. Neurology. 2013;80 (8):738–42.

46. Rose AR, Antic NA, McEvoy RD. Restless leg syndrome, dopamine agonists and sleep attacks. Intern Med J. 2008;38:872–3.
47. Möller JC, Körner Y, Cassel W, Meindorfner C, Krüger HP, Oertel WH, et al. Sudden onset of sleep and dopaminergic therapy in patients with restless legs syndrome. Sleep Med. 2006;7:333–9.
48. Dement W, Rechtschaffen A, Gulevich G. The nature of the narcoleptic sleep attack. Neurology. 1966;16:18–33.
49. Frucht S, Rogers JD, Greene PE, Gordon MF, Fahn S. Falling asleep at the wheel: motor vehicle mishaps in persons taking pramipexole and ropinirole. Neurology. 1999;52:1908–10.
50. Ryan M, Slevin JT, Wells A. Non-ergot dopamine agonist induced sleep attacks. Pharmacotherapy. 2000;6:724–6.
51. Körner Y, Meindorfner C, Möller JC, Stiasny-Kolster K, Haja D, Cassel W, et al. Predictors of sudden onset of sleep in Parkinson's disease. Mov Disord. 2004;19:1298–305.
52. 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.
53. Adler CH, Hauser RA, Sethi K, Caviness JN, Marlor L, Anderson WM, et al. Ropinirole for restless legs syndrome: a placebo-controlled crossover trial. Neurology. 2004:1405–7.
54. Trenkwalder C, Garcia-Borreguero D, Montagna P, Lainey E, de Weerd AW, Tidswell P, et al. Therapy with ropinirole; efficacy and tolerability in RLS 1 study group. 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.
55. 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.
56. 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.
57. Ramar K, Olson EJ. Management of common sleep disorders. Am Fam Physician. 2013;88:231–8.
58. Bogan RK, Cheray JA. Restless legs syndrome: a review of diagnosis and management in primary care. Postgrad Med. 2013;125:99–111.
59. 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.

Cognitive Functioning

4

Stephany Fulda

The Willis–Ekbom disease/restless legs syndrome (WED/RLS) has a substantial impact on normal daily and work productivity [1, 2]. It is characterized by a significantly reduced quality of life [3–7] and among the different domains of quality of life, the areas "energy/sleepiness" and "performance" are particularly impaired [3, 4, 6, 7]. There is also accumulating evidence that at least in severely affected WED/RLS patients, cognitive functioning is frequently found to be reduced [8–13] and this may contribute to the observed impairment in quality of life and work productivity in these patients. The question of whether pharmacological treatment affects cognitive functioning in patients with WED/RLS is therefore of substantial clinical importance. This chapter will give a review of the few available studies that contributed data on cognitive task performance during pharmacological treatment in patients with WED/RLS.

Treatment and Cognitive Function in RLS

The effect of treatment on cognitive functioning in RLS has been investigated in a series of acute treatment studies and in a limited number of studies after 2–12 weeks of continuous treatment (Tables 4.1 and 4.2).

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Table 4.1 Acute treatment effects on cognitive functions in WED/RLS

Study	Sample *n*/ sex/age	Study design/drug/duration	Comparison	Findings
Outcomes	*Grünberger alphabetical cancellation test: no. letters processed, % errors, variability* *Numerical memory test: no. of items* *Fine motor activity: Left hand (L), right hand (R), sum of left and right hand (L + R)* *Reaction time (RT) test: RT, RT variability, no. of errors of commission and of omission*			
Saletu et al. [14]	12 RLS 4M 8F 58 ± 12 y	SB PC CO (fixed order: baseline/placebo/drug) 0.5 mg ropinirole, 1 night	Ropinirole versus placebo	*Improved*: fine motor activity: R, L + R RT test: errors of commission
			Baseline versus placebo	*Improved*: fine motor activity: L RT test: errors of commission
Saletu et al. [15]	21 RLS 8M 13F 63 ± 14 y	DB PC CO 100 mg rr- + 100 mg sr-L-dopa/benserazide 1 night	L-dopa versus placebo	*No statistically significant changes*
Saletu et al. [16]	11 RLS 8M 3F 54 ± 14 y	SB PC CO (fixed order: baseline/placebo/drug) 0.27 mg pramipexole, 1 night	Pramipexole versus placebo	*No statistically significant changes*
			Baseline versus placebo	*Improved*: fine motor activity: L RT test: errors of omission
Saletu et al. [17]	10 RLS 5M 5F 53 ± 9 y	SB PC CO (fixed order: baseline/placebo/drug) 1 mg clonazepam, 1 night	Clonazepam versus placebo	*No statistically significant changes*
Saletu et al. [18]	40 RLS 12M 28F 56 ± 18 y	SB PC CO (fixed order: baseline/placebo/drug) 300 mg gabapentin, 1 night	Gabapentin versus placebo	*Worsened*: cancellation task: % errors *Improved*: numerical memory Fine motor activity: R, L + R (no RT test performed)
	40 RLS 21M 19F 58 ± 13 y	SB PC CO fixed order (adaption—placebo—drug) 0.5 mg ropinirole, 1 night	Ropinirole versus placebo	*Improved*: Fine motor activity: L, R, L + R (no RT test performed)
			Gabapentin versus ropinirole	*No statistically significant changes*

CO cross over; *DB* double-blind; *F* female; *L* left; *M* male; *PC* placebo-controlled; *R* right; *RT* reaction time; *SB* single blind; *WED/RLS* Willis-Ekbom disease/restless legs syndrome

Table 4.2 Long-term treatment and cognitive function in WED/RLS

Study	Sample *n*/sex/age	Study design/Drug/Duration	Comparison	Findings
Abler et al. [23]	12 RLS/4M 8F/58 ± 12 y	OL CO dopamine agonists	On stable DA treatment versus after short term withdrawal of treatment	Faster reaction times in tests of phasic, tonic, and divided attention tasks
Lee et al. [24]	23 untreated RLS/2M 21F/70 ± 12 y 31 treated RLS/11M 20F/64 ± 10 y	Cross-sectional case-control	Treated patients versus untreated patients	Better performance in clock copying task No difference in tasks assessing attention, memory, executive functions, and motor performance
Kim et al. [20]	16 RLS/1M 15F/50 ± 11 y	OL/12 w/pramipexole	After versus before treatment	Improved performance in short term memory, verbal fluency, attention No difference in other tasks assessing memory, attention, executive functions, and visuospatial performance
Galbiati et al. [13]	18 drug naïve RLS/40% M[a]/ 47 ± 10 y[a]	OL/12 w/pramipexole	After versus before treatment	Improved performance in all domains (16 of 17 tasks) assessing short term memory, long term memory, working memory, attention and executive function
Winkelman et al. [22]	131 RLS/35 M 76F/52 ± 13 y	DB PC CO/4 w/1200 mg gababapentin enarcabil	Drug versus placebo	Decreased improvement from baseline in executive attention (TMT-B) No difference in semantic fluency
GSK [21]	33 versus 28 versus 33 RLS ~42% M ~50 y	DB PC PG/2w/gabapentin enarcabil 1200 mg 1800 mg	Change from baseline Placebo versus 1200 mg	*Evening*: Driving simulator: Increased lane position variability (LPV) No difference in brake reaction time (BRT), average lane position (LP), average speed (SP), speed variability (SPV) Cognitive function test:

(continued)

Table 4.2 (continued)

Study	Sample *n*/sex/age	Study design/Drug/Duration	Comparison	Findings
				No difference in Brief Assessment of Cognition composite score (BAC), and subscores in verbal memory, attention, verbal fluency, executive function, and motor performance *Morning*: Driving simulator: Increased SPV No difference in LPV, BRT, LP, SP Cognitive function test: No difference in BAC and subscores
			Placebo versus 1800 mg	*Evening*: Driving simulator: Less improvement in SP No difference in LPV, SPV, BRT, LP Cognitive function test: No difference in BAC and subscores *Morning*: Driving simulator: No difference in LPF, SPV, BRT, LP, SP Cognitive function test: Less improvement in BAC and attention performance (symbol coding), decrease in motor function No difference in other subscores

BAC brief assessment of cognition composite score; *BRT* brake reaction time; *CO* cross over; *DA* dopamine agonists; *DB* double-blind; *F* female; *GSK* GlaxoSmithKline; *LP* average lane position; *LPV* lane position variability; *M* male; *OL* open label, *PC* placebo-controlled; *RT* reaction time; *SB* single blind; *SP* average speed; *SPV* speed variability; *WED/RLS* Willis-Ekbom disease/restless legs syndrome

[a]For the complete group of 20 subjects

Effects of Acute Treatment on Cognitive Function in Subjects with RLS

Effects of an acute, single-night, pharmacological treatment on cognitive functions in RLS patients have been assessed a series of studies conducted by the research group of Saletu and co-workers [14–18] (Table 4.1). All studies used similar designs and the same cognitive tasks. The cognitive test set included the following four tasks:

- *Grünberger Alphabetical Cancellation Test* [19]: Paper and pencil task. One page with 20 rows, each containing 40 Letters. The task consists of crossing out the letters A, N, E, and Y within the time limit of 10 s per row. Scoring includes the number of letters processed (total score), the percentage of errors, and line-to-line difference in number of letters processed (variability).
- *Grünberger verbal memory test (GVG)—subtest numerical memory* [19]: Ten two-digit numbers are read aloud by the experimenter. After each number the subject is asked to repeat the number and at the end to reproduce the ten numbers. The number of correctly reproduced two-digit numbers is scored.
- *Grünberger fine motor test* [19]: Paper and pencil test consisting of one sheet with 100 squares (5 × 10 mm). The subject has to draw single points in as many squares as possible within 15 s. Scoring is based on the number of points and the exact placement. The task is performed first with the right and then with the left hand.
- *Reaction time task*: Not further specified; outcomes include the mean reaction time, reaction time variability, and the number of errors of commission and omission.

The series of five studies investigated cognitive function after one night treatment with levodopa [15], ropinirole [14, 18], pramipexole [16], gabapentin [18], and clonazepam [17]. In all, except one study [15], cognitive functioning was assessed after a baseline night, one night with placebo and one night with treatment. Studies were conducted single-blind and the order of treatment was not randomized so that the drug treatment night was always the third night. Therefore, the treatment effect is possibly confounded with a learning effect across the three nights. This is supported by the observation that (i) the improvement after drug treatment were most often seen for those tasks that also showed improvement from the baseline night to the placebo night and (ii) the only randomized double-blind study with levodopa [15] did not find any differences between drug and placebo (Table 4.1).

Three of the studies did not find any difference in cognitive function between placebo and levodopa [15], pramipexole [16], and clonazepam [17]. In the two studies employing ropinirole [14, 18], an improvement in fine motor performance was reported, which was also found after acute treatment with gabapentin (see Table 4.1 for details). Across all studies, decreased performance was only observed for acute treatment with gabapentin where an increase in errors in the letter cancellation task was reported [18].

In summary, and based on the low number of studies, limitations in study design, and the inconsistency of observed effects, it must be concluded that there is no consistent evidence of acute treatment effects on cognitive functioning in RLS.

Prolonged Treatment and Cognitive Function in RLS

The effect of prolonged and continuous pharmacological treatment on cognitive function in RLS has been investigated in two open label studies with a 12 week treatment of pramipexole [13, 20] and two double-blind, placebo-controlled, cross-over studies of 2 [21] or 4 week [22] treatment with gabapentin enacarbil (Table 4.2).

Besides these clinical trials, there are two further studies that used different designs and included measures of cognitive function [23, 24] (Table 4.2). First, [23], Abler and colleagues studied RLS patients while being on stable long-term treatment with dopamine agonists and after withdrawal of medication [23]. The study included 12 females RLS patients between 43 and 66 years of age that had been treated for at least 1 months with dopamine agonists (pramipexole, cabergoline, ropinirole, and/or L-dopa). Each patient was tested on two occasions, the order of which was balanced and randomized: while taking their regular medication and after a washout phase without medication. Cognitive function testing assessed attentional performance with three reaction time tasks (Test battery for Attentional Performance, TAP). The first two tasks assessed simple reaction times to a visual stimulus which appeared after a warning tone or without any warning, thought to measure phasic and tonic alertness, respectively. The third task was a divided attention task where complex visual and auditory sequences/patterns had to be processed in parallel and reaction times to the two tasks were measured. Concerning attentional performance, the study reported that reaction times were faster, i.e., performance was better, for tonic alertness and divided attention while patients were taking their regular medication. While this result could indicate that attention had improved with pharmacological treatment, such an interpretation would have to rest on the assumption that performance in the unmedicated state represented a baseline level of performance. Given the short duration of the medication withdrawal it is, however, also plausible that it represents an acute withdrawal effect with WED/RLS severity and associated sleep disturbances potentially increased compared to a stable baseline condition without medication.

The second study, which was not a clinical trial, was conducted by Lee and colleagues [24]. They included a group of 23 untreated RLS subjects, 31 long-term treated RLS subjects, and 37 healthy, prevalently elderly (mean age around 67 years) participants. Untreated RLS subjects and healthy participants had been identified within an epidemiological study, while treated RLS patients were recruited from a sleep lab population. No information was given concerning duration and type of treatment other than individuals “were prescribed medication

for relief for their RLS symptoms" (p. 88, [24]). Cognitive tests assessed verbal intelligence, verbal and visual memory, visuospatial and motor performance, as well as verbal fluency. Analyses of between-group differences controlled for age and the significant differences in education level, which was higher in treated RLS patients. Cognitive functioning across the majority of tasks did not differ between the group of untreated RLS subjects and the treated patients. The only exception was found for visuospatial abilities where treated patients performed significantly better on the clock drawing and clock copying tasks (Table 4.2). A possible interpretation of these results in terms of a relative lack of treatment effects on cognitive functioning in subjects with RLS is, however, complicated by the a priori between-group differences in education levels and estimated RLS severity [24].

Pramipexole

There are two studies exploring the effect of pramipexole on cognitive functioning in patients with RLS [13, 20]. In both studies, treatment was open label and for 12 weeks. The study of Kim and co-workers [20] included 16 RLS patients with a mean age of 50 years and a mean IRLS score of 29 who were treated with a median dose 0.19 mg of pramipexole. Cognitive function tests were conducted at baseline and after 12 weeks and assessed attention, language, visuospatial abilities, memory and executive functions including verbal fluency. The test set included 11 tasks and 21 outcome measures derived from these tasks. After treatment, improvement was seen in 3 outcome measures, namely in the immediate recall of the Rey–Osterrieth complex figure, in the letter verbal fluency task and in the digit symbol coding task, assessing attention (Table 4.2). Concurrent with these changes, also improvement in RLS symptom severity, sleep quality and depressive symptoms were observed.

The similar study of Galbiati et al. [13] included 18 de novo RLS patients with a mean age of 47 years and a mean IRLS score of 26. Patients were treated with a fixed dose of 0.25 mg pramipexole for 12 weeks. Cognitive function tests assessed memory, language abilities, attention, and executive functioning with 14 different tasks and 17 outcome measures. In contrast to the study of Kim et al. [20], in this study statistically significant improvements were reported for all but one (semantic fluency) outcome. All patients also underwent nocturnal polysomnography before and after treatment which demonstrated increased sleep duration, sleep efficiency and a decrease in periodic leg movements during sleep, among other improvements.

For both studies [13, 20] the lack of a control group or a control condition to exclude learning or other effects on repeated test performance is of concern. In addition, given the similarities in study design, age, RLS severity, and even chosen cognitive tasks it is not readily apparent why the improvement in cognitive functioning would be so much more pronounced in the study of Galbiati [13] in contrast to the study of Kim [20].

Gabapentin Enarcabil

Cognitive function tests have also been included in two clinical trials with of gabapentin enacarbil (Table 4.2) [21, 22]. In the study of Winkelman et al. [22], 131 patients with RLS participated in a double-blind, placebo-controlled, cross-over study. Patients were treated with 1200 mg gabapentin enacarbil and placebo for 4 weeks each with a 1 week taper and 1 week washout period between treatments. Cognitive function tests were undertaken at baseline and at the end of each 4 week treatment period and included the Trail Making Test B and a semantic fluency task. Analyses compared the change from baseline between the two conditions. While there was no difference in semantic fluency, the improvement from baseline in TMT-B performance was significantly smaller for the gabapentin condition. It is important to stress, that in both conditions TMT-B performance was improved compared to baseline, however, the improvement was less pronounced with gabapentin. Similarly, repeated polysomnography assessment showed improvement of sleep with both gabapentin enacarbil and placebo which was, however, more pronounced for gabapentin enacarbil concerning wakefulness during the sleep period. The PLMS index, however, was only mildly decreased without differences between conditions.

Information on the second study assessing the effect of gabapentin enacarbil on cognitive functioning in RLS has been available as a study result report via the GlaxoSmithKline Clinical Trial Register [21]. The study was specifically designed to assess the effect of gabapentin enacarbil on driving simulator performance and cognitive function in subjects with RLS under "usual" dosing conditions and at the time of maximal plasma levels (*T*max). Performance was assessed in the evening and in the morning at baseline and after 14 days of treatment with drug or placebo intake at 5 PM. On the following two days, medication was taken in the morning so that cognitive function testing in the evening occurred at *T*max for gabapentin enacarbil. As an active control, patients were also randomized to receive a single dose of 50 mg diphenhydramine or placebo 2 h before this last assessment. In this parallel group study patients were randomized to 4 groups: two active drug conditions with 1200 mg or 1800 mg gabapentin enacarbil daily and two placebo arms. In one placebo arm, patients received a single dose diphenhydramine at day 16, all other groups received placebo 2 h before the last assessment.

The simulated driving assessments consisted of a 2-min brake reaction time test and a 1-h test drive on a rural highway. Outcome measures included lane position variability, average lane position, speed variability, average speed, and brake reaction times. In addition, all patients completed the Brief Assessment of Cognition (BAC) which assesses verbal memory, executive function, motor function, attention, and verbal fluency with six tasks and yields a score for each task as well as a general composite score. Comparing the change from baseline between the placebo group and the treatment groups under "usual" dosing conditions revealed only few differences: in the 1200 mg condition lane position variability in the evening and speed variability in the morning increased compared to baseline while it decreased with placebo; no other differences in driving simulator performance or

cognitive function testing was found. In the 1800 mg condition the improvement in speed (evening), attention (symbol coding), and BAC composite score (both morning) was less pronounced compared to the placebo arm. In addition, motor function in the morning was found decreased.

At the time of maximal plasma levels (*T*max), lane position variability was significantly increased in both the 1200 and 1800 mg condition comparable to the increase found with diphenhydramine. In addition, speed variability was found to be increased in the 1800 mg condition. No other differences compared to placebo were found.

The importance of learning effects has also been apparent in the two placebo-controlled, double-blind studies with gabapentin enacarbil [21, 22]. Taken together these studies [21, 22] showed (i) an improvement of cognitive function during the placebo arm of the studies, and both (ii) a reduced improvement and (iii) a reduced performance in only a few of the many outcome measures of cognitive function in WED/RLS. Particularly the improvement in the placebo condition underlines the need to control for learning or other unspecific effects [25].

Summary, Discussion and Outlook

So far, five acute treatment studies [14–18], four trials with prolonged treatment [13, 20–22] and two observational studies [23, 24] have assessed cognitive function in subjects with WED/RLS. Study designs included between-group comparisons [24], a withdrawal design [23], open label studies [13, 20], and double-blind, placebo-controlled studies [21, 22]. For the majority of studies methodological concerns did not permit to draw any firm conclusions. Across-study comparisons are further complicated by the fact that different pharmacological substances have used different study designs with the dopamine agonist pramipexole being employed only in studies with an open label design and gabapentin enacarbil in double-blind, placebo-controlled studies. In addition, some heterogeneity in cognitive tasks and outcome measures can be noted, which seems to be the rule rather than the exception for studies on cognitive function in sleep disorders [26]. Summarizing nevertheless, for treatment with dopaminergic agents studies reported improvements in cognitive functioning that were few or mild [14, 18, 20] or absent [15, 16], however, with the notable exception of one study that reported large improvements in a multitude of cognitive tasks [13]. For gabapentin [18] and gabapentin enacarbil [21, 22] no improvement [18, 21, 22], improvement that was comparable to improvement with placebo [21, 22] but also reduced performance [21] have been reported. Overall, it is premature to draw any conclusions about the effect of pharmacological treatment on cognitive functioning in subjects with WED/RLS.

As is apparent from this overview, there is a need for more and adequately designed studies to investigate the effect of treatment on cognitive function in WED/RLS. These future studies, however, will face several critical issues and interpretative challenges.

The expectation of treatment effects hinges foremost on the supposition that untreated subjects with WED/RLS have reduced cognitive performance. This is not fully compatible with the available evidence, which shows a pronounced disparity: studies that have recruited WED/RLS patient within a sleep lab setting all concluded that performance was reduced in WED/RLS patients [8–11, 13, 27, 28]; in contrast, studies that have sampled participants from epidemiological or community populations have found none or only very mild impairment [12, 24, 29–32]. Major differences between the two set of studies concern RLS severity (average IRLS scores: 21 [10] to 32 [28] versus 11 [31] to 23 [30]) and age. In particular, in the clinical studies, the mean age was well below 60 years of age (with one exception [9]), while it was 69 years and above for four of the six studies that sampled from community populations. Future studies on the effect of treatment on cognitive functioning in subjects with WED/RLS would therefore be well-advised to include younger subjects with at least moderate to severe RLS severity.

In addition, studies will necessarily include repeated assessments of cognitive task performance and thus are susceptible to practice effects such as memory for specific test items, test sophistication or learned strategies [33]. Practice effects can be substantial and have been found for all cognitive domains [33, 34]. Among the universally moderating effects are the length of the retest interval and the use of parallel forms with the practice effects being smaller the longer the retest interval and when parallel test forms are used [33]. Future studies should, therefore, include adequate control groups, use parallel test forms where possible and carefully choose the length of the treatment period.

Finally, even well-designed, adequately powered studies may face challenges in the interpretation of their results. The possible issue here is the potential difficulty to distinguish between a direct drug specific effect on cognitive function and effects that are achieved through its action on one or more WED/RLS associated symptoms. Today, and as detailed in other chapters in this book (see Chaps. 1, 11, 13–15), various drugs with different mechanisms of action are available and recommended in the treatment of WED/RLS [35, 36]. Currently, the two main drug classes are dopamine agonists and $\alpha_2\delta$ ligands. Both drugs are effective in treating WED/RLS sensory symptoms during wakefulness. However, dopaminergic drugs have a pronounced effect on periodic leg movements during sleep (PLMS) [37, 38], but little or no effect on the microstructure of sleep, i.e., arousals or the cyclic alternating patterns [39–41]. In contrast, $\alpha_2\delta$ ligands have little effect on PLMS but significantly reduce intra-sleep wakefulness [22, 42, 43]. A failure to demonstrate an effect of treatment on cognitive functioning with a substance from either drug class alone will therefore bear the question whether this may be due to a the fact that none of the drugs addresses all WED/RLS associated symptoms potentially relevant for cognitive functioning, such as periodic leg movements during sleep and micro- and macrostructural sleep disturbances. Furthermore, for the frequently used dopamine

agonists, studies in healthy subjects and short to medium periods of treatment have shown that dopamine agonists can improve cognitive performance after acute or prolonged periods of treatment [44–46]. In addition, a possible further mechanism of action may not be conferred via the drug's effect on WED/RLS severity, PLMS, or sleep but by its effect on depressive symptoms, which are: (i) frequent in patients with WED/RLS [47], (ii) associated with reduced cognitive performance [48–50], and (iii) may improve during drug treatment of WED/RLS [13, 51].

In summary, this chapter has given an overview over the first studies exploring the effect of pharmacological treatment on cognitive function in subjects with WED/RLS. Considerable heterogeneity in study designs and results as well as methodological concerns did not permit to draw any conclusions. Nevertheless, the question of whether treatment of WED/RLS has an effect on cognitive functioning has important clinical implications and merits to be explored in future, well-designed studies.

References

1. 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 (1):114–20.
2. Fehnel S, Zografos L, Curtice T, Shah H, McLeod L. The burden of restless legs syndrome: an assessment of work productivity, sleep, psychological distress, and health status among diagnosed and undiagnosed individuals in an internet-based panel. Patient. 2008;1(3):201–10.
3. 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.
4. 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.
5. Abetz L, Vallow SM, Kirsch J, Allen RP, Washburn T, Earley CJ. Validation of the restless legs syndrome quality of life questionnaire. Value Health. 2005;8(2):157–67.
6. Kushida CA, Allen RP, Atkinson MJ. Modeling the causal relationships between symptoms associated with restless legs syndrome and the patient-reported impact of RLS. Sleep Med. 2004;5(5):485–8.
7. 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.
8. Fulda S, Beitinger ME, Reppermund S, Winkelmann J, Wetter TC. Short-term attention and verbal fluency is decreased in restless legs syndrome patients. Mov Disord. 2010;25 (15):2641–8.
9. Pearson VE, Allen RP, Dean T, Gamaldo CE, Lesage SR, Earley CJ. Cognitive deficits associated with restless legs syndrome (RLS). Sleep Med. 2006;7:25–30.
10. Jung K-Y, Koo Y-S, Kim B-J, Ko D, Lee G-T, Kim KH, et al. Electrophysiologic disturbances during daytime in patients with restless legs syndrome: further evidence of cognitive dysfunction? Sleep Med. 2011;12(4):416–21.
11. Choi JW, Ko D, Lee G-T, Jung K-Y, Kim KH. Reduced neural synchrony in patients with restless legs syndrome during a visual oddball task. PLoS ONE. 2012;7(7):e42312.
12. Fulda S, Szesny N, Ising M, Heck A, Grübl A, Lieb R, et al. Further evidence for executive dysfunction in subjects with RLS from a non-clinical sample. Sleep Med. 2011;13(12): 1003–7.

13. Galbiati A, Marelli S, Giora E, Zucconi M, Oldani A, Ferini-Strambi L. Neurocognitive function in patients with idiopathic restless legs syndrome before and after treatment with dopamine-agonist. Int J Psychophysiol. 2015;95(3):304–9.
14. Saletu B, Gruber G, Saletu M, Brandstätter 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(4):181–9.
15. Saletu M, Anderer P, Högl B, Saletu-Zyhlarz G, Kunz A, Poewe W, et al. Acute double-blind, placebo-controlled sleep laboratory and clinical follow-up studies with a combination treatment of rr-L-dopa and sr-L-dopa in restless legs syndrome. J Neural Transm. 2003;110 (6):611–26.
16. Saletu M, Anderer P, Saletu-Zyhlarz G, Hauer C, Saletu B. Acute placebo-controlled sleep laboratory studies and clinical follow-up with pramipexole in restless legs syndrome. Eur Arch Psychiatry Clin Neurosci. 2002;252(4):185–94.
17. Saletu M, Anderer P, Saletu-Zyhlarz G, Prause W, Semler B, Zoghlami A, et al. Restless legs syndrome (RLS) and periodic limb movement disorder (PLMD): acute placebo-controlled sleep laboratory studies with clonazepam. Eur Neuropsychopharmacol. 2001;11(2):153–61.
18. Saletu M, Anderer P, Saletu-Zyhlarz GM, Parapatics S, Gruber G, Nia S, et al. Comparative placebo-controlled polysomnographic and psychometric studies on the acute effects of gabapentin versus ropinirole in restless legs syndrome. J Neural Transm. 2010;117(4): 463–73.
19. Grünberger J. Psychodiagnostik des Alkoholkranken. Ein methotischer Beitrag zur Bestimmung der Organizität in der Psychiatrie. Wien: Maudrich; 1977.
20. Kim M, Song J-Y, Kim SM, Moon YJ, Koo YS, Jung K-Y. Effect of pramipexole on cognitive functions in restless legs syndrome. J Korean Sleep Res Soc. 2014;11(1):16–20.
21. GlaxoSmithKline. A randomized, double blind, active- and placebo-controlled, parallel group safety study assessing simulated driving performance in XP13512-(GSK1838262) treated patients with restless legs syndrome [Internet]. Available from: http://www.gsk-clinicalstudyregister.com/files2/df5702c2-01e4-4770-96fc-4da1ee565ab8.
22. Winkelman JW, Bogan RK, Schmidt MH, Hudson JD, Derossett SE, Hill-Zabala CE. Randomized polysomnography study of gabapentin enacarbil in subjects with restless legs syndrome. Mov Disord. 2011;26(11):2065–72.
23. Abler B, Hahlbrock R, Unrath A, Grön G, Kassubek J. At-risk for pathological gambling: imaging neural reward processing under chronic dopamine agonists. Brain. 2009;132(Pt 9):2396–402.
24. Lee HB, Ramsey CM, Spira AP, Vachon J, Allen R, Munro CA. Comparison of cognitive functioning among individuals with treated restless legs syndrome (RLS), untreated RLS, and No RLS. J Neuropsychiatry Clin Neurosci. 2014;26(1):87–91.
25. Fulda S, Schulz H. How treatment affects cognitive deficits in patients with sleep disorders: methodological issues and results. Prog Brain Res. 2010;185:69–90.
26. Fulda S, Schulz H. Cognitive dysfunction in sleep disorders. Sleep Med Rev. 2001;5(6): 423–45.
27. 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.
28. Kim SM, Choi JW, Lee C, Lee BU, Koo YS, Kim KH, et al. Working memory deficit in patients with restless legs syndrome: an event-related potential study. Sleep Med. 2014;15 (7):808–15.
29. Celle S, Roche F, Kerleroux J, Thomas-Anterion C, Laurent B, Rouch I, et al. Prevalence and clinical correlates of restless legs syndrome in an elderly French population: the synapse study. J Gerontol A Biol Sci Med Sci. 2010;65:167–73.

30. Chen D, Shaw P, Canafax DM, Ware J. A pilot study to evaluate simulated driving performance and cognitive function in healthy subjects and patients with restless legs syndrome. J Parkinsonism Restless Legs Syndr. 2013;53–62.
31. Driver-Dunckley E, Connor D, Hentz J, Sabbagh M, Silverberg N, Hernandez J, et al. No evidence for cognitive dysfunction or depression in patients with mild restless legs syndrome. Mov Disord. 2009;24:1843–7.
32. Kim ES, Yoon IY, Kweon K, Park HY, Lee CS, Han EK, et al. Mild impairments in cognitive function in the elderly with restless legs syndrome. Sleep Med Psychophysiol. 2013;20(1): 15–21.
33. Calamia M, Markon K, Tranel D. Scoring higher the second time around: meta-analyses of practice effects in neuropsychological assessment. Clin Neuropsychol. 2012;26(4):543–70.
34. Hausknecht JP, Halpert JA, Di Paolo NT, Moriarty Gerrard MO. Retesting in selection: a meta-analysis of coaching and practice effects for tests of cognitive ability. J Appl Psychol. 2007;92(2):373–85.
35. Garcia-Borreguero D, Ferini-Strambi L, Kohnen R, O'Keeffe S, Trenkwalder C, Högl 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(11):1385–96.
36. Garcia-Borreguero D, Kohnen R, Silber MH, Winkelman JW, Earley CJ, Högl 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(7):675–84.
37. Hornyak M, Scholz H, Kohnen R, Bengel J, Kassubek J, Trenkwalder C. What treatment works best for restless legs syndrome? Meta-analyses of dopaminergic and non-dopaminergic medications. Sleep Med Rev. 2014;18(2):153–62.
38. Manconi M, Ferri R, Feroah TR, Zucconi M, Ferini-Strambi L. Defining the boundaries of the response of sleep leg movements to a single dose of dopamine agonist. Sleep. 2008;31 (9):1229–37.
39. Manconi M, Ferri R, Zucconi M, Bassetti CL, Fulda S, Aricò D, et al. Dissociation of periodic leg movements from arousals in restless legs syndrome. Ann Neurol. 2012;71:834–44.
40. Ferri R, Manconi M, Aricò D, Sagrada C, Zucconi M, Bruni O, et al. Acute dopamine-agonist treatment in restless legs syndrome: effects on sleep architecture and NREM sleep instability. Sleep. 2010;33(6):793–800.
41. Montplaisir J, Boucher S, Gosselin A, Poirier G, Lavigne G. Persistence of repetitive EEG arousals (K-alpha complexes) in RLS patients treated with L-DOPA. Sleep. 1996;19(3): 196–9.
42. Garcia-Borreguero D, Larrosa O, de la Llave Y, Verger K, Masramon X, Hernandez G. Treatment of restless legs syndrome with gabapentin: a double-blind, cross-over study. Neurology. 2002;59(10):1573–9.
43. Kushida CA, Walters AS, Becker P, Thein SG, Perkins AT, Roth T, et al. A randomized, double-blind, placebo-controlled, crossover study of XP13512/GSK1838262 in the treatment of patients with primary restless legs syndrome. Sleep. 2009;32(2):159–68.
44. Flöel A, Breitenstein C, Hummel F, Celnik P, Gingert C, Sawaki L, et al. Dopaminergic influences on formation of a motor memory. Ann Neurol. 2005;58(1):121–30.
45. Knecht S, Breitenstein C, Bushuven S, Wailke S, Kamping S, Flöel A, et al. Levodopa: faster and better word learning in normal humans. Ann Neurol. 2004;56(1):20–6.
46. Rihet P, Possamaï C-A, Micallef-Roll J, Blin O, Hasbroucq T. Dopamine and human information processing: a reaction-time analysis of the effect of levodopa in healthy subjects. Psychopharmacology. 2002;163(1):62–7.
47. Picchietti D, Winkelman JW. Restless legs syndrome, periodic limb movements in sleep, and depression. Sleep. 2005;28(7):891–8.

48. Reppermund S, Zihl J, Lucae S, Horstmann S, Kloiber S, Holsboer F, et al. Persistent cognitive impairment in depression: the role of psychopathology and altered hypothalamic-pituitary-adrenocortical (HPA) system regulation. Biol Psychiatry. 2007;62(5):400–6.
49. Carvalho AF, Miskowiak KK, Hyphantis TN, Kohler CA, Alves GS, Bortolato B, et al. Cognitive dysfunction in depression—pathophysiology and novel targets. CNS Neurol Disord: Drug Targets. 2014;13(10):1819–35.
50. Wang S, Blazer DG. Depression and cognition in the elderly. Annu Rev Clin Psychol. 2015.
51. Benes H, Mattern W, Peglau I, Dreykluft T, Bergmann L, Hansen C, et al. Ropinirole improves depressive symptoms and restless legs syndrome severity in RLS patients: a multicentre, randomized, placebo-controlled study. J Neurol. 2011;258(6):1046–54.

5 Health-Related Quality of Life and Depression Symptom Measures for the Assessment of Treatment in Restless Legs Syndrome/ Willis–Ekbom Disease

Jan Wesstrom

One way of defining the concept of health-related quality of life (HRQoL) is: "The extent to which one's usual or expected physical, emotional and social well-being are affected by a medical condition or its treatment" [1]. Individual patients with the same objective health status can report dissimilar HRQoL due to unique differences in expectations and coping abilities and it must be measured from the individual's viewpoint. There is a growing interest in HRQoL and there are several reasons for this. An increasing share of interventions is aimed at improving the quality of patients' lives rather than preventing premature deaths (e.g., hip replacement, hypnotics). As people live longer, they become more susceptible to disorders and conditions that decrease their quality of life. With a greater amount of shared decision-making in the health care, patients are also requesting treatments that can improve their HRQoL [2]. However, although reporting of several important aspects of trial methods has improved, quality of reporting remains well below an acceptable level. Without complete and transparent reporting of how a trial was designed and conducted, it is difficult for readers to assess its conduct and validity [3].

Impaired quality of life is most likely a consequence of Restless Legs Syndrome/Willis–Ekbom Disease (RLS/WED) and there is a growing knowledge in the area. However, as in most research fields there are some methodological differences between studies. Different questionnaires measuring HRQoL among RLS/WED patients have been used and the quality of life has in some studies been

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addressed in clinical samples, in some others in the general population. There are also differences in how control groups are chosen, some use general population norms, others RLS/WED negatives in the studied group. Some studies suggest that RLS/WED affects the physical aspects more than the mental aspects of quality of life [4–7], but there are studies in favor of the opposite [8, 9]. In several previous studies, RLS/WED-positives have been shown to score their own health below population norms, in analogy with patients suffering from other chronic medical conditions. As is described, sleep-related movement disorders (e.g., RLS/WED and periodic limb movements, PLM) is associated with several other comorbidities. A problem when HRQoL is evaluated in RLS/WED is that the symptomatology of the disease is very multifaceted in its character with number of different distressing symptoms, such as sleep disturbance, social deprivations, depressive or anxious mood, and side effects of treatments. The main challenge is to discriminate changes in HRQoL that are due to the key symptoms of RLS (urge to move, unpleasant sensations, circadian rhythm) from those that comes from concomitant or subsequent sleep disturbances, daytime tiredness or psychopathological symptoms. If there is RLS/WED by itself or comorbidity associated with the condition that causes poorer HRQoL is only explored, as we know of, in two previous studies [6, 10] Thus, there is likely a lack of facts in this specific area.

There are several studies using HRQoL as an assessment of treatment in WED, most of them reporting a positive effect [11, 12]. Only a few studies have examined treatment effects longer than 12 weeks [13] and the benefit on HRQoL may request a longer period of time. However, during recent years there are a few long-term studies performed. During the year of 2011, two Cochrane reviews were published, dealing with the issue on treatment for RLS/WED by levodopa [14] and dopamine agonists [15], both substances recommended for the treatment of RLS/WED. The two meta-analyses compared treatment to placebo or to other active treatment in RLS/WED. The topic HRQoL is dealt with but because of the strict criteria many/most studies were not included in the analysis. However, in the analysis of Levodopa and the effect on HRQoL, two studies were used and the result was that QoL was markedly improved. Turning to dopamine agonists and effect on HRQoL, 17 studies were included with the same positive result.

Most used instruments measures HRQoL independently of underlying medical condition, assessing more general characteristics of HRQoL (generic). The advantage with these questionnaires is the possibility to compare different conditions and its influence on HRQoL. The disadvantage is, in the case of a disease with more specific symptoms, that it can be a fairly blunt tool. RLS/WED has several disease-specific symptoms influencing quality of life and therefore there are disease-specific scales to sleep disturbance in RLS/WED created. There are examples of other used questionnaires in studies of HRQoL and RLS/WED but for an overview these has been chosen.

Generic Instruments Used in RLS/WED

- Short Form Health Survey 36, SF 36 [16]
- Short Form Health Survey 12, SF 12 [17]
- EQ-5D [18]

The SF-instruments can be used to assess and compare quality of life across a range of patient populations with different medical conditions The SF-36 contains 36 items, 35 of which are aggregated to score eight health scales: Physical functioning, role limitations due to physical health, bodily pain, general health perceptions, vitality, social functioning, role emotional and mental health. Scores on the eight scales were aggregated further to produce physical and mental component summary measures. SF scores range from 1 to 100 for the eight different attributes. A high score indicates a better physical (PCS12) and mental (MCS12) health, respectively. Values are often distributed between 12 and 70. The shorter 12-item SF-12 can be a more practical alternative for the purpose of large group comparisons. There is a high degree of correspondence between the summary physical and mental health factors estimated using the SF-12 and SF-36 [19]. Examples of the studies where SF 36 were used are Abetz et al. [4] and Kushida et al. [6]. SF 12 was used by Wesström et al. [10].

The EQ-5D is a generic instrument to assess HRQoL, comprises five triple choice questions about HRQoL dimensions (mobility, self-care, daily activity, pain, anxiety/depression), and has been used in a variety of neurological diseases, The instrument generates a health profile with five major dimensions but is also capable of expressing HRQoL as a single index value. Therefore it can be applied for clinical as well as for economic evaluations of health care. It has been used by Happe et al. in an RLS/WED study published 2008 [20]. If the purpose is to compare the impact of RLS on HRQoL with other conditions, generic instruments are suitable.

Disease-Specific Questionnaires Used in RLS/WED

- RLS-QoL (Abetz) [21]
- QoL-RLS (Kohnen) [22]
- RLS-QLI (Atkinson) [23]

When the issue is to evaluate the effect of a treatment for RLS (intervention studies) a disease-specific instrument is preferable. RLS/WED has several disease-specific symptoms influencing quality of life and the broader generic instruments might be, of this reason, insensitive.

In a review published in 2014, the quality of above specific instruments was evaluated by the Movement Disorder Society (MDS). The criteria used for the evaluation of the RLS/WED instruments were: (1) Instrument has been applied to

RS/WED populations (2) Other groups beyond the original developing group have published data on the clinical utility of the scale (3) Psychometrical studies are available that conclude that the scales are valid and reliable. The RLS-QOL was recommended for the use of both cross-sectional measure and as a tool for assessing change with treatment. The other two instruments were criticized since the patients included in the studies were drawn from patient support groups where the diagnosis of RLS/WED cannot be guaranteed as it was not done by known experts [24].

RLS and Depression

There is a high association and an overlap of symptoms between depression and RLS. A suggested cause is the influence on sleep but a common origin can also be found in the dopaminergic system. A third possible cause is known side effects of antidepressants. SSRIs have been reported to trigger or worsen symptoms of RLS.

There are not many studies where the severity of depression has been used as a tool for evaluating RLS treatment. One recent study is from Benes et al. [25] that showed that treatment with dopamine receptor agonists, by improvement of RLS symptoms, relieved mild to moderate depressive symptoms.

The author used three different questionnaires concerning severity of depression

1. Montgomery–Asberg Depression Rating Scale (**MADRS**): most frequently used and validated, broadly used in studies investing depression symptoms in somatic (organic) disorder [26].
2. Hamilton Rating Scale for Depression (**HAMD**): greater emphasis on sleep disturbance [27].
3. Beck Depression Inventory-II (**BDI-II**): assess different dimensions on depressive symptoms [28].

The value of measuring the severity of depression as a variable in the treatment of RLS is a complex issue. Since the knowledge of the comorbidity and the cause of this is still being explored and defined it might be premature to recommend a certain questionnaire. If there still is a need for using a questionnaire, the MADRS instrument can have an advantage, since it has higher sensitivity to changes during treatment and because of the relatively low interaction with RLS symptoms.

References

1. Cella DF. Measuring quality of life in palliative care. Semin Oncol. 1995;22:73–81.
2. Guyatt GH, Feeny DH, Patrick DL. Measuring health-related quality of life. Ann Intern Med. 1993;118:622–9.
3. Hopewell S, Dutton S, Yu LM, et al. The quality of reports of randomised trials in 2000 and 2006: comparative study of articles indexed in PubMed. BMJ. 2010;340:c723.
4. Abetz L, Allen R, Follet A, et al. Evaluating the quality of life of patients with restless legs syndrome. Clin Ther. 2004;26:925–35.

5. Allen RP, Walters AS, Montplaisir J, et al. Restless legs syndrome prevalence and impact: REST general population study. Arch Intern Med. 2005;165:1286–92.
6. Kushida C, Martin M, Nikam P, et al. Burden of restless legs syndrome on health-related quality of life. Qual Life Res. 2007;16:617–24.
7. Winkelman JW, Redline S, Baldwin CM, et al. Polysomnographic and health-related quality of life correlates of restless legs syndrome in the sleep heart health study. Sleep. 2009;32:772–8.
8. Rothdach AJ, Trenkwalder C, Haberstock J, et al. Prevalence and risk factors of RLS in an elderly population: the MEMO study. Memory and morbidity in Augsburg elderly. Neurology. 2000;54:1064–8.
9. Cesnik E, Casetta I, Turri M, et al. Transient RLS during pregnancy is a risk factor for the chronic idiopathic form. Neurology. 2010;75:2117–20.
10. Wesstrom J, Nilsson S, Sundstrom-Poromaa I, et al. Health-related quality of life and restless legs syndrome among women in Sweden. Psychiatry Clin Neurosci. 2010;64:574–9.
11. Trenkwalder C, Benes H, Poewe W, 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.
12. Oertel WH, Benes H, Bodenschatz R, et al. Efficacy of cabergoline in restless legs syndrome: a placebo-controlled study with polysomnography (CATOR). Neurology. 2006;67:1040–6.
13. Trenkwalder C, Stiasny-Kolster K, Kupsch A, et al. Controlled withdrawal of pramipexole after 6 months of open-label treatment in patients with restless legs syndrome. Mov Disord. 2006;21:1404–10.
14. Scholz H, Trenkwalder C, Kohnen R, et al. Levodopa for restless legs syndrome. Cochrane Database Syst Rev. 2011;Cd005504.
15. Scholz H, Trenkwalder C, Kohnen R, et al. Dopamine agonists for restless legs syndrome. Cochrane Database Syst Rev. 2011;Cd006009.
16. McHorney CA, Ware JE Jr, Raczek AE. The MOS 36-item short-form health survey (SF-36): II. Psychometric and clinical tests of validity in measuring physical and mental health constructs. Med Care. 1993;31:247–63.
17. Ware J Jr, Kosinski M, Keller SD. A 12-item short-form health survey: construction of scales and preliminary tests of reliability and validity. Med Care. 1996;34:220–33.
18. Hurst NP, Kind P, Ruta D, et al. Measuring health-related quality of life in rheumatoid arthritis: validity, responsiveness and reliability of EuroQol (EQ-5D). Br J Rheumatol. 1997;36:551–9.
19. Gandek B, Ware JE, Aaronson NK, et al. Cross-validation of item selection and scoring for the SF-12 health survey in nine countries: results from the IQOLA project. International quality of life assessment. J Clin Epidemiol. 1998;51:1171–8.
20. Happe S, Reese JP, Stiasny-Kolster K, et al. Assessing health-related quality of life in patients with restless legs syndrome. Sleep Med. 2009;10:295–305.
21. Abetz L, Vallow SM, Kirsch J, et al. Validation of the restless legs syndrome quality of life questionnaire. Value Health. 2005;8:157–67.
22. Kohnen RBH, Heinrich CR, Kurella B. Development of the disease-specific Restless legs syndrome quality of life (RLS-QOL) questionnaire. Mov Disord 2002;17s232.
23. Atkinson MJ, Allen RP, DuChane J, et al. Validation of the restless legs syndrome quality of life instrument (RLS-QLI): findings of a consortium of national experts and the RLS Foundation. Qual Life Res. 2004;13:679–93.
24. Walters AS, Frauscher B, Allen R, et al. Review of quality of life instruments for the restless legs syndrome/Willis-Ekbom Disease (RLS/WED): critique and recommendations. J Clin Sleep Med. 2014;10:1351–7.
25. Benes H, Mattern W, Peglau I, et al. Ropinirole improves depressive symptoms and restless legs syndrome severity in RLS patients: a multicentre, randomized, placebo-controlled study. J Neurol. 258:1046–54.

26. Davidson J, Turnbull CD, Strickland R, et al. The Montgomery-Asberg depression scale: reliability and validity. Acta Psychiatr Scand. 1986;73:544–8.
27. Hamilton M. A rating scale for depression. J Neurol Neurosurg Psychiatry. 1960;23:56–62.
28. Beck AT, Steer RA, Ball R, et al. Comparison of beck depression inventories -IA and -II in psychiatric outpatients. J Pers Assess. 1996;67:588–97.

Epidemiologic Evidence in Cardiovascular Disease

6

Xiang Gao and Brian Koo

Restless legs syndrome (RLS) and periodic limb movements during sleep (PLMS) are two common sleep disorders, affecting approximately 5–10% of the general population. These two disorders are correlated to each other closely—the PLMS occurs in up to 90% of persons suffering from RLS. Previous epidemiological studies have shown that these two disorders are associated with diverse chronic disorders, such as initial insomnia and sleep fragmentation, depression, anxiety, obesity, cardiovascular diseases, diabetes, erectile dysfunction, end-stage renal disease [1–12]. Among these disorders, increasing attention has been drawn to the potential association between RLS/PLMS and cardiovascular diseases (CVD) recently, as reviewed below.

RLS and Cardiovascular Diseases

RLS and Cardiovascular Risk Factors

Obesity

A positive association between obesity and RLS prevalence has been seen in most cross-sectional studies, [13–18], but not all [19, 20]. Among 1803 men and women aged 18 years of older, Phillips et al. found that each increase of 5 kg/m^2 BMI was

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associated with a 31% increased likelihood of having RLS [13]. In another cross-sectional study conducted in five European countries (n = 18,890), the crude OR for RLS was 1.22 (95% CI: 1.0, 1.5) for BMI of >27 versus 20–25 kg/m^2 [14]. In a Korean population (n = 9939), Kim et al. found a significant association between BMI and RLS among women (OR = 1.2 for BMI >25 vs. $\leq$ 25 kg/m^2) but not among men (OR = 1.1) [15].

We conducted the first systemic analysis between several obesity indices (e.g., BMI, waist circumference, waist-to-hip ratio, and weight gain) and risk of having RLS among 88,673 men and women free of diabetes, and arthritis, and pregnancy. Information of RLS was assessed using a set of standardized questions, recommended by the international RLS study group (IRLSSG). Higher BMI and waist circumference were associated with increased risk of having RLS, after adjusting for age, smoking, use of antidepressant, phobic anxiety score, medical history, and other covariates (P-trend < 0.001 for both). BMI in early adulthood (age 18–21 years) and weight gain were also positively associated with prevalence of RLS (P-trend < 0.01 for both), suggesting that obesity could be a risk factor for RLS.

We subsequently conducted a prospective study to look at whether obesity at baseline was associated with increased risk of developing RLS during 4–6 years of follow-up [21]. This study consisted of 42728 women and 12812 men free of RLS at baseline, and free of diabetes and arthritis through follow-up. We found that obesity was associated with an increased risk RLS both in men and women. The pooled multivariate-adjusted OR for RLS was 1.57 (95% confidence interval (CI): 1.33–1.85; P-trend < 0.0001) for body mass index >30 kg/m^2 versus $\leq$ 23 kg/m^2, and 1.56 (95% CI: 1.29–1.89; P-trend = 0.0001) comparing two extreme waist circumference quintiles, adjusting for potential cofounders (Fig. 6.1). Consistently, in a recent prospective study including 5620 adults from two Germany-based cohorts: the Dortmund Health Study (DHS; n = 1312; median of follow-up 2.1 year) and the Study of Health in Pomerania (SHIP; n = 4308; median follow-up of 5.0 years), a positive association between obesity and higher future risk of RLS was also observed [22]. Interestingly, in this study, individuals with RLS at the baseline tended to have a higher risk of developing obesity in the DHS cohort (adjusted OR = 2.2; p = 0.34) but not in the SHIP (adjusted OR = 0.95; p = 0.82). These results suggested that obesity could be a risk factor for RLS. However, whether individuals with RLS are more likely to gain weight in the future remains to be elucidated in the future prospective studies.

Hypertension

Previous studies have suggested that individuals with RLS are at increased risk of developing hypertension because of the presence of periodic limb movements of sleep (PLMS) which are seen in majority of patients with RLS. The population-based studies have also suggested that hypertension may act as an intermediary risk factor leading to cardiovascular diseases [14, 23] in people with RLS. In a survey including 4000 men selected from the general population in central Sweden, participants with RLS symptoms were more likely to report hypertension (OR: 1.5, 95% CI: 0.9–2.4), after adjusting for age, smoking, and

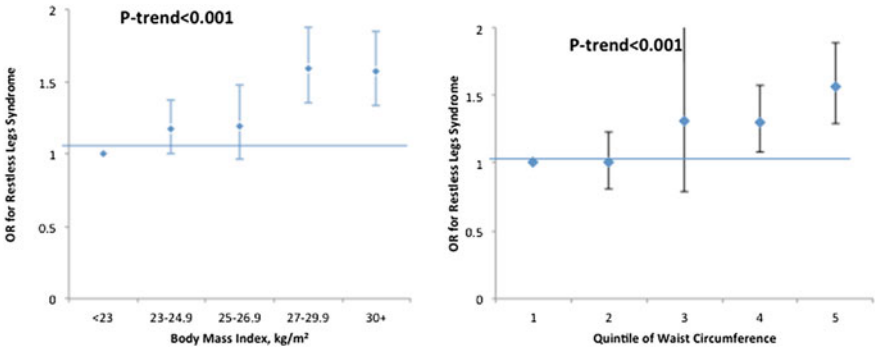

Fig. 6.1 Adjusted odds ratios (ORs) and 95% confidence intervals (CIs) of restless legs syndrome according to baseline body mass index (Panel 1) and waist circumference (Panel 2) status. Adjusted for age (yrs), race (white/other), physical activity (quintile), caffeine intake (quintile), alcohol intake (gm/day), smoking status (never, or current smoker: cigarettes/d, 1–14 or ≥ 15), the Crown-Crisp anxiety score, antidepressant medication (Y/N), use of iron specific supplement (Y/N), presence of myocardial infraction, stroke at baseline (each of them, yes/no), serum cholesterol level (mg/dL), high blood pressure (Y/N), and menopausal status (Y/N, for women only)

alcohol consumption [23]. Another cross-sectional study of 18,980 participants, found a significant association between RLS and hypertension (OR: 1.36, 95% CI: 1.14–1.61) [14], as did telephone survey which ascertained these two diseases and found direct relation ($p < 0.05$) [24]. In contrast, history of hypertension was not significantly associated with having RLS in two large US-based cohorts of men ($n = 22{,}786$) [17] and women ($n = 30{,}262$) [18]. We conducted a large-scale cross-sectional study including 65,544 women (aged 41–58 years) without diabetes and arthritis (two common RLS mimics) and found that RLS was associated with 20% increased risk of having hypertension. We also observed a clear dose-response relationship between RLS severity, as assessed by RLS symptom frequency, and higher concurrent systolic and diastolic blood pressures (P-trend < 0.0001 for both).

In our recently published prospective analysis of hypertension and future risk of developing RLS during 4–6 years of follow-up ($n = 55{,}540$), we failed to find significant association between these two conditions (adjusted OR = 0.90, 95% CI: 0.79–1.02) [21]. Similar nonsignificant results were also observed in a recent small prospective study [25]. In another prospective study including two cohorts, hypertension at baseline was significantly associated with a higher risk of RLS in one cohort (OR = 1.41; $P = 0.04$), but not in the other (OR = 1.09; $P = 0.76$) [26].

Hyperlipidemia

A positive association between high blood cholesterol and triglyceride and RLS risk has been consistently observed in most cross-sectional studies [17, 18, 27] and prospective cohorts [21, 22]. In our recent prospective analysis, we found that higher levels of total serum cholesterol was significantly associated with

development of RLS (*P*-trend = 0.002; *n* = 55,540) [21]. High triglyceride levels were also significantly associated with developing RLS; for men the adjusted RR was 1.45 (95% CI: 1.18, 1.77; *n* = 12,812) (this information was unavailable for women). The association between higher cholesterol and RLS risk did not change materially after we excluded those who reported use of cholesterol lowering drugs, suggesting that the observed association may not be due to potential adverse effects of these medicines.

Epidemiologic Studies of RLS and CVD Risk

Cross-sectional Studies

Most previously published cross-sectional studies have reported a positive association between RLS and cardiovascular disease. The association between RLS and heart disease was first reported in 4000 Swedish men. In that study participants with RLS more frequently reported heart problems (odds ratio (OR): 2.5; 95% CI: 1.4–4.3). This study was followed by a large multinational sample of European adults that reported an odds ratio of 1.4 (95% CI: 1.2–7.2) between RLS and self-reported heart disease. In the following 10 years, similar significant associations were also observed in several, but not all, cross-sectional studies. Among 18,980 adults living in Europe, ORs for RLS were 1.4 (95% CI: 1.1, 1.9) for subjects with heart disease and 1.4 (95% CI: 1.1, 1.6) for those with hypertension [14]. In the Wisconsin sleep cohort [28], Winkelman et al. observed a linear association between RLS symptom frequency and an increased likelihood of having cardiovascular disease. The OR for cardiovascular disease comparing restless legs ≥ 7 times/wk to no RLS was 2.6 (95% CI: 1.4, 4.8). A similar positive trend was seen for hypertension, but this was not significant. It is noteworthy that none of above studies employed the set of questions of RLS diagnosis recommended by IRLSSG, and, therefore, may introduce misclassification of RLS diagnosis. However, a recent cross-sectional study (*n* = 3831) using IRLSSG diagnostic criteria also found that restless legs ≥ 5 times/month were associated with 2 times increased risk of having coronary artery disease and cardiovascular disease [29]. The association was stronger in those with greater frequency or severity of RLS symptoms. Moreover, PLMS, which is seen in $\sim 80\%$ of RLS patients, has been shown to be associated with the severity of hypertension [30].

Prospective Studies

Prospective studies of RLS and future risk of CVD generated inconsistent results. The first prospective study on this topic included 1986 adults aged 55–69 years who lived in South Wales participating in the Caerphilly cohort [31]. In this study, restless legs symptom at baseline was associated with increased risk of stroke (OR = 1.7; 95% CI: 1.1, 2.6) and of ischemic heart disease (OR = 1.24; 95% CI: 0.89, 1.74) after 5 years' follow-up.

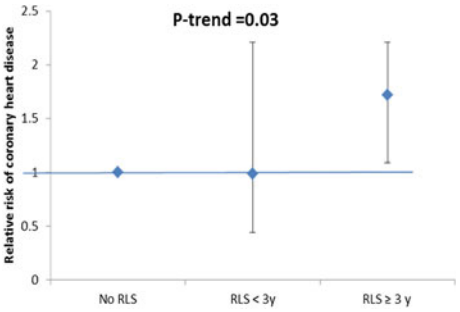

Fig. 6.2 Adjusted relative risks and 95% confidence intervals of myocardial infarction according to baseline restless legs syndrome (RLS) status [32]. Adjusted for age (years), BMI (<23, 23−, 25 −, 30−, 35+ kg/m^2), ethnicity (Caucasian or not), smoking status (never, past, current smoker: 1–14, 15–24, 25+ cigarettes/day), menopausal status (pre- or post-menopausal), menopausal hormone use (never, past, or current user:), alcohol intake (g/d: 0, 0.1–4.9, 5.0–9.9, 10.0–14.9, and >15), physical activity (quintiles), alterative healthy eating index (quintile) use of aspirin (yes or no), use of antidepressant, antihypertensive and anti-arrhythmic, presence of diabetes, arthritis, hypertension, high cholesterol, Parkinson's disease, cancer or renal failure (each, yes/no), use of iron specific supplements, sleep duration (hrs: ≤ 5, 6, 7, 8, or ≥ 9 per 24 h) and snoring frequency (every night, most nights, a few nights a week, occasionally, or almost never) (From [11], with permission.)

The authors conducted a large prospective study including 70, 694 women (mean age 67 years) who were free of myocardial infarction (MI) and stroke at the baseline (2002) were followed until 2008 [32]. Physician-diagnosed RLS was collected via questionnaire. Women with RLS at baseline had a marginally higher risk of developing MI ((RR) = 1.46; 95% confidence interval (CI): 0.98–2.19; $P = 0.06$) relative to women without RLS, after adjusting for age, body mass index, and other potential confounders. The multivariable-adjusted RRs were 0.99 (95% CI: 0.44–2.21; $P = 0.97$) for women with RLS less than three years and 1.72 (95% CI: 1.09, 2.21; $P = 0.02$) for those with RLS for three years or longer, as compared with women without RLS (P-trend = 0.03) (Fig. 6.2).

In contrast, another prospective analysis based on two ongoing US cohorts, the women's health study (WHS; $n = 29{,}756$) and the physicians' health study (PHS; $n = 19{,}182$) failed to find significant association between RLS and risk of any cardiovascular event [33]. In the women-only WHS cohort, RLS history was associated with small-to-modest but insignificant increased risk of major cardiovascular event (adjusted RR = 1.15; 95% CI: 0.88, 1.50), MI (adjusted RR = 1.01; 95% CI: 0.65, 1.57), stroke (adjusted RR = 1.29; 95% CI: 0.91, 1.82), coronary revascularization (adjusted RR = 1.24; 95% CI: 0.96, 1.59), and CVD death (adjusted RR = 1.11; 95% CI: 0.55, 2.25). In the men-only PHS, RLS was generally not associated with any cardiovascular events, with RRs ranged 0.73–1.22. Similarly, in the SHIP cohort, RLS was not associated with MI risk (adjusted RR = 0.53; 95% CI: 0.12, 2.27; incident MI case number = 37). However, there was a trend between RLS and higher risk of stroke in both SHIP (adjusted RR = 1.20;

95% CI: 0.48, 3.17) and the DHS (adjusted RR = 1.59; 95% CI: 0.17, 15.2). Of note, the incident stroke case numbers were rather small ($n < 36$ for both cohorts). Another limitation of these four cohorts is lack of information on RLS duration and severity, which could be of importance for development of unfavorable disease outcomes.

Potential Biological Mechanisms

RLS may lead to heart disease through several potential mechanisms: its negative effect on sleep quality and duration, the coexisting sympathetic activation accompanying PLMS, or the presence of common risk factors for heart disease. Reduced sleep quality could be an intermediate factor between the observed association of RLS and CVD. Insufficient and disturbed sleep has been noted among 75% of primary RLS sufferers. Both short and long sleep duration had been reported to increase the risk of heart disease. Dopamine dysfunction in CNS is a potential mechanism underlying the association of RLS and cardiovascular disease and hypertension. The dopaminergic system (e.g., D2-like receptor) is involved in the CNS regulation of systemic blood pressure [34]. Individuals with RLS may be at an increased risk of developing CHD because of the presence of PLMS, seen in 80–90% of patients with RLS. Coexisting PLMS are associated with sympathetically mediated elevations in both heart rate and blood pressure [35–40]. Arousals from sleep have also been shown to increase daytime pulse rate and blood pressure through elevated peripheral sympathetic tone in individuals without PLMS [41, 42]. The repeated long-standing increased heart rate and blood pressure may in turn increase the risk of CVD. Recent study suggests that RLS is characterized by autonomic dysregulation.

Periodic Limb Movements During Sleep

The phenomenon of PLMS occurs in up to 90% of persons suffering from RLS. When considering potential mechanisms that underlie the relationship between RLS and cardiovascular disease, PLMS are a conspicuous suspect. Physiologically, each individual movement of a PLMS cluster in the setting of RLS is associated with stereotypic increases in both heart rate and blood pressure on the order of 10 beats per minute and 20 systolic units. When PLMS is frequent, these repetitive autonomic surges can number into the hundreds each night. So, it is reasonable to question whether PLMS adds to cardiovascular burden. Despite the importance of doing so, to date, epidemiologic studies that have assessed the association between RLS and cardiovascular disease have not considered PLMS, as most were designed to address cardiovascular outcomes in relation to disorders other than RLS such as sleep apnea. Nevertheless, there is some epidemiologic data that have aimed to assess if PLMS relates to cardiovascular disease and the following section will outline some of them.

PLMS Prevalence and Comorbidities

The prevalence of PLMS in the general population is likely between 5 and 11%. In a sample of randomly chosen adults between the ages of 18 and 65 years, 7.6% of 592 individuals had PLMS recorded by PSG. Interestingly, PLMS was significantly more common in Caucasians than African-Americans (9.3% vs. 4.3%). The prevalence of PLMS also seems to increase in the elderly, as 45% of 427 elderly over 65 years were found to have PLMS on PSG; a similar number of persons with PLMS were found in a community-dwelling elderly female population. It is important to review the nonspecificity of PLMS as the majority of PLMS outcomes research has been carried out in populations not assessed for RLS symptomatology. Although PLMS is present in the great majority of persons suffering from RLS, these movements during sleep also occur in many circumstances or conditions outside of RLS and in many elderly persons without any sleep complaints. PLMS can be seen in conjunction with other disorders of sleep including obstructive sleep apnea, narcolepsy, and REM sleep behavior disorder, or in disease states outside of sleep including essential hypertension, congestive heart failure (CHF), and end-stage renal disease.

PLMS and Hypertension

As noted above, in subjects with RLS, individual movements within PLMS clusters are associated with discrete increases in blood pressure. In adults, these observations were noted in two separate but small studies in which 8 and 10 RLS subjects underwent polysomnography and noninvasive blood pressure measurement. Universally, in all subjects and with all movements, there were increases in blood pressure on the order of 25 mmHg systolic units when there was cortical arousal and 18 mmHg systolic units without arousal. In children PLMS also seems to associate with nocturnal hypertension. A study of 17 children with PLMS and 297 children without PLMS who were not assessed for RLS symptomatology, showed that the children with PLMS had an elevated odds of 6.25 (95% CI: 1.87, 20.88) of having nocturnal hypertension, although there was no difference in mean nocturnal blood pressures in the two groups.

Outside of the immediate sympathetic hyperactivity related to PLMS, there is also evidence that nocturnal PLMS associates with diurnal hypertension. In a sample of 91 patients (mean age 49.1 $\pm$ 2.3) with essential hypertension without information on RLS symptomatology, PLMS were found in 18.7% more than in the general population. Perhaps more striking was the higher rate of PLMS in patients with grade III than grades I and II hypertension (36.4% vs. 13%). A smaller study of patients with essential grade I hypertension, 14 hypertensive patients, and 28 age- and obesity-matched controls failed to show an increased rate of PLMS in those with hypertension. In a larger study of 861 patients with self-reported RLS symptoms, the odds of having hypertension was more than 2-fold (OR: 2.26; 95% CI: 1.28, 3.99) for persons with a PLMS frequency of more than 30 per hour of sleep, after controlling for age and body mass index.

It should be noted that the relationship between RLS and hypertension, as stated in previous sections of this chapter, is controversial. Data from both the Wisconsin Sleep and Sleep Heart Health cohorts, showed an unadjusted relationship between RLS and hypertension but these relationships became nonsignificant after controlling for age, sex, body mass index, and blood pressure. In the final section of this chapter concerning PLMS and incident cardiovascular disease, evidence further complicating this relationship between hypertension and PLMS will be considered.

PLMS in Chronic Disease

PLMS are very common in the setting of CHF, occurring in up to one-half of CHF patients. Most studies have found that about 20–25% of patients with CHF have PLMS but the significance of this finding is uncertain. In a longitudinal study of patients with CHF, 218 subjects with newly diagnosed systolic heart failure were divided into those having a PLMS frequency of more than 5 per hour of sleep (37%) and less than 5 per hour of sleep (63%). The presence of PLMS was associated with a greater than 2-fold increased hazard ratio of death (hazard ratio 2.42, 95% CI: 1.16, 5.02) after adjusting for age, heart failure severity, and sleep apnea. It should be noted that in this analysis, there was a difference in the two groups with those with PLMS compared to without PLMS being significantly older and having more severe heart failure. It is possible that the statistical adjustments were inadequate to offset the dissimilarity of the groups. Other studies have shown that approximately 20% of heart failure subjects have PLMS with an average PLMS index of about 35 per hour [43, 44]. In these studies, other than being older, those with PLMS did not differ from those without PLMS in terms of heart failure severity or presence of sleep disordered breathing, the caveat being the small number in these studies with 55 and 79 subjects, respectively.

PLMS is very prevalent in persons suffering chronic kidney disease, especially those undergoing hemodialysis. Although studies that have assessed the prevalence of PLMS in this population have been small, they have consistently shown that nearly 50% of those with end-stage renal disease have PLMS [45, 46]. Symptoms of RLS are also quite common among the renal disease population. In fact, the presence of RLS in addition to adversely affecting sleep and dialysis compliance has been shown to predict mortality. Mortality may also be increased for end-stage renal disease patients with frequent PLMS. In a study of 29 end-stage renal patients, those with PLMS > 20 per hour of sleep compared to those with less than 20 had 50% versus 10% mortality in 20 months ($p = 0.0007$). It is important to note the small sample size of 29 subjects and also that those with frequent PLMS were significantly older than those without PLMS. In a larger study of 150 renal failure patients, PLMS independently predicted 10-year risk of coronary heart disease risk, estimated using the Framingham Cardiovascular disease risk profile [47].

PLMS and Cardiovascular Disease

While there have been a number of studies which have looked at the potential association between RLS and cardiovascular disease in population samples, such epidemiologic studies are few in regard to PLMS and community samples. One

Table 6.1 Hazard ratios associating incident cardiovascular disease to periodic limb movement index and periodic limb movement arousal index

	N (%) of event	Relative hazard (95% CI)	
		Unadjusted	Fully adjusted[b]
PLMI			
Incident CVD	500 (17.30)		
PLMI <5	120 (14.23)	1.0 (ref)	1.0 (ref)
PLMI 5 to <30	136 (18.28)	1.32 (1.03–1.68)	1.31 (1.02–1.67)
PLMI 30+	244 (18.73)	1.38 (1.11–1.72)	1.27 (1.00–1.56)
P-trend		0.0055	0.0731
PLMAI			
Incident CVD	500 (17.30)		
PLMAI <1	171 (14.84)	1.0 (ref)	1.0 (ref)
PLMI 1 to <5	172 (18.05)	1.24 (1.00–1.53)	1.19 (0.96–1.47)
PLMI 5+	157 (20.00)	1.42 (1.14–1.76)	1.26 (1.01–1.57)
P-trend		0.0015	0.0402

Adjusted for clinic site, age, and body mass index

PLMI indicates periodic limb movement index; *PLMAI*, periodic limb movement arousal index; *CVD*, all-cause cardiovascular disease

[b]Adjusted for clinic site, age, body mass index, race, depression, prevalent diabetes mellitus, prevalent hypertension, smoking, alcohol use, physical activity, use of antidepressants, use of benzodiazepines, and apnea-hypopnea index

study looked at the association of PLMS on a single night sleep study and incident cardiovascular disease. This study consisted of 2911 community-dwelling older men with a mean age of 76.4 ± 5.5. In this sample, 2063 men (70.9%) had a PLMS index (PLMI) of more than 5 per hour and 1751 men (60.2%) had a PLMS arousal index (PLMAI) of more than 1 per hour. Impressively, 1313 men (45.1%) had a PLMI of greater than 30 per hour and 793 men (27.2%) had a PLMAI of greater than 5 per hour. In more than 4 years of follow-up, 500 men had a cardiovascular disease event consisting of myocardial infarction, unstable angina, revascularization procedure, stroke, or acute arterial occlusion or dissection. Both high PLMAI (>5/h) and PLMI categories (>30/h) compared to referent PLMAI < 1 and PLMI < 5 categories were associated with an approximately 25% increased risk of incident cardiovascular disease event. Most of these events were accounted for by coronary disease and peripheral arterial disease and less so by cerebrovascular disease. This association remained in the high PLMS categories after adjusting for multiple potential confounders (Table 6.1).

The study also aimed to assess the relationship between PLMS and hypertension. There was no association between either PLMI or PLMAI and incident hypertension. There was, however, an interaction between PLMI or PLMAI and prevalent hypertension relative to incident cardiovascular disease events, such that

Table 6.2 Hazard ratios associating incident cardiovascular disease to periodic limb movement index and periodic limb movement arousal index by prevalent hypertension

	No prevalent hypertension (n = 923)	Prevalent hypertension (n = 1986)	P-value for interaction[a]
PLMI Incident CVD			
PLMI <5	1.0 (ref)	1.0 (ref)	0.09
PLMI 5 to <30	1.83 (1.02–3.27)	1.23 (0.93–1.62)	
PLMI 30+	1.89 (1.11–3.22)	1.14 (0.90–1.47)	
P-trend	0.0115	0.3563	
PLMAI Incident CVD			
PLMAI <1	1.0 (ref)	1.0 (ref)	0.07
PLMI 1 to <5	1.66 (1.01–2.73)	1.10 (0.87–1.39)	
PLMI 5+	1.74 (1.04–2.93)	1.15 (0.90–1.48)	
P-trend	0.011	0.2478	

PLMI indicates periodic limb movement index; *PLMAI*, periodic limb movement arousal index; *CVD*, all-cause cardiovascular disease

[a]Adjusted for clinic site, age, BMI, race, depression, prevalent diabetes, smoking, alcohol use, physical activity, use of antidepressants, use of benzodiazepines, apnea-hypopnea index, and arousal index

significant association between PLMS frequency and incident cardiovascular disease events was only seen in those without prevalent hypertension. In those without prevalent hypertension, being in the highest PLMI or PLMAI categories compared to the lowest PLMS frequency categories was associated with a 89 and 74% increase risk, respectively, of having an incident cardiovascular disease event. This is shown in tabular format in Table 6.2 and graphic format in Fig. 6.3.

In conclusion, the association between RLS/PLMS and CVD and cardiovascular risk factors has been examined extensively during past decade. However, most of these studies are cross-sectional and thus the temporary relationship between RLS/PLMS and CVD cannot be determined. There are only few well-designed prospective studies on this topic available to date. Because of difference in RLS ascertainment (physician-diagnosis versus. questionnaire) and collected information (e.g., disease duration and severity), results generated from these prospective studies have been inconsistent. These studies are also limited by their short follow-up and relatively small sample number of incident cases and thus the estimation of effect size could not be stable. Further large-scale prospective studies which employ standardized approach for RLS/PLMS assessment and have longer follow-up period are warranted.

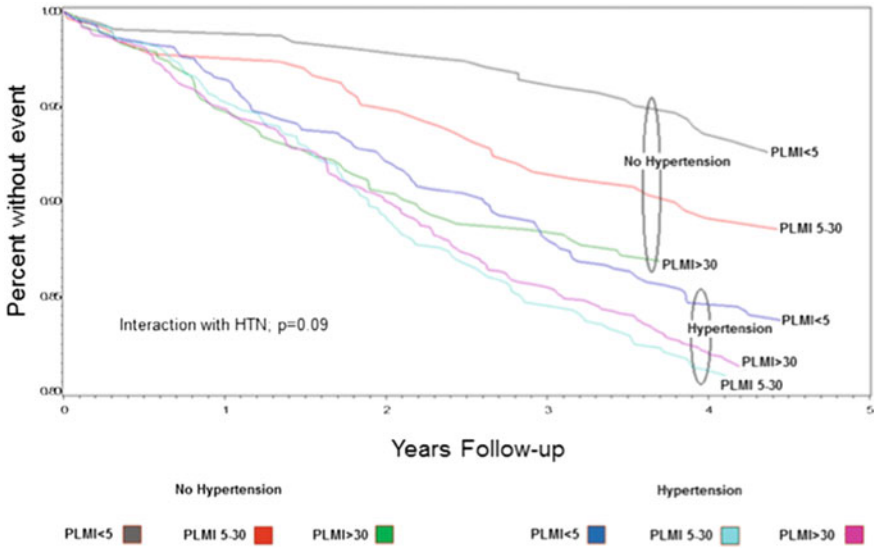

Fig. 6.3 Incident cardiovascular disease by PLMS frequency and hypertension

References

1. 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.
2. Earley CJ, Silber MH. Restless legs syndrome: understanding its consequences and the need for better treatment. Sleep Med. 2010;11:807–15.
3. Yang C, Winkelman JW. Clinical and polysomnographic characteristics of high frequency leg movements. J Clin Sleep Med. 2010;6:431–8.
4. Allen RP, Walters AS, Montplaisir J, Hening W, Myers A, et al. Restless legs syndrome prevalence and impact: REST general population study. Arch Intern Med. 2005;165:1286–92.
5. Hornyak M. Depressive disorders in restless legs syndrome: epidemiology, pathophysiology and management. CNS Drugs. 2010;24:89–98.
6. Ohayon MM, O'Hara R, Vitiello MV. Epidemiology of restless legs syndrome: a synthesis of the literature. Sleep Med Rev. 2012;16:283–95.
7. Loewen A, Siemens A, Hanly P. Sleep disruption in patients with sleep apnea and end-stage renal disease. J Clin Sleep Med. 2009;5:324–9.
8. Merlino G, Fratticci L, Valente M, Del Giudice A, Noacco C, et al. Association of restless legs syndrome in type 2 diabetes: a case-control study. Sleep. 2007;30:866–71.
9. Araujo SM, de Bruin VM, Nepomuceno LA, Maximo ML, Daher Ede F, et al. Restless legs syndrome in end-stage renal disease: clinical characteristics and associated comorbidities. Sleep Med. 2010;11:785–90.
10. Gao X, Schwarzschild MA, Wang H, Ascherio A. Obesity and restless legs syndrome in men and women. Neurology. 2009;72:1255–61.
11. Li Y, Walters AS, Chiuve SE, Rimm EB, Winkelman JW, et al. Prospective study of restless legs syndrome and coronary heart disease among women. Circulation. 2012;126:1689–94.

12. Li Y, Mirzaei F, O'Reilly EJ, Winkelman JW, Malhotra A, et al. Prospective study of restless legs syndrome and risk of depression in women. Am J Epidemiol. 2012;176:279–88.
13. Phillips B, Young T, Finn L, Asher K, Hening WA, et al. Epidemiology of restless legs symptoms in adults. Arch Intern Med. 2000;160:2137–41.
14. Ohayon MM, Roth T. Prevalence of restless legs syndrome and periodic limb movement disorder in the general population. J Psychosom Res. 2002;53:547–54.
15. Kim J, Choi C, Shin K, Yi H, Park M, et al. Prevalence of restless legs syndrome and associated factors in the Korean adult population: the Korean health and genome study. Psychiatry Clin Neurosci. 2005;59:350–3.
16. 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.
17. Winter AC, Berger K, Glynn RJ, Buring JE, Gaziano JM, et al. Vascular risk factors, cardiovascular disease, and restless legs syndrome in men. Am J Med. 2013; 126:228–35, e221–2.
18. Winter AC, Schurks M, Glynn RJ, Buring JE, Gaziano JM, et al. Vascular risk factors, cardiovascular disease, and restless legs syndrome in women. Am J Med. 2013;126:220–27, e221–2.
19. Sevim S, Dogu O, Camdeviren H, Bugdayci R, Sasmaz T, et al. Unexpectedly low prevalence and unusual characteristics of RLS in Mersin, Turkey. Neurology. 2003;61:1562–9.
20. Berger K, Luedemann J, Trenkwalder C, John U, Kessler C. Sex and the risk of restless legs syndrome in the general population. Arch Intern Med. 2004;164:196–202.
21. De Vito K, Li Y, Batool-Anwar S, Ning Y, Han J, et al. Prospective study of obesity, hypertension, high cholesterol and risk of restless legs syndrome. Mov Disord. 2014;29 (8):1044–52.
22. Szentkiralyi A, Volzke H, Hoffmann W, Happe S, Berger K. A time sequence analysis of the relationship between cardiovascular risk factors, vascular diseases and restless legs syndrome in the general population. J Sleep Res. 2013;22:434–42.
23. Ulfberg J, Nyström B, Carter N, Edling C. Prevalence of restless legs syndrome among men aged 18 to 64 years: an association with somatic disease and neuropsychiatric symptoms. Mov Disord. 2001;16:1159–63.
24. Phillips B, Hening W, Britz P, Mannino D. Prevalence and correlates of restless legs syndrome*. Chest. 2006;129:76–80.
25. Budhiraja P, Budhiraja R, Goodwin JL, Allen RP, Newman AB, et al. Incidence of restless legs syndrome and its correlates. J Clin Sleep Med JCSM Official Publ Am Acad Sleep Med. 2012;8:119–24.
26. Szentkiralyi A, Volzke H, Hoffmann W, Baune BT, Berger K. The relationship between depressive symptoms and restless legs syndrome in two prospective cohort studies. Psychosom Med. 2013;75:359–65.
27. Schlesinger I, Erikh I, Avizohar O, Sprecher E, Yarnitsky D. Cardiovascular risk factors in restless legs syndrome. Mov Disord. 2009;24:1587–92.
28. 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.
29. 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.
30. Espinar-Sierra J, Vela-Bueno A, Luque-Otero M. Periodic leg movements in sleep in essential hypertension. Psychiatry Clin Neurosci. 1997;51:103–7.
31. Elwood P, Hack M, Pickering J, Hughes J, Gallacher J. Sleep disturbance, stroke, and heart disease events: evidence from the Caerphilly cohort. J Epidemiol Commun Health. 2006;60:69–73.
32. Li Y, Walters AS, Chiuve SE, Rimm EB, Winkelman JW, et al. Prospective study of restless legs syndrome and coronary heart disease among women. Circulation. 2012;126:1689–94.

33. Winter AC, Schurks M, Glynn RJ, Buring JE, Gaziano JM, et al. Restless legs syndrome and risk of incident cardiovascular disease in women and men: prospective cohort study. BMJ Open. 2012;2:e000866.
34. Jose PA, Eisner GM, Felder RA. Role of dopamine in the pathogenesis of hypertension. Clin Exp Pharmacol Physiol Suppl. 1999;26:S10–3.
35. Ali NJ, Davies RJ, Fleetham JA, Stradling JR. Periodic movements of the legs during sleep associated with rises in systemic blood pressure. Sleep. 1991;14:163–5.
36. Gangwisch JE, Heymsfield SB, Boden-Albala B, Buijs RM, Kreier F, et al. Short sleep duration as a risk factor for hypertension: analyses of the first national health and nutrition examination survey. Hypertension. 2006;47:833–9.
37. 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.
38. Siddiqui F, Strus J, Ming X, Lee IA, Chokroverty S, et al. Rise of blood pressure with periodic limb movements in sleep and wakefulness. Clin Neurophysiol. 2007;118:1923–30.
39. Walters AS, Rye DB. Review of the relationship of restless legs syndrome and periodic limb movements in sleep to hypertension, heart disease, and stroke. Sleep. 2009;32:589–97.
40. Winkelman JW. The evoked heart rate response to periodic leg movements of sleep. Sleep. 1999;22:575–80.
41. Davies RJ, Belt PJ, Roberts SJ, Ali NJ, Stradling JR. Arterial blood pressure responses to graded transient arousal from sleep in normal humans. J Appl Physiol. 1993;74:1123–30.
42. Ekstedt M, Akerstedt T, Soderstrom M. Microarousals during sleep are associated with increased levels of lipids, cortisol, and blood pressure. Psychosom Med. 2004;66:925–31.
43. Javaheri S. Sleep disorders in systolic heart failure: a prospective study of 100 male patients. The final report. Int J Cardiol. 2006;106:21–8.
44. Skomro R, Silva R, Alves R, Figueiredo A, Lorenzi-Filho G. The prevalence and significance of periodic leg movements during sleep in patients with congestive heart failure. Sleep Breath. 2009;13:43–7.
45. Kimmel PL, Miller G, Mendelson WB. Sleep apnea syndrome in chronic renal disease. Am J Med. 1989;86:308–14.
46. Pressman MR, Benz RL, Schleifer CR, Peterson DD. Sleep disordered breathing in ESRD: acute beneficial effects of treatment with nasal continuous positive airway pressure. Kidney Int. 1993;43:1134–9.
47. Lindner A, Fornadi K, Lazar AS, Czira ME, Dunai A, et al. Periodic limb movements in sleep are associated with stroke and cardiovascular risk factors in patients with renal failure. J Sleep Res. 2012;21:297–307.

Heart Rate and Blood Pressure Changes Associated with Periodic Limb Movements

7

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Over the last two decades, considerable data has been published to elaborate the association between periodic limb movements in sleep (PLMS) with heart rate (HR) and blood pressure (BP), making PLMS as a potential and an emerging cardiovascular and cerebrovascular risk factor [1]. This chapter will review the present data available to establish the relationship of PLMS with HR and BP.

HR and BP Correlate of LMS in Controls and Patients

Heart Rate and PLMS

Multiple recent studies on HR and PLMS have convincingly established that PLMS are associated with significant HR variability (HRV); PLMS with arousals are associated with a higher degree of autonomic activation. Winkelman et al. [2] first demonstrated changes in the HR with PLMS in eight patients. HR was recorded for 10 cardiac cycles before and after the onset of PLMS; no statistical significant difference was noted in HR rises with PLMS with or without arousal. HR began to peak three cycles prior to onset of PLMS, peaked at 4 cycles after and then declined below baseline at cardiac cycles 8–10. The authors concluded that pulse rate elevation occurred with PLMS irrespective of the presence of arousal. This study was

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followed by a similar study by Sforza et al. [3] where electroencephalographic (EEG) activation and tachycardia were noticed in PLMS with or without arousals. In this study 10 patients with restless legs syndrome (RLS)/PLMS were included. EEG correlates of PLMS were analyzed by visual scoring and spectral analysis during PLMS with and without arousals; also electrocardiographic R-R wave interval was analyzed. 34% of PLMS were associated with arousals lasting >3 s; 3% of PLMS were associated with arousals lasting <3 s and the rest were associated with changes in the EEG theta and delta activity. Tachycardia was seen with all types of PLMS; the authors concluded for a presence of hierarchy of arousal from autonomic activation, to bursts of delta activity, to alpha activity, and then to a full awakening. Ferri et al. [4] studied the changes in HR and EEG spectra not only in PLMS but also in nonperiodic (isolated) leg movements (NPLMS) in 16 RLS patients. EEG activation specifically in the delta band was seen prior to PLMS and NPLMS. EEG activation preceded leg movements (LM) in both NREM and REM sleep for NPLMS and only in NREM sleep for PLMS. In a subsequent study; Sforza et al. [5] studied 12 patients with RLS/PLMS. HR and EEG spectral analyses were done for 10 s before and 10 s after PLMS onset. PLMS were divided into those with arousals, without arousals and with K-complex or delta burst. The authors found an increase in HR and delta band activity before all three types of PLMS and concluded that cardiac and cerebral changes occur with PLMS with or without visible arousal and confirmed their prior theory of a hierarchy of arousal. A similar study [6] analyzed the effects of age and gender on HR changes associated with PLMS in 42 RLS patients. PLMS were again found to be associated with HR changes, i.e., tachycardia followed by bradycardia. Women were noticed to have higher amplitude of bradycardia. In 2004, Ferrillo et al. [7] studied the temporal pattern of cardiac and EEG activation changes with PLMS in NREM sleep, in 5 patients without RLS and with periodic limb movement disorder (PLMD). HR activation and delta activity power were noted 4.25 and 3 s, respectively, before PLMS onset. With the use of the spectral analysis, HRV and EEG activation were measured as a marker for autonomic activation and sleep instability [7, 8]. In one study, autonomic activation was reported several seconds before the EEG activation and movement; Guggisberg et al. [9] demonstrated that the sympathetic activation accompanying PLMS (in subjects without RLS) is greater than for all movement types, as measured by HRV spectra. However, the results of this study were possibly biased by some methodological factor [10]. Lavoie et al. [11] also demonstrated that the EEG and HR activation with PLMS is more evident during sleep than wakefulness.

Blood Pressure and PLMS

Even if already implicitly mentioned by Lugaresi et al. [12] in 1972, BP variation with periodic limb movements in sleep was first demonstrated by Ali et al. [13] in 1991 in a patient with narcolepsy. This phenomenon was separately analyzed in two different polysomnographic labs. RLS patients with PLMS were monitored

overnight with concomitant continuous BP measurement. Both studies showed statistically significant elevation of systolic and diastolic BP with periodic limb movements in sleep and wakefulness as compared to fake PLMS [14, 15]. The elevation in BP was higher in PLMS with cortical arousal, as compared with PLMS without cortical arousal. A recent study demonstrated a rise in BP with PLMS in healthy normal subjects [16]. PLMS were associated with significant increases of HR, systolic BP and diastolic BP in RLS patients and healthy subjects; however, cardiovascular increases were more pronounced in RLS subjects than healthy subjects, in agreement with a previous study which had shown the same difference for HR only [17].

Effects of the Interaction Between PLMS and Apnea on HR and BP

As also seen above, PLMS are embedded in a general sleep oscillatory pattern involving not only the motor system but also the autonomic function, cortical EEG activities, the respiratory system and several other functions too [18, 19]. Thus, the interaction between PLMS and these systems is of utmost importance.

The amplitude of the HR changes associated with PLMS varies with age and is higher with bilateral movements as compared to unilateral movements [4]. HRV is higher when LM are associated with respiratory events. In 2006, Yang et al. [20] demonstrated that maximal HR rise for respiratory events with leg movements (7.9 beats/min) was significantly greater than for respiratory events without leg movements (5.1 beats/min). In the context of sleep apnea, it is important to note that the interaction can be bidirectional with the rhythm of apnea events taking the lead and forcing PLMS to change their time structure with longer intervals and clustered around the end of the respiratory pauses [21, 22].

Searching for the Effects of PLMS-Related Rises in HR and BP

Repetitive abnormal HR and BP rises can play a role in increased cardiovascular risk in RLS patients with PLMS. Trotti et al. studied the level of C-reactive protein (CRP) in 137 RLS patients with PLMS and found an association of high CRP with PLMS index >45/h, suggesting again a relation between systemic inflammation, cardiovascular risk and RLS [23]; however, a prior study showed no relation of RLS and CRP and other inflammatory markers [24]. Becki et al. [25] measured the serum level of Lipoprotein-associated phospholipase A2 in 70 newly polysomnographically diagnosed PLMS patients. The levels were significantly high in patients with PLMS as compared to controls. The study also noticed a similar relation with CRP and high PLMS index. The authors concluded that risk of vascular events may be increased in patients with PLMS. Chronic sleep restriction from RLS/PLMS can

potentially increase inflammatory activity, subsequently contributing to the development of cardiovascular disease [26].

Various epidemiological, retrospective and anecdotal studies in the past two decades have shown association of vascular risk factors such as hypertension, heart disease, and stroke with RLS and PLMS.

Systemic Hypertension and PLMS

Espinar-Sierra et al. [27] in 1997, found PLMS in 18% of a group of 91 subjects with essential hypertension, a percentage considerably higher than that found in normal controls. The prevalence of PLMS was proportional to the severity of hypertension; Grade 1 and 2 hypertension had a PLMS prevalence of 13%, whereas Grade 3 hypertension had a prevalence of 36.4%. This relationship was independent of confounding risk factors such as age, sex, obesity, alcohol use, smoking, apnea severity, and use of anti-hypertensive medications. In a larger study of 861 patients, Billars et al. [28] also found a direct relation between PLMS and systemic hypertension as well. The authors found a higher risk of having hypertension in patients with PLMS index 50/h or more.

Heart Disease and PLMS

In one of the largest studies on RLS and coronary artery disease [26], more than 70,000 women, some of them with RLS were prospectively followed for 3 years and were found to have a higher risk of developing coronary artery disease. The prevalence of PLMS and their effect on sleep and daytime alertness were studied in 23 men with severe, stable congestive heart failure and 9 healthy control subjects [29]. Patients with congestive heart failure had a more frequently moderately severe PLMS, higher amount of NREM sleep and shorter mean sleep latency the day after the recording. In another large prospective case series of heart failure patients, without control group, Javaheri et al. [30] found that 20% of patients had PLMS with an average index of 35/h. PLMS also had a slightly higher number of arousals (3.4 ± 2 per hour). In a prospective study, Skomro et al. [31] enrolled 79 congestive heart failure patients who underwent echocardiogram and in lab polysomnograms. The authors found a 19% prevalence of PLMS >5/h. No difference was seen in sleep architecture or daytime sleepiness in patients with or without PLMS. This study also confirmed a significant elevation of HR after PLMS (80.1 ± 9.4 vs. 81.5 ± 9.2; $p < 0.001$). After the report of a small study indicating PLMS as a potential predictor of mortality in patients with renal insufficiency [32], in 2011 Yumino et al. [33] analyzed the relation between PLMS and mortality in patients with systolic heart failure; 218 patients with congestive heart failure were prospectively enrolled over 7 years and underwent polysomnographic studies. Eighty-one patients (37%) had PLMS >5/h; these patients were older and had lower left ventricular ejection fraction. The authors also found a significant higher mortality rate in patients with PLMS index >5/h than those with PLMS index <5/h (10.4 vs. 3.4 deaths/100 patient-years, $p = 0.002$). Even after adjusting for confounding variables, PLMS index >5/h was found to be an independent risk factor for mortality (hazard ratio 2.42, 95% CI = 1.16–5.02, $p = 0.018$). In summary, the

prevalence of PLMS in patients with congestive heart failure varies from 19 to 35%. PLMS index has recently been proposed as an independent risk factor for mortality.

Stroke and PLMS

Very few studies have tried to address the relation of stroke with PLMS and RLS. Only few case reports [34–36] suggested the onset of PLMS as a result of stroke. The strokes occurred in the left corona radiata, left pallidum and internal capsule, and right basal ganglia. More recently, 35 patients with acute supratentorial ischemic stroke and 35 age- and sex-matched control subjects were studied [37]; 27 patients (77.2%) had PLMS index >5/h, while only 10 participants (28.5%) in the control group had PLMS index >5/h ($p < 0.05$). A retrospective analysis [38] of 40 stroke patients and 40 controls matched for age, sex, and risk factors showed 19 patients (47.5%) and 5 controls (12.5%) had a PLMS index >5/h ($p < 0.001$). Walters et al. [39] compared the MRI scans from patients with RLS to those of control subjects without RLS; when controlled for age, gender, and comorbidities, the likelihood for any stroke was higher in patients with RLS compared to controls, but was not significant (OR 2.46; 95% CI = 0.97–6.28; $p = 0.06$). Patients with RLS also had a nonsignificantly higher incidence of silent infarctions (19.2% of patients vs. 12.0% of controls), larger subcortical lesions, and slightly higher mean cerebral atrophy scores, compared to age-matched controls without RLS.

Challenging the Cause/Effect Relationship Between PLMS and EEG or Autonomic Activations

It has been known, for decades, that the rhythm of PLMS is strictly interconnected with a general sleep oscillatory pattern. Already in 1972, Lugaresi et al. [12] showed in controls and patients with sleep apnea, primary alveolar hypoventilation, RLS and PLMS, that several vegetative and somatic phenomena (systemic arterial pressure, pulmonary arterial pressure, cardiac rate, arteriolar tone, breathing, peripheral motor neuron excitability and level of consciousness) tended to oscillate or repeat themselves periodically every 20–30 s during sleep, and especially during light sleep. This generalized, rather regular, oscillatory pattern, involving primarily the EEG, was later shown to be a feature of NREM sleep, occupying a variable portion of it, depending on age and clinical condition of the subject and was termed and coded as cyclic alternating pattern [40, 41]. As already noticed by Lugaresi et al. [12], these oscillations can be observed also without the participation of one or two of the above systems, or even involve only one parameter under analysis [18].

Regarding PLMS, a series of observational and experimental studies have been published with the aim to clarify their role and participation to this general sleep oscillatory behavior. First of all PLMS, that have been reported in patients with spinal cord injury [42–44], can occur in these patients without any accompanying HR rise and asynchronously with EEG transients [45]. This can also be observed in

other patients with an impaired anatomical connection between the spinal cord and the cortex [46].

Manconi et al. [47] have reported that different drugs can selectively abolish PLMS, without affecting EEG oscillations (dopamine agonists) or dampen EEG oscillations without modifications of PLMS (benzodiazepines). On the contrary, experimentally increasing EEG and autonomic oscillations during sleep is not accompanied by the appearance of PLMS in young normal subjects [48].

All this demonstrates that LMs during sleep can be dissociated from arousals (and its autonomic correlates) in a variety of conditions including pharmacological interventions, experimental procedures, and pathological states inducing an anatomical/functional disconnection between the spinal cord and higher nervous structures.

The possibility to dissociate events that occur often as a cluster, such as cortical arousals, autonomic events, and PLMS, suggests that the interrelationships between these events are not likely to follow the simple paradigm of any one event leading to another; however, the lack of a cause/effect relationship between these events does not exclude the possibility that, when they do occur concurrently, one modifies the biological effects of the other [20]. The resulting possibly enhanced effect may represent the basis of adverse consequences of various clinical conditions in which PLMS are particularly abundant such as RLS [1, 49] or PLMD [50].

References

1. Walters AS, Rye DB. Review of the relationship of restless legs syndrome and periodic limb movements in sleep to hypertension, heart disease, and stroke. Sleep. 2009;32:589–97.
2. Winkelman JW, Cunningham S. Autonomic consequences of periodic leg movements of sleep. Sleep. 1998;21(suppl):S67.
3. Sforza E, Nicolas A, Lavigne G, Gosselin A, Petit D, Montplaisir J. EEG and cardiac activation during periodic leg movements in sleep: support for a hierarchy of arousal responses. Neurology. 1999;52:786–91.
4. Ferri R, Zucconi M, Rundo F, Spruyt K, Manconi M, Ferini-Strambi L. Heart rate and spectral EEG changes accompanying periodic and nonperiodic leg movements during sleep. Clin Neurophsiol. 2007;118:438–48.
5. 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.
6. Gosselin N, Lanfranchi P, Michaud M, Fantini L, Carrier J, Lavigne G, Montplaisir J. Age and gender effects on heart rate activation associated with periodic leg movements in patients with restless legs syndrome. Clin Neurophysiol. 2003;114:2188–95.
7. Ferrillo F, Beelke M, Canovaro P, Watanabe T, Aricò D, Rizzo P, Garbarino S, Nobili L, De Carli F. Changes in cerebral and autonomic activity heralding periodic limb movements in sleep. Sleep Med. 2004;5:407–12.
8. Sforza E, Pichot V, Barthelemy JC, Haba-Rubio J, Roche F. Cardiovascular variability during periodic leg movements: a spectral analysis approach. ClinNeurophysiol. 2005;116: 1096–104.
9. Guggisberg AG, Hess CW, Mathis J. The significance of the sympathetic nervous system in the pathophysiology of periodic leg movements in sleep. Sleep. 2007;30:755–66.

10. Ferri R, Zucconi M, Rye D. Heart rate changes accompanying periodic leg movements during sleep in narcoleptic patients. Sleep. 2011;34:409–10.
11. Lavoie S, de Bilbao F, Haba-Rubio J, Ibanez V, Sforza E. Influence of sleep stage and wakefulness on spectral EEG activity and heart rate variations around periodic leg movements. Clin Neurophysiol. 2004;115:2236–46.
12. Lugaresi E, Coccagna G, Mantovani M, Lebrun R. Some periodic phenomena arising during drowsiness and sleep in man. Electroencephalogr Clin Neurophysiol. 1972;32:701–5.
13. Ali NJ, Davies RJO, Fleetham JA, Stradling JR. Periodic movements of the legs during sleep associated with rises in systemic blood pressure. Sleep. 1991;14:163–5.
14. 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.
15. 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.
16. Pennestri MH, Montplaisir J, Fradette L, Lavigne G, Colombo R, Lanfranchi PA. Blood pressure changes associated with periodic leg movements during sleep in healthy subjects. Sleep Med. 2013;14:555–61.
17. Manconi M, Ferri R, Zucconi M, et al. Effects of acute dopamine-agonist treatment in restless legs syndrome on heart rate variability during sleep. Sleep Med. 2011;12:47–55.
18. Ferri R. Two legs, one heart, one sleeping brain. Sleep Med. 2006;7:299–300.
19. Ferri R. The time structure of leg movement activity during sleep: the theory behind the practice. Sleep Med. 2012;13:433–41.
20. Yang CK, Jordan AS, White DP, Winkelman JW. Heart rate response to respiratory events with or without leg movements. Sleep. 2006;29:553–6.
21. Manconi M, Zavalko I, Bassetti CL, Colamartino E, Pons M, Ferri R. Respiratory-related leg movements and their relationship with periodic leg movements during sleep. Sleep. 2014;37 (3):497–504.
22. Fulda S, Zavalko I, Ferri R, Manconi M. Respiratory-related leg movements: What is the evidence behind the results? Sleep. 2013;35(suppl):A241–2.
23. Trotti LM, Rye DB, De Staercke C, Hooper WC, Quyyumi A, Bliwise DL. Elevated C-reactive protein is associated with severe periodic leg movements of sleep in patients with restless legs syndrome. Brain Behav Immun. 2012;26:1239–43.
24. Siddiqui F, Strus J, Sun YJ, Walters AS. No significant difference in cytokine levels in patients with restless legs syndrome versus controls - preliminary data. Sleep Med. 2007;8:98–9.
25. Bekci TT, Kayrak M, Kiyici A, Ari H, Teke T, Maden E, Akilli H. The relation between Lp-PLA2 levels with periodic limb movements. Sleep Breath. 2012;16:117–22.
26. Li Y, Walters AS, Chiuve SE, Rimm EB, Winkelman JW, Gao X. Prospective study of restless legs syndrome and coronary heart disease among women. Circulation. 2012;126:1689–94.
27. Espinar-Sierra J, Vela-Bueno A, Luque-Otero M. Periodic leg movements in sleep in essential hypertension. Psychiatry Clin Neurosci. 1997;51:103–7.
28. Billars L, Hicks A, Bliwise D, Sigmundsson T, Sigurdsson A, Kristjansson K, Gulcher J, Stefansson K, Rye D. Hypertension risk and PLMS in restless legs syndrome. Sleep. 2007;30: A297–8.
29. Hanly PJ, Zuberi-Khokhar N. Periodic limb movements during sleep in patients with congestive heart failure. Chest. 1996;109:1497–502.
30. Javaheri S. Sleep disorders in systolic heart failure: a prospective study of 100 male patients. The final report. Int J Cardiol. 2006;106:21–8.
31. Skomro R, Silva R, Alves R, Figueiredo A, Lorenzi-Filho G. The prevalence and significance of periodic leg movements during sleep in patients with congestive heart failure. Sleep Breath. 2009;13:43–7.
32. Benz RL, Pressman MR, Hovick ET, Peterson DD. Potential novel predictors of mortality in end-stage renal disease patients with sleep disorders. Am J Kidney Dis. 2000;35:1052–60.

33. Yumino D, Wang H, Floras JS, Newton GE, Mak S, Ruttanaumpawan P, Parker JD, Bradley TD. Relation of periodic leg movements during sleep and mortality in patients with systolic heart failure. Am J Cardiol. 2011;107:447–51.
34. Kang SY, Sohn YH, Lee IK, Kim JS. Unilateral periodic limb movement in sleep after supratentorial cerebral infarction. Parkinsonism Relat Disord. 2004;10:429–31.
35. Lee JS, Lee PH, Huh K. Periodic limb movements in sleep after a small deep subcortical infarct. Mov Disord. 2005;20:260–1.
36. Anderson KN, Bhatia KP, Losseff NA. A case of restless legs syn-drome in association with stroke. Sleep. 2005;28:147–8.
37. Benbir G, Karadeniz D. Periodic leg movements in sleep in patients with supratentorial cerebral infarction. Acta Neurol Belg. 2012;112:27–32.
38. Coelho FM, Georgsson H, Narayansingh M, Swartz RH, Murray BJ. Higher prevalence of periodic limb movements of sleep in patients with history of stroke. J Clin Sleep Med. 2010;6:428–30.
39. Walters AS, Moussouttas M, Siddiqui F, Silveira DC, Fuentes K, Wang L, Berger K. Prevalence of stroke in restless legs syndrome: initial results point to the need for more sophisticated studies. Open Neurol J. 2010;4:73–7.
40. Terzano MG, Mancia D, Salati MR, Costani G, Decembrino A, Parrino L. The cyclic alternating pattern as a physiologic component of normal NREM sleep. Sleep. 1985;8: 137–45.
41. Parrino L, Ferri R, Bruni O, Terzano MG. Cyclic alternating pattern (CAP): the marker of sleep instanbility. Sleep Med Rev. 2012;16:27–45.
42. Brown LK, Heffner JE, Obbens EA. Transverse myelitis associated with restless legs syndrome and periodic movements of sleep responsive to an oral dopaminergic agent but not to intrathecal baclofen. Sleep. 2000;23:591–4.
43. Lee MS, Choi YC, Lee SH, Lee SB. Sleep-related periodic leg movements associated with spinal cord lesions. Mov Disord. 1996;11:719–22.
44. Nogues M, Cammarota A, Leiguarda R, Rivero A, Pardal A, Encabo H. Periodic limb movements in syringomyelia and syringobulbia. Mov Disord. 2000;15:113–9.
45. Salminen AV, Manconi M, Rimpilä V, Luoto TM, Koskinen E, Ferri R, Öhman J, Polo O. Disconnection between periodic leg movements and cortical arousals in spinal cord injury. J Clin Sleep Med. 2013;9:1207–9.
46. Raggi A, Ferri R. Sleep disorders in neurodegenerative diseases. Eur J Neurol. 2010;17: 1326–38.
47. Manconi M, Ferri R, Zucconi M, Bassetti C, Fulda S, Aricò D, Ferini-Strambi L. Dissociation of periodic leg movements from arousals in restless legs syndrome. Ann Neurol. 2012;71:834–44.
48. Ferri R, Manconi M, Aricò D, Punjabi NM, Zucconi M. Experimentally induced arousals do not elicit periodic leg motor activity during sleep in normal subjects. Sleep Med. 2013;14: 85–90.
49. 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.
50. Saletu M, Anderer P, Saletu B, Hauer C, Mandl M, Semler B, Saletu-Zyhlarz G. Sleep laboratory studies in periodic limb movement disorder (PLMD) patients as compared with normals and acute effects of ropinirole. Hum Psychopharmacol. 2001;16:177–87.

8 Willis–Ekbom Disease, Periodic Limb Movements of Sleep, and Cardiovascular Disease: Putative Mechanisms and Implications for Long-Term Treatment

Lynn Marie Trotti

As detailed in earlier chapters, there are compelling although not always consistent epidemiological associations between Willis–Ekbom Disease (WED) and/or periodic limb movements during sleep (PLMS) and cardiovascular disease (CVD). At present, the pathway or pathways of causality are somewhat speculative. That is, it remains to be determined whether WED/PLMS cause CVD, share common risk factors or pathogenesis with CVD, are caused by CVD, or are markers for clinical or subclinical CVD. It is possible, perhaps even likely, that a number of different causal relationships may be acting at the same time [1] (Fig. 8.1). In this chapter, we will discuss available evidence for or against these different directions of causality, then briefly discuss the potential implications for WED/PLMS treatment.

Mechanisms by Which WED and/or PLMS Could Cause Cardiovascular Disease

Several potential mechanisms have been proposed by which WED or PLMS could cause CVD, including insufficient sleep time, mood disturbance, and sympathetic overactivity related to PLMS. Insufficient sleep may be caused by WED either because the waking sensory symptoms delay sleep onset (at the start of the night or after an awakening) or because the associated PLMS result in arousal/awakening from sleep. In the large REST study, a detailed epidemiologic investigation of over 1000 WED sufferers, 75% of people with WED reported sleep disruption (manifesting as difficulty falling asleep, difficulty remaining asleep, disturbed sleep,

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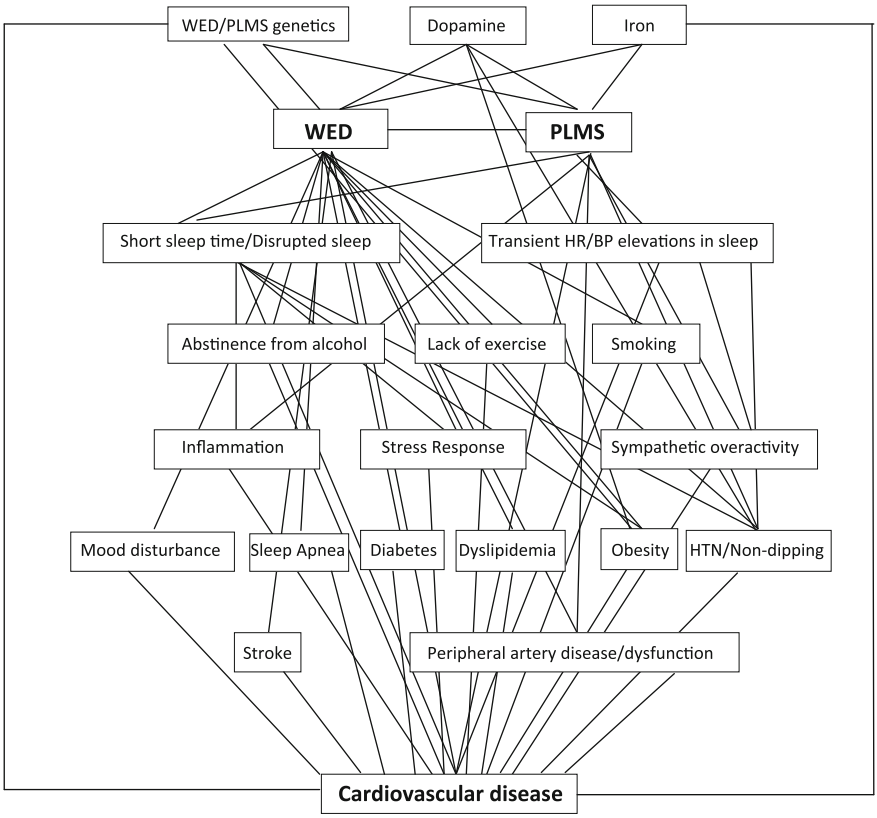

Fig. 8.1 Relationships between Willis–Ekbom disease (WED), periodic limb movements of sleep (PLMS), and cardiovascular disease are complex and potentially multidirectional

insufficient sleep, or some combination of these) [2]. Problems with sleep related to WED were rated as the most distressing part of the WED experience by nearly 40% [2]. Sleep deprivation has been consistently associated with features of CVD [3]. There are multiple mechanisms by which sleep deprivation might cause CVD that could be at play in WED patients, including obesity/metabolic dysregulation [4], inflammation [5, 6], hypertension [7, 8], alterations of the stress response [9], and so on. However, it is worth noting that not all studies that have found an association between WED and CVD have shown that it is mediated by sleep time. In particular, in their prospective study, Li et al. found an increase in incident CVD events in chronic WED sufferers that was independent of short sleep time [10].

WED is associated with impaired mood, although not necessarily fully causal to mood symptoms [11, 12]. Supporting the idea that WED may contribute directly to severity of mood symptoms, treatment of WED may improve severity of mood disturbance [13, 14]. Mood disorders are themselves associated with, and may predict incident development of, CVD [15, 16]. Thus WED-induced mood

disturbance might be the intermediary by which WED causes CVD [1, 17]. Alternatively, to the extent that WED or PLMS serve as a physiologic stressor, they might in turn cause CVD by this mechanism. Some authors have suggested that sympathetic overactivity related to WED symptoms might impair baroreceptor modulation and thus increase blood pressure, akin to the effects seen in sleep deprivation or sleep apnea [18]. Finally, although small early studies did not demonstrate any relationship between cortisol levels and WED [19, 20], a larger study has recently confirmed that WED patients have increased nocturnal urinary cortisol levels, which might contribute to CVD [21]. At this point, it is unclear whether cortisol abnormalities result in WED symptoms or the reverse, but it is biologically plausible that the distress from WED or associated sleep disruption results in elevations in cortisol [21].

Separate from these possibilities, much of the research assessing a possible causal link between WED/PLMS and CVD has focused on the interplay between WED, PLMS, repetitive nocturnal elevations in blood pressure and heart rate occurring with PLMS, and hypertension (HTN). Results from cross-sectional studies evaluating the association between WED and hypertension have been quite mixed, with positive [18, 22–24], null [25, 26], and inverse [27, 28] associations all reported. A recent meta-analysis reported 10 of 17 studies investigating a potential link between HTN and WED showing a significant positive association [1]. Some of these studies have suggested a dose effect of WED symptom frequency or severity on the likelihood of hypertension [23], such that the distribution of symptom severity across different study populations might account for the discrepant study findings [29]. The relationship might be bidirectional, as suggested by a study of two separate cohorts, one of which demonstrated that hypertension at baseline predicted the subsequent development of WED [30]. Importantly, studies assessing a WED and HTN association have typically not measured PLMS, which might drive the association with hypertension more strongly than the WED symptoms themselves (and, to the extent that asymptomatic PLMS may be present before the onset of WED symptoms, might obscure a temporal relationship between hypertension and WED). WED severity and PLMS are only modestly correlated (Pearson's correlations $r = 0.22–0.46$) (52–54), so without direct measurement of PLMS, it may be hard to accurately assess the relationship of WED and hypertension. This is suggested by studies by Billars [31] and Espinar-Sierra [32], which demonstrated dose response relationships between PLMS and HTN. However, considering only those patients with grade I hypertension (i.e., mild HTN) versus controls results in no difference in PLMS between groups [33], suggesting that a certain degree of PLMS or HTN severity may be necessary to drive the association. Among patients with heart failure, PLMS do not appear to be positively associated with prevalent hypertension [34, 35], and may even be negatively associated [36].

Individual leg movements during sleep are accompanied by transient increases in heart rate and blood pressure in patients with WED as well as in those with PLMS but without any sleep symptoms [37–43]. Whether this cardiovascular activation is a result of PLMS themselves is an unresolved question. Most, although not all, studies assessing heart rate changes associated with limb movements have shown a

change in heart rate that begins before the onset of movement as measured by surface EMG of the anterior tibialis muscle [39–43]. Although this suggests that the leg movements must not be causing the autonomic activation, there are several caveats of importance. First, although the default muscle with which to study PLMS is the anterior tibialis, only 32–53% of PLMS in WED patients begin in the anterior tibialis muscle [44, 45], so a careful evaluation of the relative onset of movement and cardiovascular activation will require monitoring of multiple muscle groups. Second, other features of limb movements do appear to affect the amplitude of autonomic activation, suggesting that the movement at a minimum modifies the autonomic response. Specifically, movements that are bilateral, have a shorter intermovement interval or are more frequent, or have a longer movement duration are associated with greater autonomic activation [42, 46, 47]. Changes in heart rate and blood pressure are also known to occur in association with apneas, and the magnitude of these changes is increased in those apneas associated with a leg movement relative to those apneas without leg movement [48], suggesting an additive effect from the leg movement.

Several alternate explanations for the coexistence of movement and autonomic activation may be hypothesized. First, the increase in heart rate and blood pressure might be a physical consequence of the movement itself, for example, due to increased venous return caused by movement [49]. However, voluntary leg movements during wakefulness that simulate PLMS are not associated with the same pattern of autonomic activation (either heart rate or blood pressure), suggesting this explanation does not underlie the observed relationship [39, 49].

Alternatively, there may be a common pacemaker that drives both the autonomic activation and leg movements. Most studies have suggested that the presence of an electrographic arousal, which may also begin before the measured onset of the leg movement, increases the degree of autonomic activation [39, 41, 50, 51], suggesting the influence of a common pacemaker that may influence movement, cerebral arousal, and autonomic arousal [40]. As experimentally induced arousals do not trigger leg movements, it does not appear that either phenomenon (PLMS or arousal) is necessarily causal to the other [52, 53]. Furthermore, treatment effects show a clear separation between cortical arousal and leg movement, such that treatment of PLMS does not remove repetitive arousals and treatment of arousals does not remove PLMS [37, 54–57]. The fact that the magnitude of autonomic activation associated with leg movements depends on whether there is comorbid WED [37, 43] suggests that such a pacemaker may also be affected by underlying neurologic substrate. Arguing against the pacemaker argument is the fact that, while limb movements and autonomic activity are tightly associated, the presence or absence of a cortical arousal with a limb movement is much more variable; a common pacemaker would be expected to cause all three phenomena consistently [47].

Finally, increased sympathetic activation might cause PLMS [47]. This is particularly suggested by the temporal association of autonomic activation and PLMS [47], and would explain the association between conditions of increased sympathethic activation, such as heart failure, and increased PLMS [36, 58, 59]. However,

the presence of normal autonomic tone, at least as measured by heart rate variability metrics, between individual PLMS and during wakefulness in otherwise healthy subjects with PLMS argues somewhat against this possibility [43, 53]. Further, if increased autonomic activation were causal to PLMS, patients with autonomic failure would be expected to have fewer PLMS than patients with normal functioning autonomic nervous systems; a small study of patients with multiple systems atrophy or primary autonomic failure compared to healthy controls did not support this hypothesis, as PLM indices were no different [60]. As has been pointed out elsewhere, it is important to keep in mind that these directions of causality are not necessarily mutually exclusive [53], and multiple directions of relationship may exist.

Regardless of direction(s) of causality, PLMS associated with frequent blood pressure elevations will presumably result in a nondipping blood pressure pattern, as frequent blood pressure elevations will result in a higher average nocturnal blood pressure. Indeed, patients with WED (the vast majority of whom will also have PLMS [61]) have been shown to be more likely to demonstrate a nondipping pattern (OR 1.96) [18], and nocturnal dipping is reduced in those WED patients with frequent PLMS compared to WED patients with fewer PLMS [62]. Nondipping itself is associated with CVD [63]. The increase in CVD risk seen with nondipping may be related to the development of structural heart disease, thought to be related to increased hemodynamic stress from the lack of dipping or increased sympathetic activity, or from carotid intima-media thickening [35, 62, 64, 65]. Supporting this, several studies have found an association between severe PLMS and LVH. Patients undergoing polysomnography who have PLMS > 35/h, regardless of WED status, have an adjusted OR for LVH of 2.45 (1.67–3.59) [35]. WED patients with end-stage renal disease on hemodialysis with frequent PLMS (>25/h) have a higher left ventricular mass and left ventricular diameter during diastole, which in turn predicts mortality in these patients [62].

More broadly, a number of studies have evaluated for the effect of PLMS on future development of CVD, cardiovascular mortality, and all-cause mortality. Studies of PLMS have demonstrated that among non-hypertensive elderly men, frequent PLMS predict incident vascular disease, although this relationship was not significant for hypertensive men [66]. Among patients with renal disease, frequent PLMS consistently predict increased mortality [67–69], and the same is true of patients with heart failure [36]. These studies do not directly answer the question of causality between sympathetic activity and PLMS, but do underscore the substantial clinical relevance of this question. If the primary driver for these events (leg movements, autonomic activation, and cortical activation) can be identified and modified, there is real potential for improved clinical outcomes.

Mechanisms by Which Shared Pathophysiology or Risk Factors Could Lead to Both WED/PLMS and Cardiovascular Disease

Features Involved in Pathogenesis of WED/PLMS and Their Potential Role in Causing CVD

A common risk factor might result in both WED and CVD, accounting for the observed association. The pathophysiology of WED involves a number of important factors, some of which might also increase CVD risk. At present, single-nucleotide polymorphisms (SNPs) in or near several different genes, including BTBD9, Meis1, MAP2K5/SKOR1, PTPRD2, and TOX3, have been shown to be associated with WED/PLMS in genome-wide association studies [70–73]. Although understanding of the precise mechanisms by which these SNPs contribute to WED/PLMS continues to develop, it is possible that the implicated genes or regions might also increase CVD risk. In particular, the Meis1 risk variant has been suggested as a potential common genetic risk factor for both CVD and WED based on the observation that it is key in endothelial cell development and vascular patterning [74]. Manipulation of the Meis1 gene in mice results in cardiac structural abnormalities [75]. Further, a SNP within Meis1 has been associated with PR interval in several genome-wide association studies; PR interval predicts risk for the development of atrial fibrillation [76, 77]. Other risk alleles for WED have also been associated with heart disease or its mediators. MAP2K5 has recently been identified as containing a susceptibility SNP for the development of obesity [78]. SNPs within PTPRD have been associated in genome-wide association studies with levels of homocysteine (itself associated with vascular disease) [79] and coronary artery disease [80]. These genome-wide association studies for WED/PLMS and those for cardiac disease have not necessarily identified the same SNPs, but the co-occurrence of the same gene as a risk for both diseases is intriguing and warrants further investigation.

Dopamine dysfunction has been hypothesized as a common link between WED and CVD, mediated by HTN [81]. The renal dopamine system is involved in the pathogenesis of HTN [82]. Hypotheses of dopamine dysfunction in WED have focused on central nervous system dopamine dysfunction, but to the extent that dopamine function might be affected more broadly in patients with WED, dopamine dysfunction might underlie the development of both WED and HTN (predisposing for the subsequent development of CVD) in the same individuals [81]. Alternatively, some authors have proposed that dysfunction of the diencephalospinal tract, originating with the hypothalamic A11 cell group and projecting to the spinal cord, results in increased peripheral sympathetic activity and heightened spinal sensory signaling that both manifests as WED sensory symptoms and increases risk for CVD through increased sympathetic activity [74, 81, 83].

Low peripheral iron stores and low measured central nervous system iron have been associated with WED, and appear to be important in the development of WED

symptoms in at least some WED patients [84]. Wing et al. have proposed that alterations in iron might serve as the link between WED and CVD, in that higher dietary iron results in lower blood pressure [81, 85]. The interplay between iron and CVD is complex, with potentially opposite effects of harmful heme iron intake (e.g., from red meats) and beneficial nonheme iron intake, but pooled analyses from nearly 300,000 participants support an association between low iron stores (as are frequently seen in WED patients) and coronary heart disease incidence and mortality [86].

Known Risk Factors for Cardiovascular Disease that May Cause or Exacerbate WED Symptoms

Several cardiovascular risk factors have been implicated as possibly causative to or exacerbating existing WED symptoms, and thus an association between WED and CVD might reflect such a shared risk factor. Some CVD risk factors are plausibly causal to WED, some have a demonstrated significant association with WED although the mechanism of causality is unclear, and others do not appear to be related to WED. Those that may be causal to WED include lack of exercise, obesity, and abstinence from alcohol. Exercise is a well-established adjunctive treatment or preventative measure for heart disease [87, 88]. Although relief with exercise is not universally reported by people with WED, the benefit of exercise on WED symptoms has been demonstrated in several randomized, controlled trials [13, 89]. If exercise improves symptoms, lack of exercise is likely to worsen (or at least not improve) symptoms, and it has been shown that, for both women and men, having WED is associated with being less likely to exercise regularly [22, 90].

Obesity is a known risk factor for CVD. WED and BMI are linearly related in a dose-dependent manner, such that the OR for WED in obese individuals (relative to those with BMI <23) is 1.42 [91]. Other studies have found similarly positive associations between WED and obesity [27, 90, 92], present in 10 of 18 studies reported in a recent comprehensive review [1]. Furthermore, there appears to be a temporal relationship, such that obesity predicts the subsequent development of WED [30]. It is interesting to note that one of the few studies to show no association between WED and CVD also found no association with obesity [26]. An association between obesity and WED might reflect the relationship between obesity and brain dopamine, such that obese individuals have fewer striatal D2 dopamine receptors (as measured by raclopride binding on PET scanning) [93]. Studies of postsynaptic D2 receptor binding in WED patients have been mixed but tend also to favor a decrease in binding [94].

Alcohol consumption may exhibit a j-shaped (or possibly even linear) relationship with adverse cardiovascular outcomes, such that abstinence is less beneficial than moderate alcohol consumption [95]. People with WED may be less likely to consume alcohol than those without WED [22, 90]. The reason for this is unclear, but speculatively may be related to the clinical observation that alcohol may worsen WED symptom and abstinence may benefit them [96].

Known Risk Factors for Cardiovascular Disease that Are Associated with WED

A separate group of CVD risk factors have been shown to be associated with WED/PLMS, but the direction of causality is less clear. This includes obstructive sleep apnea, smoking, inflammation, dyslipidemia, diabetes, and vitamin D deficiency. Obstructive sleep apnea is strongly associated with CVD and related conditions [97], and also appears from smaller studies to be associated with WED and PLMS [98, 99]. This association does not appear to be mediated by iron stores [100] but might be related to the increase in obesity seen in both conditions [101]. Alternatively, an animal model suggests that intermittent hypoxia, such as that seen in sleep apnea, at a critical period of brain development causes alterations in dopamine functioning and motor hyperactivity [102]; if such effects persist in adulthood, intermittent hypoxia might link the two conditions. People with WED are also more likely to smoke or have a history of smoking [22, 26, 92, 103], perhaps related to psychopathologic traits common to WED patients [103], and smoking is a major CVD risk factor.

The majority of comorbid diseases that have been shown to be associated with WED are conditions of systemic inflammation [104], itself a risk factor for CVD [105]. Weinstock et al. speculate that inflammation resulting in iron deficiency triggers WED [104]. The precise relationship between WED, PLMS, and systemic inflammation remains to be determined, as the presence or absence of WED does not predict elevations in serum inflammatory markers such as CRP or IL-6 [26]. However, in patients with WED, those with severe PLMS (>45/h) are more likely to have elevated levels of CRP, and CRP levels correlate modestly but significantly with number of PLMS/hour [106]. In a group of patients not assessed for WED, PLMS were associated with elevations in CRP in an unadjusted, but not adjusted model [107]. In the same group, PLMS remained significantly associated with another marker, Lp-PLA2 (which predicts future cardiovascular and cerebrovascular events, after multivariate adjustment [107]).

Dyslipidemia has been associated with prevalence of WED [22, 92] and may predict the development of WED (seen in one but not the other studied cohort) [30]. A recent study of cerebrospinal fluid proteomics in a small group of WED patients demonstrated downregulation of apolipoprotein A1 [108]. Because apolipoprotein A1 is the main component of HDL, and because low serum levels of apolipoprotein A1 are associated with CVD, the author speculated that the low observed levels of CSF apolipoprotein A1 might explain the association between WED and CVD [108]. Diabetes is associated with WED in the majority of studies to evaluate it [1, 22, 90, 92], including a study that determined that diabetes predicts future development of WED [30]. Although some of this association may be mediated by diabetic peripheral neuropathy, only part of the increased risk is accounted for by neuropathy [109]. Vitamin D deficiency is receiving increasing attention as a risk factor for CVD [110], although the lack of benefit of vitamin D supplementation on heart disease or stroke in meta-analysis [111] suggests vitamin D deficiency might

be a marker, rather than a cause, of CVD. A single study suggests lower vitamin D levels in WED patients [112].

Arguments Against Common Risk Factors Explaining the Association Between WED/PLMS and CVD

Several authors have attempted to extensively control for cardiovascular risk factors when evaluating the association between WED and PLMS and have not found that such risk factors explain the association (e.g., [113]). Winter et al. [22] argue that the association between WED and CVD is entirely mediated by comorbidities based on their data. However, it has been pointed out by other investigators that neither Winter study (among others) measured the frequency nor severity of WED symptoms, which other studies have suggested is an important mediator of the WED-CVD relationship [29]. In contrast, Li et al. found an increased risk of incident cardiovascular events in women who had WED for at least 3 years, independent of major comorbidities including age, smoking, activity, diet, BMI, antidepressants, hypertension, diabetes, dyslipidemia, sleep length, and snoring [10]. Similarly, Winkelman et al. found a stronger cross-sectional relationship between CVD and WED in those with more frequent or bothersome symptoms, which was also independent of multiple comorbidities [114], and La Manna et al. found that frequency of WED symptoms had a dose-dependent effect on CVD in a multivariate model [115]. Adding to the complexity of the question of comorbidities, a careful assessment by Cosentino et al. determined that the increased prevalence of dyslipidemia in WED patients is explained by comorbid OSA, rather than WED per se [27].

Mechanisms by Which Cardiovascular Disease Could Cause WED or PLMS

It is certainly possible that WED or PLMS are caused by CVD itself. One of two cohorts evaluating this question demonstrated a significant association between myocardial infarction and the subsequent development of WED (OR 2.04); the other cohort found no significant relationship between the two, with an OR of 0.80 [30]. It is unclear how CVD per se might cause WED or PLMS, but it is plausible that associated vascular diseases might do so. That is, either cerebrovascular disease or peripheral arterial disease, both of which are tend to associate with CVD, might cause WED symptoms or PLMS.

Among patients evaluated for WED following an ischemic stroke, anatomical localization is a strong predictor of whether or not WED will be present. That is, patients with subcortical or brainstem (especially basal ganglia, corona radiata, and pons) strokes are much more likely to have WED than patients with cortical strokes [116]. In addition to providing insight into the anatomy of WED itself, this

observation argues that cerebrovascular disease, at least when it affects particular brain regions, may cause WED. However, another study evaluating stroke and WED did not find an association between stroke location and WED [117]. Patients with a history of stroke are more likely to have PLMI > 5 than those without a history of stroke (out of 80 total subjects) [118].

Historically, WED has been conceptualized as a disorder of vascular function related to impaired peripheral blood flow or sympathetic dysfunction [74, 119], including during Karl Ekbom's early descriptions of the disorder [120, 121]. Two small controlled trials of clonidine showed a benefit on WED symptoms and clonidine is considered as an option for the treatment of WED [122, 123]. Ware showed that PLMS patients have blunted peripheral pulses in response to certain maneuvers suggestive of sympathetic overactivity, and vasodilatory agents decreased number of PLMS [124]. This has been confirmed in patients with heart failure; those on vasodilators are less likely to have PLMI > 10 than those not on vasodilators [125]. Thus, patients with peripheral artery disease might be more likely to develop WED. Speaking somewhat against this direction of causality is the young average age of onset of WED symptoms (with bimodal peaks in mid-20s and mid-40s) [126]. However, to the extent that CVD is a disorder marked by years or decades of subclinical damage prior to first clinical manifestations [127], temporal relationships may be somewhat obscured.

Potential Role of Treatment of WED/PLMS in the Primary or Secondary Prevention of CVD

Depending on the direction of causality, treatment of WED/PLMS might result in prevention of CVD events. That is, if WED symptoms or PLMS are causal to CVD, their treatment might represent a novel opportunity to intervene to prevent the development or progression of CVD. At present, this is speculative, as scant data are available assessing this question.

In the single prospective study to date designed specifically to address the question of whether WED/PLMS treatment affects CVD risk parameters, Manconi et al. performed a night of polysomnography before and after beginning treatment of WED with pramipexole [43]. As expected, pramipexole decreased the frequency of PLMS. Importantly, pramipexole also decreased the magnitude of the heart rate variability increase accompanying the remaining leg movements [43]. Although this clearly cannot be extrapolated to suggest that treatment of PLMS will have beneficial effects on CVD events, it at least suggests a mechanism by which such benefit might occur. More recently, a retrospective chart review has suggested that in those patients with PLMI > 35/h (but not those with less frequent PLMS), use of dopaminergic treatment was associated with lower progression rate of atrial fibrillation (11.6% progression in treated group vs. 32% in the untreated group) [34]. Somewhat tempering enthusiasm for use of dopamine agonists in patients with WED or PLMS for cardioprotection, at least in the absence of additional data, is the

United States Food and Drug Administration's 2012 safety announcement regarding a possible increase in heart failure risk with pramipexole, requiring further evaluation to establish or refute [128].

Gabapentin enacarbil and other alpha-2-delta ligands are commonly used for WED, but we are not aware of any data specifically addressing the question of CVD risk and WED treatment for this medication class. Less commonly, benzodiazepines may be used for WED. A single case report, notable for its role as the first report of elevations in blood pressure associated with individual periodic leg movements during sleep, demonstrated reduction in arousals associated with PLMS after administration of temazepam. However, elevations in systolic blood pressure were persistent despite temazepam (21.8 mmHg before vs. 22.7 mmHg after temazepam) [56].

In summary, there is a rapidly expanding body of literature attempting to tease out the complex and likely multidirectional relationships between WED, PLMS, and CVD. Given that CVD is the leading cause of morbidity and mortality and the high prevalence of WED, studies determining the potential benefit of WED/PLMS treatment on CVD prevention are urgently needed.

References

1. Innes KE, Selfe TK, Agarwal P. Restless legs syndrome and conditions associated with metabolic dysregulation, sympathoadrenal dysfunction, and cardiovascular disease risk: a systematic review. Sleep Med Rev. 2012;16(4):309–39 (Epub 2011/07/08).
2. 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(11):1286–92 (Epub 2005/06/16).
3. Cappuccio FP, Cooper D, D'Elia L, Strazzullo P, Miller MA. Sleep duration predicts cardiovascular outcomes: a systematic review and meta-analysis of prospective studies. Eur Heart J. 2011;32(12):1484–92 (Epub 2011/02/09).
4. Knutson KL. Sleep duration and cardiometabolic risk: a review of the epidemiologic evidence. Best Pract Res Clin Endocrinol Metab. 2010;24(5):731–43 (Epub 2010/11/30).
5. Solarz DE, Mullington JM, Meier-Ewert HK. Sleep, inflammation and cardiovascular disease. Front Biosci (Elite Ed). 2012;4:2490–501 (Epub 2012/06/02).
6. Faraut B, Boudjeltia KZ, Vanhamme L, Kerkhofs M. Immune, inflammatory and cardiovascular consequences of sleep restriction and recovery. Sleep Med Rev. 2012;16(2):137–49 (Epub 2011/08/13).
7. Palagini L, Bruno RM, Gemignani A, Baglioni C, Ghiadoni L, Riemann D. Sleep loss and hypertension: a systematic review. Curr Pharm Des. 2013;19(13):2409–19 (Epub 2012/11/24).
8. Guo X, Zheng L, Wang J, Zhang X, Li J, Sun Y. Epidemiological evidence for the link between sleep duration and high blood pressure: a systematic review and meta-analysis. Sleep Med. 2013;14(4):324–32 (Epub 2013/02/12).
9. Meerlo P, Sgoifo A, Suchecki D. Restricted and disrupted sleep: effects on autonomic function, neuroendocrine stress systems and stress responsivity. Sleep Med Rev. 2008;12(3):197–210 (Epub 2008/01/29).
10. Li Y, Walters AS, Chiuve SE, Rimm EB, Winkelman JW, Gao X. Prospective study of restless legs syndrome and coronary heart disease among women. Circulation. 2012;126(14):1689–94 (Epub 2012/09/13).

11. Szentkiralyi A, Volzke H, Hoffmann W, Baune BT, Berger K. The relationship between depressive symptoms and restless legs syndrome in two prospective cohort studies. Psychosom Med. 2013;75(4):359–65 (Epub 2013/04/12).
12. Gupta R, Lahan V, Goel D. A study examining depression in restless legs syndrome. Asian J Psychiatry. 2013;6(4):308–12 (Epub 2013/07/03).
13. Giannaki CD, Sakkas GK, Karatzaferi C, Hadjigeorgiou GM, Lavdas E, Kyriakides T, et al. Effect of exercise training and dopamine agonists in patients with uremic restless legs syndrome: a six-month randomized, partially double-blind, placebo-controlled comparative study. BMC Nephrol. 2013;14:194 (Epub 2013/09/13).
14. Hornyak M, Scholz H, Kohnen R, Bengel J, Kassubek J, Trenkwalder C. What treatment works best for restless legs syndrome? Meta-analyses of dopaminergic and non-dopaminergic medications. Sleep Med Rev. 2014;18(2):153–64 (Epub 2013/06/12).
15. Thurston RC, Rewak M, Kubzansky LD. An anxious heart: anxiety and the onset of cardiovascular diseases. Prog Cardiovasc Dis. 2013;55(6):524–37 (Epub 2013/04/30).
16. Elderon L, Whooley MA. Depression and cardiovascular disease. Prog Cardiovasc Dis. 2013;55(6):511–23 (Epub 2013/04/30).
17. Gholamrezaei A, Amra B, Mortazavi M. Cardiovascular risk and mortality in end-stage renal disease patients with restless legs syndrome; need for further investigation and looking for underlying mechanisms. Sleep Med. 2013;14(4):385–6 (Epub 2013/01/23).
18. Erden EC, Erden I, Turker Y, Sivri N, Dikici S, Ozsahin M. Incremental effects of restless legs syndrome on nocturnal blood pressure in hypertensive patients and normotensive individuals. Blood pressure monitoring. 2012;17(6):231–4 (Epub 2012/11/01).
19. Garcia-Borreguero D, Larrosa O, Granizo J, de la Llave Y, Hening W. Circadian variation in neuroendocrine response to L-dopa in patients with restless legs syndrome. Sleep. 2004;27:669–73.
20. Wetter TC, Collado-Seidel V, Oertel H, Uhr M, Yassouridis A, Trenkwalder C. Endocrine rhythms in patients with restless legs syndrome. J Neurol. 2002;249(2):146–51 (Epub 2002/05/03).
21. Schilling C, Schredl M, Strobl P, Deuschle M. Restless legs syndrome: evidence for nocturnal hypothalamic-pituitary-adrenal system activation. Mov Disord. 2010;25(8):1047–52 (Epub 2010/06/11).
22. Winter AC, Schurks M, Glynn RJ, Buring JE, Gaziano JM, Berger K, et al. Vascular risk factors, cardiovascular disease, and restless legs syndrome in women. Am J Med. 2013;126 (3):220–7, 7 e1–2 (Epub 2013/02/16).
23. Batool-Anwar S, Malhotra A, Forman J, Winkelman J, Li Y, Gao X. Restless legs syndrome and hypertension in middle-aged women. Hypertension. 2011;58(5):791–6 (Epub 2011/10/12).
24. Aguera-Ortiz L, Perez MI, Osorio RS, Sacks H, Palomo T. Prevalence and clinical correlates of restless legs syndrome among psychogeriatric patients. Int J Geriatr Psychiatry. 2011;26 (12):1252–9 (Epub 2011/07/13).
25. Giannini G, Zanigni S, Melotti R, Gogele M, Provini F, Facheris MF, et al. Association between restless legs syndrome and hypertension: a preliminary population-based study in South Tyrol, Italy. Eur J Neurol. 2014;21(1):72–8 (Epub 2013/08/03).
26. 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(10):1043–8 (Epub 2010/10/22).
27. Cosentino FI, Arico D, Lanuzza B, Raggi A, Sciortino G, Tripodi M, et al. Absence of cardiovascular disease risk factors in restless legs syndrome. Acta Neurol Scand. 2012;125 (5):319–25 (Epub 2011/07/02).
28. 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(5):1064–8 (Epub 2000/03/17).

29. Budhiraja R, Quan SF. Is restless legs syndrome associated with cardiovascular disease? Am J Med. 2013;126(3):189–90 (Epub 2013/02/16).
30. Szentkiralyi A, Volzke H, Hoffmann W, Happe S, Berger K. A time sequence analysis of the relationship between cardiovascular risk factors, vascular diseases and restless legs syndrome in the general population. J Sleep Res. 2013;22(4):434–42 (Epub 2013/02/05).
31. Billars L, Hicks A, Bliwise D, Sigmundsson T, Sigurdsson A, Kristjansson K, et al. Hypertension risk and PLMS in restless legs syndrome. Sleep. 2007;30:A297–8.
32. Espinar-Sierra J, Vela-Bueno A, Luque-Otero M. Periodic leg movements in sleep in essential hypertension. Psychiatry Clin Neurosci. 1997;51(3):103–7 (Epub 1997/06/01).
33. Grimaldi D, Provini F, Calandra-Buonaura G, Barletta G, Cecere A, Pierangeli G, et al. Cardiovascular-sleep interaction in drug-naive patients with essential grade I hypertension. Chronobiol Int. 2013;30(1–2):31–42 (Epub 2012/10/18).
34. Mirza M, Shen WK, Sofi A, Tran C, Jahangir A, Sultan S, et al. Frequent periodic leg movement during sleep is an unrecognized risk factor for progression of atrial fibrillation. PLoS One. 2013;8(10):e78359 (Epub 2013/10/23).
35. Mirza M, Shen WK, Sofi A, Jahangir A, Mori N, Tajik AJ. Frequent periodic leg movement during sleep is associated with left ventricular hypertrophy and adverse cardiovascular outcomes. J Am Soc Echocardiogr (official publication of the American Society of Echocardiography). 2013;26(7):783–90 (Epub 2013/04/30).
36. Yumino D, Wang H, Floras JS, Newton GE, Mak S, Ruttanaumpawan P, et al. Relation of periodic leg movements during sleep and mortality in patients with systolic heart failure. Am J Cardiol. 2011;107(3):447–51 (Epub 2011/01/25).
37. Pennestri MH, Montplaisir J, Fradette L, Lavigne G, Colombo R, Lanfranchi PA. Blood pressure changes associated with periodic leg movements during sleep in healthy subjects. Sleep Med. 2013;14(6):555–61 (Epub 2013/05/07).
38. Pennestri MH, Montplaisir J, Colombo R, Lavigne G, Lanfranchi PA. Nocturnal blood pressure changes in patients with restless legs syndrome. Neurology. 2007;68(15):1213–8 (Epub 2007/04/11).
39. Winkelman J. The evoked heart rate response to periodic leg movements of sleep. Sleep. 1999;22:575–80.
40. Ferrillo F, Beelke M, Canovaro P, Watanabe T, Arico D, Rizzo P, et al. Changes in cerebral and autonomic activity heralding periodic limb movements in sleep. Sleep Med. 2004;5 (4):407–12 (Epub 2004/06/30).
41. Sforza E, Nicolas A, Lavigne G, Gosselin A, Petit D, Montplaisir J. EEG and cardiac activation during periodic leg movements in sleep: support for a hierarchy of arousal responses. Neurology. 1999;52(4):786–91 (Epub 1999/03/17).
42. 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(2):438–48 (Epub 2006/12/05).
43. Manconi M, Ferri R, Zucconi M, Clemens S, Rundo F, Oldani A, et al. Effects of acute dopamine-agonist treatment in restless legs syndrome on heart rate variability during sleep. Sleep Med. 2011;12(1):47–55 (Epub 2010/09/21).
44. de Weerd AW, Rijsman RM, Brinkley A. Activity patterns of leg muscles in periodic limb movement disorder. J Neurol Neurosurg Psychiatry. 2004;75(2):317–9 (Epub 2004/01/27).
45. Provini F, Vetrugno R, Meletti S, Plazzi G, Solieri L, Lugaresi E, et al. Motor pattern of periodic limb movements during sleep. Neurology. 2001;57(2):300–4 (Epub 2001/07/27).
46. Sforza E, Pichot V, Barthelemy JC, Haba-Rubio J, Roche F. Cardiovascular variability during periodic leg movements: a spectral analysis approach. Clin Neurophysiol. 2005;116 (5):1096–104 (Epub 2005/04/14).
47. Guggisberg AG, Hess CW, Mathis J. The significance of the sympathetic nervous system in the pathophysiology of periodic leg movements in sleep. Sleep. 2007;30(6):755–66 (Epub 2007/06/22).

48. Yang CK, Jordan AS, White DP, Winkelman JW. Heart rate response to respiratory events with or without leg movements. Sleep. 2006;29(4):553–6 (v).
49. 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(9):1923–30 (Epub 2007/06/26).
50. 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(6):883–91 (Epub 2002/06/06).
51. Lavoie S, de Bilbao F, Haba-Rubio J, Ibanez V, Sforza E. Influence of sleep stage and wakefulness on spectral EEG activity and heart rate variations around periodic leg movements. Clin Neurophysiol. 2004;115(10):2236–46 (Epub 2004/09/08).
52. Ferri R, Manconi M, Arico D, Punjabi NM, Zucconi M. Experimentally induced arousals do not elicit periodic leg motor activity during sleep in normal subjects. Sleep Med. 2013;14 (1):85–90 (Epub 2012/11/07).
53. Palma JA, Alegre M, Valencia M, Artieda J, Iriarte J, Urrestarazu E. Basal cardiac autonomic tone is normal in patients with periodic leg movements during sleep. J Neural Transm. 2014;121(4):385–90 (Epub 2013/11/19).
54. Ferri R, Manconi M, Arico D, Sagrada C, Zucconi M, Bruni O, et al. Acute dopamine-agonist treatment in restless legs syndrome: effects on sleep architecture and NREM sleep instability. Sleep. 2010;33(6):793–800 (Epub 2010/06/17).
55. Montplaisir J, Boucher S, Gosselin A, Poirier G, Lavigne G. Persistence of repetitive EEG arousals (K-alpha complexes) in RLS patients treated with L-DOPA. Sleep. 1996;19(3):196–9 (Epub 1996/04/01).
56. Ali NJ, Davies RJ, Fleetham JA, Stradling JR. Periodic movements of the legs during sleep associated with rises in systemic blood pressure. Sleep. 1991;14(2):163–5 (Epub 1991/04/01).
57. Manconi M, Ferri R, Zucconi M, Bassetti CL, Fulda S, Arico D, et al. Dissociation of periodic leg movements from arousals in restless legs syndrome. Ann Neurol. 2012;71 (6):834–44 (Epub 2012/06/22).
58. Floras JS. Sympathetic activation in human heart failure: diverse mechanisms, therapeutic opportunities. Acta Physiol Scand. 2003;177(3):391–8 (Epub 2003/03/01).
59. Hanly PJ, Zuberi-Khokhar N. Periodic limb movements during sleep in patients with congestive heart failure. Chest. 1996;109(6):1497–502 (Epub 1996/06/01).
60. Freilich S, Goff EA, Malaweera AS, Twigg GL, Simonds AK, Mathias CJ, et al. Sleep architecture and attenuated heart rate response to arousal from sleep in patients with autonomic failure. Sleep Med. 2010;11(1):87–92 (Epub 2009/12/08).
61. Trotti LM, Bliwise DL, Greer SA, Sigurdsson AP, Gudmundsdottir GB, Wessel T, et al. Correlates of PLMs variability over multiple nights and impact upon RLS diagnosis. Sleep Med. 2009;10(6):668–71 (Epub 2008/11/22).
62. 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(2):147–53 (Epub 2013/02/02).
63. Kang YY, Li Y, Wang JG. Ambulatory blood pressure monitoring in the prediction and prevention of coronary heart disease. Curr Hypertens Rep. 2013;15(3):167–74 (Epub 2013/03/29).
64. Birkenhager AM, van den Meiracker AH. Causes and consequences of a non-dipping blood pressure profile. The Netherlands journal of medicine. 2007;65(4):127–31 (Epub 2007/04/25).
65. Verdecchia P, Schillaci G, Guerrieri M, Gatteschi C, Benemio G, Boldrini F, et al. Circadian blood pressure changes and left ventricular hypertrophy in essential hypertension. Circulation. 1990;81(2):528–36 (Epub 1990/02/01).

66. 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(11):1223–31 (Epub 2011/08/24).
67. 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(2):388–96.
68. Benz RL, Pressman MR, Hovick ET, Peterson DD. Potential novel predictors of mortality in end-stage renal disease patients with sleep disorders [see comment]. Am J Kidney Dis. 2000;35(6):1052–60.
69. Jung HH, Lee JH, Baek HJ, Kim SJ, Lee JJ. Nocturnal hypoxemia and periodic limb movement predict mortality in patients on maintenance hemodialysis. Clin J Am Soc Nephrol CJASN. 2010;5(9):1607–13 (Epub 2010/05/29).
70. 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(7):639–47.
71. Schormair B, Kemlink D, Roeske D, Eckstein G, Xiong L, Lichtner P, et al. PTPRD (protein tyrosine phosphatase receptor type delta) is associated with restless legs syndrome. Nat Genet. 2008;40(8):946–8 (Epub 2008/07/29).
72. Winkelmann J, Czamara D, Schormair B, Knauf F, Schulte EC, Trenkwalder C, et al. Genome-wide association study identifies novel restless legs syndrome susceptibility loci on 2p14 and 16q12.1. PLoS Genet. 2011;7(7):e1002171 (Epub 2011/07/23).
73. 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(8):1000–6 (Epub 2007/07/20).
74. Walters AS, Rye DB. Review of the relationship of restless legs syndrome and periodic limb movements in sleep to hypertension, heart disease, and stroke. Sleep. 2009;32(5):589–97 (Epub 2009/06/02).
75. Stankunas K, Shang C, Twu KY, Kao SC, Jenkins NA, Copeland NG, et al. Pbx/Meis deficiencies demonstrate multigenetic origins of congenital heart disease. Circ Res. 2008;103 (7):702–9 (Epub 2008/08/30).
76. Smith JG, Magnani JW, Palmer C, Meng YA, Soliman EZ, Musani SK, et al. Genome-wide association studies of the PR interval in African Americans. PLoS Genet. 2011;7(2): e1001304 (Epub 2011/02/25).
77. Pfeufer A, van Noord C, Marciante KD, Arking DE, Larson MG, Smith AV, et al. Genome-wide association study of PR interval. Nat Genet. 2010;42(2):153–9 (Epub 2010/01/12).
78. Hong KW, Oh B. Recapitulation of genome-wide association studies on body mass index in the Korean population. Int J Obes (Lond). 2012;36(8):1127–30 (Epub 2011/11/02).
79. Malarstig A, Buil A, Souto JC, Clarke R, Blanco-Vaca F, Fontcuberta J, et al. Identification of ZNF366 and PTPRD as novel determinants of plasma homocysteine in a family-based genome-wide association study. Blood. 2009;114(7):1417–22 (Epub 2009/06/16).
80. Saade S, Cazier JB, Ghassibe-Sabbagh M, Youhanna S, Badro DA, Kamatani Y, et al. Large scale association analysis identifies three susceptibility loci for coronary artery disease. PLoS One. 2011;6(12):e29427 (Epub 2012/01/05).
81. Wing YK, Zhang J, Ho CK, Au CT, Li AM. Periodic limb movement during sleep is associated with nocturnal hypertension in children. Sleep. 2010;33(6):759–65 (Epub 2010/06/17).
82. Carey RM. The intrarenal renin-angiotensin and dopaminergic systems: control of renal sodium excretion and blood pressure. Hypertension. 2013;61(3):673–80 (Epub 2013/02/15).
83. Clemens S, Rye D, Hochman S. Restless legs syndrome: revisiting the dopamine hypothesis from the spinal cord perspective. Neurology. 2006;67(1):125–30 (Epub 2006/07/13).
84. Trotti LM, Rye DB. Restless legs syndrome. Handb Clin Neurol. 2011;100:661–73 (Epub 2011/04/19).

85. Tzoulaki I, Brown IJ, Chan Q, Van Horn L, Ueshima H, Zhao L, et al. Relation of iron and red meat intake to blood pressure: cross sectional epidemiological study. BMJ. 2008;337: a258 (Epub 2008/07/18).
86. Hunnicutt J, He K, Xun P. Dietary iron intake and body iron stores are associated with risk of coronary heart disease in a meta-analysis of prospective cohort studies. J Nutr. 2014 (Epub 2014/01/10).
87. Heran BS, Chen JM, Ebrahim S, Moxham T, Oldridge N, Rees K, et al. Exercise-based cardiac rehabilitation for coronary heart disease. Cochrane Database Syst Rev. 2011(7): CD001800 (Epub 2011/07/08).
88. Shaw K, Gennat H, O'Rourke P, Del Mar C. Exercise for overweight or obesity. Cochrane Database Syst Rev. 2006(4):CD003817 (Epub 2006/10/21).
89. Aukerman MM, Aukerman D, Bayard M, Tudiver F, Thorp L, Bailey B. Exercise and restless legs syndrome: a randomized controlled trial. J Am Board Fam Med. 2006;19 (5):487–93 (Epub 2006/09/05).
90. Winter AC, Berger K, Glynn RJ, Buring JE, Gaziano JM, Schurks M, et al. Vascular risk factors, cardiovascular disease, and restless legs syndrome in men. Am J Med. 2013;126 (3):228–35, 35 e1-2 (Epub 2013/02/16).
91. Gao X, Schwarzschild MA, Wang H, Ascherio A. Obesity and restless legs syndrome in men and women. Neurology. 2009;72(14):1255–61 (Epub 2009/04/08).
92. Schlesinger I, Erikh I, Avizohar O, Sprecher E, Yarnitsky D. Cardiovascular risk factors in restless legs syndrome. Mov Disord. 2009;24(11):1587–92 (Epub 2009/06/16).
93. Wang GJ, Volkow ND, Logan J, Pappas NR, Wong CT, Zhu W, et al. Brain dopamine and obesity. Lancet. 2001;357(9253):354–7 (Epub 2001/02/24).
94. Desseilles M, Dang-Vu T, Schabus M, Sterpenich V, Maquet P, Schwartz S. Neuroimaging insights into the pathophysiology of sleep disorders. Sleep. 2008;31(6):777–94 (Epub 2008/06/14).
95. Poli A, Marangoni F, Avogaro A, Barba G, Bellentani S, Bucci M, et al. Moderate alcohol use and health: a consensus document. Nutrition, metabolism, and cardiovascular diseases: NMCD. 2013;23(6):487–504 (Epub 2013/05/07).
96. Silber M, Ehrenberg B, Allen R, Buchfuhrer M, Earley C, Hening W, et al. An algorithm for the management of restless legs syndrome. Mayo Clin Proc. 2004;79:916–22.
97. Somers VK, White DP, Amin R, Abraham WT, Costa F, Culebras A, et al. Sleep apnea and cardiovascular disease: an American Heart Association/american College Of Cardiology Foundation Scientific Statement from the American Heart Association Council for High Blood Pressure Research Professional Education Committee, Council on Clinical Cardiology, Stroke Council, and Council On Cardiovascular Nursing. In collaboration with the National Heart, Lung, and Blood Institute National Center on Sleep Disorders Research (National Institutes of Health). Circulation. 2008;118(10):1080–111 (Epub 2008/08/30).
98. Lakshminarayanan S, Paramasivan KD, Walters AS, Wagner ML, Patel S, Passi V. Clinically significant but unsuspected restless legs syndrome in patients with sleep apnea. Mov Disord. 2005;20(4):501–3 (Epub 2004/12/15).
99. Al-Alawi A, Mulgrew A, Tench E, Ryan CF. Prevalence, risk factors and impact on daytime sleepiness and hypertension of periodic leg movements with arousals in patients with obstructive sleep apnea. J Clin Sleep Med. 2006;2(3):281–7 (Epub 2007/06/15).
100. O'Brien LM, Koo J, Fan L, Owusu JT, Chotinaiwattarakul W, Felt BT, et al. Iron stores, periodic leg movements, and sleepiness in obstructive sleep apnea. J Clin Sleep Med. 2009;5 (6):525–31 (Epub 2010/05/15).
101. Roux FJ. Restless legs syndrome: impact on sleep-related breathing disorders. Respirology. 2013;18(2):238–45 (Epub 2012/08/14).
102. Decker MJ, Jones KA, Solomon IG, Keating GL, Rye DB. Reduced extracellular dopamine and increased responsiveness to novelty: neurochemical and behavioral sequelae of intermittent hypoxia. Sleep. 2005;28(2):169–76 (Epub 2005/09/21).

103. Provini F, Antelmi E, Vignatelli L, Zaniboni A, Naldi G, Calandra-Buonaura G, et al. Increased prevalence of nocturnal smoking in restless legs syndrome (RLS). Sleep Med. 2010;11(2):218–20 (Epub 2010/01/13).
104. Weinstock LB, Walters AS, Paueksakon P. Restless legs syndrome–theoretical roles of inflammatory and immune mechanisms. Sleep Med Rev. 2012;16(4):341–54 (Epub 2012/01/20).
105. Libby P, Lichtman AH, Hansson GK. Immune effector mechanisms implicated in atherosclerosis: from mice to humans. Immunity. 2013;38(6):1092–104 (Epub 2013/07/03).
106. Trotti LM, Rye DB, Staercke CD, Hooper WC, Quyyumi A, Bliwise DL. Elevated C-reactive protein is associated with severe periodic leg movements of sleep in patients with restless legs syndrome. Brain Behav Immun. 2012;26(8):1239–43 (Epub 2012/07/04).
107. Bekci TT, Kayrak M, Kiyici A, Ari H, Teke T, Maden E, et al. The relation between Lp-PLA2 levels with periodic limb movements. Sleep Breath. 2012;16(1):117–22 (Epub 2011/01/12).
108. Patton SM, Cho YW, Clardy TW, Allen RP, Earley CJ, Connor JR. Proteomic analysis of the cerebrospinal fluid of patients with restless legs syndrome/Willis-Ekbom disease. Fluids barriers CNS. 2013;10(1):20 (Epub 2013/06/14).
109. Merlino G, Fratticci L, Valente M, Del Giudice A, Noacco C, Dolso P, et al. Association of restless legs syndrome in type 2 diabetes: a case-control study. Sleep. 2007;30(7):866–71.
110. Kassi E, Adamopoulos C, Basdra EK, Papavassiliou AG. Role of vitamin D in atherosclerosis. Circulation. 2013;128(23):2517–31 (Epub 2013/12/04).
111. Bolland MJ, Grey A, Gamble GD, Reid IR. The effect of vitamin D supplementation on skeletal, vascular, or cancer outcomes: a trial sequential meta-analysis. Lancet Diabetes Endocrinol. 2014;2(4):307–20.
112. Balaban H, Yildiz OK, Cil G, Senturk IA, Erselcan T, Bolayir E, et al. Serum 25-hydroxyvitamin D levels in restless legs syndrome patients. Sleep Med. 2012;13 (7):953–7 (Epub 2012/06/19).
113. Lindner A, Fornadi K, Lazar AS, Czira ME, Dunai A, Zoller R, et al. Periodic limb movements in sleep are associated with stroke and cardiovascular risk factors in patients with renal failure. J Sleep Res. 2012;21(3):297–307 (Epub 2011/09/16).
114. 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(1):35–42 (Epub 2008/01/02).
115. La Manna G, Pizza F, Persici E, Baraldi O, Comai G, Cappuccilli ML, et al. Restless legs syndrome enhances cardiovascular risk and mortality in patients with end-stage kidney disease undergoing long-term haemodialysis treatment. Nephrol dialysis transplant (official publication of the European Dialysis and Transplant Association - European Renal Association). 2011;26(6):1976–83 (Epub 2010/11/09).
116. Lee SJ, Kim JS, Song IU, An JY, Kim YI, Lee KS. Poststroke restless legs syndrome and lesion location: anatomical considerations. Mov Disord. 2009;24(1):77–84 (Epub 2008/09/26).
117. Medeiros CA, de Bruin PF, Paiva TR, Coutinho WM, Ponte RP, de Bruin VM. Clinical outcome after acute ischaemic stroke: the influence of restless legs syndrome. Eur J Neurol. 2011;18(1):144–9 (Epub 2010/06/10).
118. Coelho FM, Georgsson H, Narayansingh M, Swartz RH, Murray BJ. Higher prevalence of periodic limb movements of sleep in patients with history of stroke. J Clin Sleep Med. 2010;6(5):428–30 (Epub 2010/10/21).
119. Coccagna G, Vetrugno R, Lombardi C, Provini F. Restless legs syndrome: an historical note. Sleep Med. 2004;5(3):279–83 (Epub 2004/05/29).
120. Ekbom K. Restless legs. Acta Med Scand Suppl. 1945;158:1–123.
121. Ekbom K. Restless legs syndrome. Neurology. 1960;10:868–75.
122. 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: an American Academy of Sleep Medicine Clinical Practice Guideline. Sleep. 2012;35(8):1039–62 (Epub 2012/08/02).
123. Wagner ML, Walters AS, Coleman RG, Hening WA, Grasing K, Chokroverty S. Randomized, double-blind, placebo-controlled study of clonidine in restless legs syndrome. Sleep. 1996;19(1):52–8 (Epub 1996/01/01).
124. Ware J, Blumoff R, Pittard J. Peripheral vasoconstriction in patients with sleep related periodic leg movements. Sleep. 1988;11:182–6.
125. Koo BB, Mehra R, Blackwell T, et al. Periodic limb movements during sleep and cardiac arrhythmia in older men (MrOS sleep). J Clin Sleep Med. 2014;10(1):7–11.
126. Whittom S, Dauvilliers Y, Pennestri MH, Vercauteren F, Molinari N, Petit D, et al. Age-at-onset in restless legs syndrome: a clinical and polysomnographic study. Sleep Med. 2007;9(1):54–9 (Epub 2007/07/24).
127. Toth PP. Subclinical atherosclerosis: what it is, what it means and what we can do about it. Int J Clin Pract. 2008;62(8):1246–54 (Epub 2008/06/20).
128. Administration FaD. FDA Drug Safety Communication: Ongoing safety review of Parkinson's drug Mirapex (pramipexole) and possible risk of heart failure. 2012 [updated 2/15/20132/13/2014]; Available from: http://www.fda.gov/Drugs/DrugSafety/ucm319779.htm.

Peripheral Muscle Changes

9

B. Wåhlin-Larsson and J. Ulfberg

Skeletal muscle composes up to 40% of the adult human body weight and is a very adaptive tissue which can adjust its metabolic and contractile characteristics in response to alteration in environmental demands [1–4]. An important process of adaptation in the muscle is angiogenesis, developing of new capillaries in the muscle. If the oxygen supply is insufficient in the muscle, it will induce an increase of different growth factors promoting angiogenesis [5, 6]. Vascular endothelial growth factor (VEGF) is one of the most specific factor acting as an inducer of angiogenesis and can in turn be regulated by hypoxia [5, 6]. It is known that repetitive bouts of exercise until exhaustion or exercise during restricted blood flow can enhance basal VEGF protein levels [7–9] meaning that local hypoxia in the muscle can induce angiogenesis as an adaptation to low oxygen tension.

Patients with obstructive sleep apnea syndrome (OSAS) and patients with chronic obstructive pulmonary disease (COPD) are two different states were the oxygen supply is insufficient, i.e., in a hypoxic state. Patients with OSAS have an intermittent hypoxia due to apneas or hypopneas during sleep at night [10, 11]. COPD patients have a chronic hypoxia caused by air flow limitations [12]. The intermittent hypoxia seen in OSAS patients has been shown to induce angiogenesis compared to age-matched health subjects despite the low physical capacity shown in the patients group, meaning that the lager capillary network in the subjects with OSAS is not due to exercise but to the intermittent hypoxia [13]. This is strengthened by the fact that the expression of VEGF in the skeletal muscle of

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OSAS patients is significantly higher compared with age-matched healthy controls [14].

As symptoms of restless leg syndrome (RLS) are often located in the limb and typically occur during periods of inactivity, and are alleviated by movement including muscle contraction the skeletal muscle in a patients group suffering from RLS has been studied. The findings with a lager capillary network compared to age-matched healthy controls indicate existence of hypoxia [15]. These changes could not be explained by the low intensity movement RLS patients often do as an increased exercise induced VEGF expression seems to require a much higher intensity [9].

Muscle Biology

All movement depends on the correct functioning of skeletal muscle. The entire muscle is surrounded by the epimysium, and the perimysium divides the skeletal muscle into a series of compartments. Within the perimysium, the endomysium surrounds the individual skeletal muscle cells or muscle fibers. The endomysium contains a capillary network, satellite cells, and nerve fibers.

Muscle Capillarization

Capillaries can be identified by the size of their cross-section. Vessels in the endomysium with a diameter <15 μm are mostly capillaries [16]. The histological structure of the capillaries permits a two-way exchange of gases and substances. It is known that muscle fiber types characterized by a high aerobic metabolism have a much denser capillary network than muscle fiber types characterized by a high glycolytic metabolism [3]. However, capillaries do not function as individual units but as part of an interconnected network, the capillary bed or capillary network. In this network, the entrance to each capillary is guarded by a precapillary sphincter. Contraction of the sphincter leads to a stop or reduction in blood flow in the specific capillary, and blood is diverted into other branches of the network. Relaxation of the precapillary sphincter results in increased blood flow in the capillary [17]. Skeletal muscle blood flow is closely coupled to metabolic demand, and its regulation is mainly the result of the interplay of neural vasoactivity and local vasoactive substances such as change in pH, PO2, as well as adrenaline [18].

Angiogenesis

Angiogenesis is the development of new capillaries from an already established capillary network [19, 20]. Endothelial cells form capillaries and are thus centrally involved in angiogenesis; they migrate and proliferate and then assemble into tubes

with tight cell–cell connections to contain the blood [21]. The process of angiogenesis is controlled by both growth promoting factors and by growth inhibitory factors [22]. Although a variety of growth factors act as inducers of angiogenesis, one of the most specific factors for vascular endothelium is the VEGF [5, 6]. VEGF in turn can be regulated by several factors including growth factors, tumor suppressor factors, and hypoxia through stimulation by hypoxia inducible factor (HIF) [23, 24].

It is still controversial whether systemic hypoxia causes capillary growth in skeletal muscle. There are studies showing that systemic hypoxia induces angiogenesis [25–27], but there are also studies showing no change in capillary supply [28, 29]. These results indicate that the degree of systemic hypoxia and the duration of exposure are important factors for angiogenesis in skeletal muscle.

Local hypoxia is known to cause capillary growth [4, 20, 30]. It is known that endurance exercise with restricted blood flow to working muscle enhances the expression of VEGF mRNA and that repetitive bouts of endurance exercise increase basal VEGF protein levels [7, 8]. Angiogenesis could also be induced by metabolic or mechanical factors. AMP activated protein kinase (AMPK) is activated when energy consumption exceeds energy production leading to an increase in VEGF expression [31]. It is also demonstrated that adenosine might be essential mediator for angiogenesis [32]. Growth of capillaries can also be initiated by mechanical factors related to increased blood flow (shear stress, capillary wall tension) [33].

Local Inflammation in Skeletal Muscle

VEGF is also known as vascular permeability factor (VPF), and VEGF expression can be increased in relation to inflammation [23]. On the one hand, VEGF stimulates endothelial cells to proliferate and to migrate and, on the other hand, VEGF increase the permeability of microvessel [34]. Monocytes are part of the immune system and differentiate to macrophages entering the tissue from the blood. The macrophages are very powerful phagocytes and are necessary for both normal muscle function and tissue repair [35–37]. In resting healthy human vastus lateralis muscle 0–8 macrophages per 100 muscle fibers were found [36]. The numbers of macrophages are increased in different inflammatory myopathies [38, 39]. T-lymphocytes belong to the adaptive immune system and are normally present in a low amount in healthy muscle [36] and will increase due to inflammation [40].

There are two types of major histocompatibility complex (MHC) molecules: MHC class I and MHC class II. The proteins encoded by the MHC are expressed on the surface of cells and present the antigen long enough for T-cells to recognize it. MHC class I is generally absent or very weakly expressed in healthy skeletal muscle but are highly expressed in different inflammatory myopathies [40].

RLS Patients

The structural characteristics of musculus tibialis anterior and the aerobic capacity in patients with RLS compared with healthy age-matched controls have been investigated.

RLS patients had a significantly lower predicted maximal oxygen uptake expressed in ml/min/kg compared with the control group (33.8 ± 8.1 vs. 40.2 ± 5.7 ml min^{-1} kg^{-1}, $p = 0.012$) meaning that the physical capacity is lower in the group of RLS patients [15].

Examining the musculus tibialis anterior, the results show a lager capillary network in the patient group compared with controls indicating that there is a peripheral influence (Fig. 9.1). It is the same pattern as after hypoxic environment [15]. Looking further into the cause of a more developed capillary network, it is now also known that the expression of VEGF is higher in the endothelial cells of RLS patients compared with healthy controls [14].

The expression of VEGF could be stimulated by inflammation in the muscle but that is not the case in these patients. None of the subjects showed any expression of MHC class I according to the criteria for grading the expression of MHC class I. All patients with RLS as well as the control group were graded as normal (0–1) [41].

Staining for T-cells (anti-CD3) and macrophages (anti-CD68) showed presence of both T-cells and macrophages in both groups, but there were no significant difference between the groups according to CD3 + cells and CD68 + cells [41].

This means that the higher expression of VEGF is not due to any inflammation in the muscle of RLS patients.

Increased capillary network is in agreement with earlier reported findings after endurance training [16, 42]. The cause for this adaptation is proposed to be the occurrence of local hypoxia within the muscle during exercise. VEGF and HIF are also enhanced during exercise, most probably due to local hypoxia in the muscle, thus stimulating angiogenesis [7, 8].

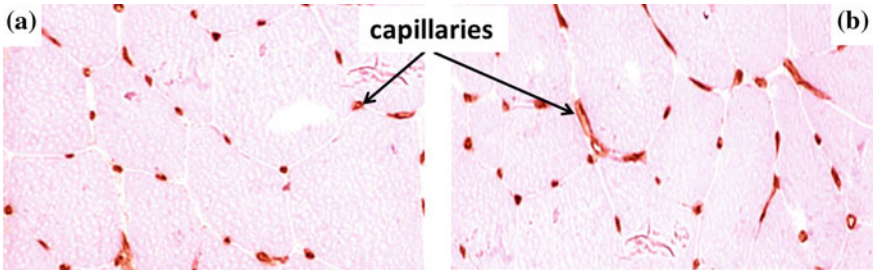

Fig. 9.1 A cross-section of m tibialis anterior, immunohistochemically stained for capillaries (CD31), from an age-matched control (**a**) and from a RLS patient with a larger capillary network (**b**)

RLS patients do not show arterial hypoxia; however, local hypoxia due to vasoconstriction might exist in these patients. This hypothesis is strengthened by the relief of symptoms by limb movement which cause muscle contraction that are known to increase blood flow and oxygen supply [18, 43]. The fact that RLS patients often move their legs to temporarily relieve the symptoms; this could therefore be a strategy to increase the blood flow.

It is well known that the endothelium reacts to and also produces a variety of vasoactive substances, including vasoconstrictors as well as vasodilators. To provide adequate blood flow to the muscle, there should be a balance between the activity of vasoconstriction and vasodilatation. An imbalance favoring a vasoconstriction might induce local hypoxia. In RLS patients, there may be an imbalance between vasoconstriction and vasodilatation as the symptoms are temporarily relieved by limb movements, which increase the blood flow. Vasoconstriction as well as systemic hypoxia may cause capillary growth in skeletal muscle.

Regarding systemic hypoxia which occurs at high altitude or under pulmonary insufficiency there are conflicting results [44–46]. As our RLS patients have not experienced systemic hypoxia, this factor cannot account for the observed effect on the capillarization. However, a vasoconstriction might cause a local tissue hypoxia in these patients.

It was claimed by Ekbom in 1945 that the symptoms of RLS were due to impaired circulation in the small vessels of the lower extremities [47]. Very recently, Anderson and collaborators demonstrated impaired microvascular circulation in patients with RLS in comparison to matched controls by using bilateral great toe laser Doppler flowmetry together with whole-body thermography [48]. This is in line with our results showing that patients suffering from RLS are affected by hypoxia.

According to these current scattering data on impaired microvascular circulation in the legs of RLS patients, it may give a hypothesis open for speculation that the urge to move the legs during nighttime might be an efficacy of a circadian downregulation of dopamine, which has vasodilative characters.

References

1. Booth FW, Thomason DB. Molecular and cellular adaptation of muscle in response to exercise: perspectives of various models. Physiol Rev. 1991;71(2):541–85.
2. Clanton TL, Klawitter PF. Invited review: adaptive responses of skeletal muscle to intermittent hypoxia: the known and the unknown. J Appl Physiol. 2001;90(6):2476–87.
3. Hudlicka O, Brown M, Egginton S. Angiogenesis in skeletal and cardiac muscle. Phys Rev. 1992;72(2):369–417.
4. Sundberg CJ. Exercise and training during graded leg ischaemia in healthy man with special reference to effects on skeletal muscle. Acta Physiol Scand Suppl. 1994;615:1–50.
5. Bloor CM. Angiogenesis during exercise and training. Angiogenesis. 2005;8(3):263–71.
6. Klagsbrun M, D'Amore PA. Vascular endothelial growth factor and its receptors. Cytokine Growth Factor Rev. 1996;7(3):259–70.

7. Gustafsson T, Knutsson A, Puntschart A, Kaijser L, Nordqvist AC, Sundberg CJ, Jansson E. Increased expression of vascular endothelial growth factor in human skeletal muscle in response to short-term one-legged exercise training. Pflugers Arch. 2002;444(6):752–9.
8. Gustafsson T, Puntschart A, Kaijser L, Jansson E, Sundberg CJ. Exercise-induced expression of angiogenesis-related transcription and growth factors in human skeletal muscle. Am J Physiol. 1999;276(2Pt2):H679–85.
9. Takano H, Morita T, Iida H, Asada K, Kato M, Uno K, Hirose K, Matsumoto A, Takenaka K, Hirata Y, et al. Hemodynamic and hormonal responses to a short-term low-intensity resistance exercise with the reduction of muscle blood flow. Eur J Appl Physiol. 2005;95(1):65–73.
10. Gibson GJ. Obstructive sleep apnoea syndrome: underestimated and undertreated. Br Med Bull. 2005;29(72):49–65.
11. Lindberg E, Gislason T. Epidemiology of sleep-related obstructive breathing. Sleep Med Rev. 2000;4(5):411–33.
12. Eliason G, Abdel-Halim S, Arvidsson B, Kadi F, Piehl-Aulin K. Physical performance and muscular characteristics in different stages of COPD. Scand J Med Sci Sports. 2009;19 (6):865–70.
13. Wåhlin-Larsson B, Kadi K, Ulfberg J, Piehl-Aulin K. Skeletal Muscle Morphology and Aerobic Capacity in Patients with Obstructive Sleep Apnoea Syndrome. Respiration. 2008;76 (1):21–7.
14. Wåhlin-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 (4):556–61.
15. Wåhlin-Larsson B, Kadi F, Ulfberg J, Piehl-Aulin K. Skeletal muscle morphology in patients with restless legs syndrome. Eur Neurol. 2007;58(3):133–7.
16. Charifi N, Kadi F, Feasson L, Costes F, Geyssant A, Denis C. Enhancement of microvessel tortuosity in the vastus lateralis muscle of old men in response to endurance training. J Physiol (Lond). 2003;554(2):559–69.
17. Martini FH, Nath JL. Fundamental of anatomy & physiology. 8 ed. Pearson Education: New Jersey; 2008. p. 724–7.
18. Clifford PS, Hellsten Y. Vasodilatory mechanisms in contracting skeletal muscle. J Appl Physiol. 2004;97(1):393–403.
19. Carmeliet P. Mechanisms of angiogenesis and arteriogenesis. Nat Med. 2000;6(4):389–95.
20. Risau W. Mechanism of angiogenesis. Nature. 1997;386:671–4.
21. Hudlicka O. What makes blood vessels grow? J Physiol. 1991;444:1–25.
22. Gupta K, Zhang J. Angiogenesis: a curse or cure? Postgrad Med J. 2004;81:236–42.
23. Breen E, Tang K, Olfert M, Knapp A, Wagner P. Skeletal muscle capillarity during hypoxia: VEGF and its activation. High Alt Med Biol. 2008;9(2):158–66.
24. Ferrara N, Gerber HP, LeCouter J. The biology of VEGF and its receptors. Nat Med. 2003;9 (6):669–76.
25. Deveci D, Marshall JM, Egginton S. Relationship between capillary angiogenesis, fiber type, and fiber size in chronic systemic hypoxia. Am J Physiol Heart Circ Physiol. 2001;281(1): H241–52.
26. Deveci D, Marshall JM, Egginton S. Chronic hypoxia induces prolonged angiogenesis in skeletal muscles of rat. Exp Physiol. 2002;87(3):287–91.
27. Mathieu-Costello OAP, Wu L, Szewczak JM, MacMillen RE. Increased fiber capillarization in flight muscle of finch at altitude. Respir Physiol. 1998;11(2):189–99.
28. Lundby C, Pilegaard H, Andersen JL, van Hall G, Sander M, Calbet JA. Acclimatization to 4100 m does not change capillary density or mRNA expression of potential angiogenesis regulatory factors in human skeletal muscle. J Exp Biol. 2004;207(Pt22):3865–71.
29. Poole DC, Mathieu-Costello O. Skeletal muscle capillary geometry: adaptation to chronic hypoxia. Respir Physiol. 1989;77(1):21–9.

30. Gustafsson T, Rundqvist H, Norrbom J, Rullman E, Jansson E, Sundberg CJ. The influence of physical training on the angiopoietin and VEGF-A systems in human skeletal muscle. J Appl Physiol. 2007;103(3):1012–20.
31. Ouchi N, Shibata R, Walsh K. AMP-activated protein kinase signaling stimulates VEGF expression and angiogenesis in skeletal muscle. Circ Res. 2005;96(8):838–46.
32. Adair TH. Growth regulation of the vascular system: an emerging role for adenosine. Am J Physiol Regul Integr Comp Physiol. 2005;289(2):R283–96.
33. Hudlicka O. Is physiological angiogenesis in skeletal muscle regulated by changes in microcirculation? Microcirculation. 1998;5(1):5–23.
34. Dvorak HF, Brown LF, Detmar M, Dvorak AM. Vascular permeability factor/vascular endothelial growth factor, microvascular hyperpermeability, and angiogenesis. Am J Pathol. 1995;146(5):1029–39.
35. Lescaudron L, Peltékian E, Fontaine-Pérus J, Paulin D, Zampieri M, Garcia L, Parrish E. Blood borne macrophages are essential for the triggering of muscle regeneration following muscle transplant. Neuromuscul Disord. 1999;9(2):72–80.
36. Malm C, Nyberg P, Engström M, Sjödin B, Lenkei R, Ekblom B, Lundberg I. Immunological changes in human skeletal muscle and blood after eccentric exercise and multiple biopsies. J physiol. 2000;529(1):243–62.
37. Malm C, Sjödin B, Sjöberg B, Lenkei R, Renström R, Lundberg I, Ekblom B. Leukocytes, cytokines, growth factors and hormones in human skeletal muscle and blood after uphill or downhill running. J physiol. 2003;556(3):983–1000.
38. Dubowitz V, Sevrey CA. Muscle biopsy—a practical approach, 3 ed. Elsevier: North Holland; 2007.
39. Tucci M, Quatraro C, Dammacco F, Silvestris F. Increased IL-18 production by dendritic cells in active inflammatory myopathies. Ann NY Acad Sci 2007; 1107184–92.
40. Lindvall B, Dahlbom K, Henriksson KG, Srinivas U, Ernerudh J. The expression of adhesion molecules in muscle biopsies: the LFA-1/VLA-4 ratio in polymyositis. Acta Neurol Scand. 2003;107(2):134–41.
41. Wåhlin-Larsson B. Skeletal muscle in patients with Restless Legs Syndrome (RLS) and Obstructive Sleep Apnoea Syndrome (OSAS). Örebro: Örebro University; 2009.
42. Jensen L, Bangsbo J, Hellsten Y. Effect of high intensity training on capillarization and presence of angiogenic factors in human skeletal muscle. J physiol. 2004;1(557):571–82.
43. Andersen P, Saltin B. Maximal perfusion of skeletal muscle in man. J Physiol. 1985;366:233–49.
44. Douglas NJ, Thomas S, Jan MA. Clinical value of polysomnography. Lancet 1992; 8(339 (8789)):347–50.
45. Dubowitz V, Pearse AGE. Oxidative enzymes and phosphorylase in central core disease of muscle. Lancet. 1960;2(7140):23–4.
46. Elmenhorst EM, Elmenhorst D, Luks N, Maass H, Vejvoda M, Samel A. Partial sleep deprivation: impact on the architecture and quality of sleep. Sleep Med. 2008;9(8):840–50.
47. Ekbom KA. Restless legs: a clinical study. Acta Med Scand Supply. 1945;158:1–123.
48. Anderson KN, Di Maria C, Allen J. Novel assessment of microvascular changes in idiopathic restless legs syndrome (Willis-Ekbom disease). J Sleep Res. 2013;22(3):315–21.

Outcome and Mortality in Renal Failure Related RLS

10

S. Lorenzut, S. de Biase and G.L. Gigli

Restless legs syndrome (RLS) is a common neurological disorder that is characterized by an urge to move the legs (rarely also the arms) and peculiar unpleasant deep sensations in the legs. The urge to move begins or worsens during periods of rest or inactivity, particularly in the evening and at night, and is partially or totally relieved by movement [1]. Prevalence of RLS in general population ranges between 2.2 and 7.9% [2]. Based on the etiology, RLS can be divided into primary (idiopathic) and secondary (symptomatic) forms. The main secondary forms are iron deficiency [3, 4], pregnancy [5], diabetes [6, 7], use of drugs (e.g., neuroleptics) and kidney disease [8, 9]. RLS secondary to end stage renal disease (ESRD) is one of the most important secondary forms.

Different data described RLS as a risk factor for cardio- and cerebrovascular events and for mortality in general population [10–12].

RLS and Chronic Kidney Disease

RLS has an increased prevalence in patients suffering of ESRD undergoing dialysis, ranging from 6.6 to 83% in different case series [13, 14]. This large variability is due to the heterogeneity of the study population and to the different criteria used to

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diagnose RLS. More recent studies using the International Restless Legs Syndrome Study Group (IRLSSG) criteria reported that the prevalence of RLS was 7–22% in dialysis patients [8, 15], which is substantially higher than the prevalence observed in the general population.

The association between RLS and ESRD has been confirmed by numerous studies [8, 9]. In the last years, a growing interest is developing regarding RLS in the "pre-dialytic" phase of chronic kidney disease. This interest is supported by the negative impact that sleep disorders have on quality of life (QoL), on immune response and on the development of cardiovascular events, which are the most frequent cause of death in patient with chronic renal failure. First studies conducted on this population analyzed the quality of sleep in general but did not focus on a specific sleep disturbance (e.g., RLS). In this population, it was showed a high prevalence of "poor sleepers" and psychological factors were identified as the only predictor of disrupted sleep [16, 17]. More recent studies demonstrated a high prevalence of intrinsic sleep disorders, such as RLS, in nondialyzed patients, both adults and children. The prevalence found in the literature ranges between 10.9% [18] and 35% [19]. These studies did not identify a direct correlation between the decline of renal function and the presence of RLS. The only two risk factors that have been identified were female sex and iron deficiency [18].

Although the pathophysiology of RLS in chronic renal failure remains unclear, previous studies have suggested a primary role of iron deficiency and calcium/phosphate imbalance in the occurrence of the sleep disorder in this specific population [20, 21]. In a study on 55 dialyzed patients, authors found RLS symptoms in 40% of patients and showed that patients complaining RLS symptoms had lower hemoglobin levels, compared to the other dialyzed patients ($p = 0.03$). They subsequently demonstrated that RLS symptoms improved after correcting anemia with alpha-erythropoietin [20]. It has also been hypothesized a role of the calcium/phosphate balance in the pathogenesis of RLS. In a study on 136 dialyzed patients (RLS prevalence of 23%), authors did not found statistical differences between patients having or not RLS, except for intact parathyroid hormone levels (iPTH). Uremic patients with RLS showed significantly lower iPTH concentration ($p < 0.01$) [21]. However, this hypothesis has not been confirmed by other studies.

Successful renal transplantation has an immediate and dramatic effect on uremic RLS. In a study including 11 patients with a long-term course of RLS symptoms, they all had a complete recovery within 1–21 days after kidney transplantation. However, among those who again became dependent to dialysis due to a chronic transplant failure, RLS symptoms reoccurred within a few days after restarting hemodialysis [22]. Molnar et al. (2005) showed that RLS symptoms were less frequent in patients after kidney transplantation than in patients on maintenance dialysis. The authors suggested that "uremic factors," thought to be responsible for the higher prevalence of RLS in dialysis patients, are largely eliminated after a successful kidney transplantation [23]. Differently from transplantation, dialysis did not show any positive effect on RLS. Indeed, there are studies reporting that the frequency of dialysis session per week and dialysis dependency are higher in

uremic patients with RLS than in those without the syndrome [8, 24]. Several observations have suggested an association between RLS and neuropathy, especially with the involvement of small sensory fibers [25].

RLS and Outcome

The presence of RLS symptoms in dialyzed patients may have different consequences; in particular, they can increase mortality, cardio- and cerebrovascular events and may have a negative impact on quality of life and depression (Fig. 10.1).

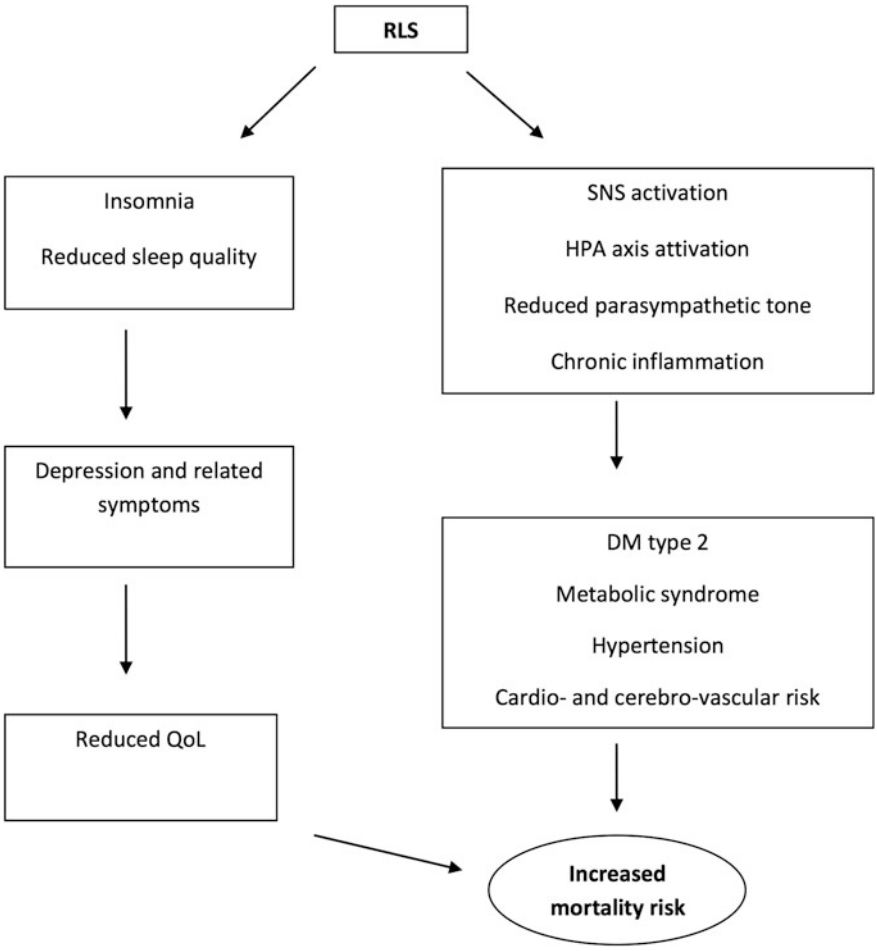

Fig. 10.1 RLS in chronic renal failure and outcome

Cardio- and Cerebrovascular Risk

RLS from different studies seems to be associated with an increased risk of cardiovascular events, hypertension, diabetes, and related disorders. Concerning the relationship between RLS and cardiovascular disease (CVD), there are different hypothesis. First, RLS may increase the risk for CVD and related disorders due to a chronic activation of the sympathetic nervous system (SNS) and hypothalamic-pituitary-adrenal (HPA) axis. Several recent studies suggested that RLS is characterized by autonomic dysregulation. Compared with general population, adults with RLS have shown significant elevations in nocturnal blood pressure and pulse rate [26, 27], as well as cortical (electroencephalography) arousals, in association with periodic limb movements during sleep (PLMS). PLMS are stereotyped, repetitive jerking movements of the lower limbs that frequently accompany RLS. Cortical arousals often precede PLMS onset [28], suggesting that increased sympathetic drive may play a key etiological role in RLS-associated PLMS. The repetitive occurrence of such arousals may lead to a cumulative increase in sympatho-excitation and consequently of the cardiovascular risk. In addition, certain anti-hypertensive medications, including beta-blockers (e.g., propranolol) and alpha-adrenergic agonists (e.g., clonidine), which reduce sympathetic activation, are known to attenuate symptoms of RLS [29, 30]. This is another finding in support to a possible role of autonomic dysfunction in RLS etiology, with the emerging evidence that RLS is associated with HPA axis activation. In a recent study on 73 RLS patients and 34 controls, Schilling et al. found a significantly increased nocturnal cortisol release in the group of RLS patients. Cortisol levels were unrelated to the frequency of PLMS, suggesting that the presence of PLMS may not completely explain the HPA activity in RLS [31]. Sympathetic hyperactivity, chronic HPA axis activation, and reduced parasympathetic tone have been strongly implicated in the pathogenesis of metabolic syndrome and in the development and progression of Diabete type 2 (DM2), hypertension (HTN), and CVD [32, 33].

Second, RLS could also increase the risk for CVD and diabetes due to its well-documented negative effect on sleep and mood. Sleep disturbance can promote glucose intolerance, proinflammatory changes, dyslipidemia, obesity, and HTN [34, 35]. In different studies, an impaired sleep has been linked with an increased risk for DM2 disease [36] and for CVD morbidity and mortality. [37, 38].

In patients affected by chronic kidney disease, cardio- and cerebrovascular events represent the first cause of morbidity and mortality, a risk that can be aggravated by the presence of RLS. Patients with CKD not only have a higher prevalence of traditional CVD risk factors than general population, but they are also exposed to other nontraditional uremia-related CVD risk factors [39, 40].

In a recent article, La Manna et al. enrolled 100 patients in ESRD and they observed that RLS affected 31% of the study population. After a follow up of 18 month, they showed a higher number of cardiovascular events and a higher short-term mortality in patients with RLS than in those without RLS. New cardiovascular events occurred in 64.5% of patients with and 39.1% without RLS

($p = 0.019$). Furthermore, the authors showed that new cardiovascular events increased with the severity of RLS, being higher in patients with continuous RLS than in patients with intermittent RLS [41].

The increased cardiovascular events are not completely attributable to well-known cardiovascular risk factors such as arterial hypertension, diabetes, smoking, obesity, and physical inactivity. Additional specific risk factors related to ESRD condition such as uraemia, mineral metabolism disorders, inflammation, oxidative stress, and malnutrition may be involved in cardiovascular events [42]. In particular, chronic inflammation affects 30–50% of haemodialysis patients and high C-reactive protein (CRP) levels are strongly associated with a three to fivefold increased rate of coronary events and of cardiovascular or all-causes mortality in the general population as well as in ESRD patients undergoing haemodialysis [43]. Some data have shown a correlation between sleep restriction and increased inflammation, both in general population [44] and in dialysis patients [45]. In a recent study, Merlino et al. (2012) observed that CRP levels were significantly higher in HD patients with RLS than in those without the sleep disorder. In addition, the multivariate analysis, including several variables known to be able to cause inflammation in HD patients, confirmed that RLS was independently associated with CRP in this specific population [46].

More recently, authors had access to echocardiographic data of some dialyzed patients, including 32 cases on hemodialysis and 16 on peritoneal dialysis. In these patients, echocardiography was not based on specific medical indication. The comparison between those with and without RLS showed no difference in any echocardiographic data, including left ventricular ejection fraction (LVEF), cardiac dimensions, systolic and diastolic cardiac dysfunction, and pulmonary artery pressure (PAP).

To our knowledge, only few data regarding RLS with CKD not under dialysis are available. In particular, in a study of 301 CKD patients (RLS prevalence of 18.3%), Quinn et al. showed no significant differences regarding hypertension, congestive heart failure, diabetes and COPD between patients having or not the sleep disorder [47].

RLS and Mortality

In general population only few studies analyzed the relationship between RLS and mortality.

In a cohort of 5102 subjects, Mallon et al. applied a questionnaire including questions about RLS, daytime sleepiness, demographic and lifestyle variables, sleep habits, medical conditions, and depression. In a multivariate model, they showed that the women complaining of restless legs symptoms and daytime sleepiness were associated with increased mortality risk, compared to women without RLS and daytime sleepiness (HR: 1.85 95% CI: 1.20–2.85; $p = 0.005$) [48]. On the contrary, in a recent work, Szentkirályi et al. compared four independently conducted prospective cohort studies. The prevalence of RLS ranged between 7.4% and 11.9%

and during a follow up ranging between 6 and 11 years, the presence of RLS did not increase the risk of all-cause mortality in any of the four studies [49].

If we considered RLS in patients with chronic kidney disease, Unruh et al. in a population of 894 dialyzed patients observed, after adjustment for others risk factors, that the presence of RLS was associated to an increased risk of death (HR: 1.39 95% CI: 1.08–1.79). In particular, a higher risk of death was associated with patients complaining of the most severe RLS symptoms. There was no difference in the distribution of atherosclerotic CVD as the primary cause of death between those with and those without severe RLS (58.0% vs. 56.4%; $p = 0.84$) [15]. La Manna et al. in a population of dialyzed patients showed an increased risk of death in RLS patients. Mortality was 20.0% in all patients, 32.3% in those with and 14.5% in patients without RLS ($p = 0.04$) [41]. This study confirmed the associations between the severity of RLS and the risk of new cardiovascular events and higher short-term mortality.

In a previous study, Winkelmann et al. found an increased mortality risk in dialyzed patients with RLS than in those without the sleep disorder. They also observed that RLS was independently associated with an increased rate of premature discontinuation of dialysis. The poor adherence to dialysis prescription may play a role in increasing the mortality risk in the RLS population [45].

RLS and Quality of Life

Patients undergoing dialysis therapy due to ESRD present a high prevalence of sleep disorders such as insomnia, excessive daytime sleepiness (EDS), sleep disordered breathing, and movement disorders during sleep than in general population. These disturbances appear to have a negative impact on the life quality of these patients [50, 51]. One of the most important effects on sleep is represented by insomnia. There is a bidirectional, very strong link between insomnia and depression; insomnia is considered to be a symptom of depression, but it is also a risk factor for developing major depressive disorder [52]. Several potential mechanisms, such as fatigue, social isolation, chronic pain, lack of diagnosis and treatment, could contribute to the sleep-independent association between RLS and depression [44]. Szentkiralyi et al. in a large cohort of patients with chronic renal failure (already transplanted or in transplantation waiting list) found that depressive symptoms were more than twice as frequent among patients with RLS compared with those without RLS symptoms (56 and 22%). In a multivariate analysis, they demonstrated that RLS symptoms were associated with depression, independently of the presence of insomnia. However, the strength of the association was attenuated when insomnia was entered into the multivariate model. These results suggest that both sleep-related and sleep-independent factors may play a role in depressive symptoms in RLS patients [44]. RLS symptoms that are not exclusively related to sleep, specifically paraesthesias, discomfort and restlessness, may also have a significant negative impact on the QoL of patients suffering from the syndrome [53].

As well as the severity of RLS symptoms tend to increase with the impairment of the renal function, also the prevalence of depression appeared to be higher in patients with renal failure, rather than in those with preserved renal function. Aritake-Okada et al. found that the presence of depressive symptoms was associated with the existence of RLS and the level of chronic kidney disease, being more severe in those with renal failure [54]. In different case series it has been analyzed the important impact of depression in RLS patients, the prevalence of depression ranging from 15 to 61% [55, 56].

Patients undergoing dialysis due to ESRD present a higher prevalence of sleep disorders than the general population. Gigli et al. demonstrated than in a sample of 407 dialysis patients (31.2% with RLS symptoms), RLS patients were significantly more affected by symptoms of insomnia, difficultly in falling asleep, higher number of nocturnal awakenings, early morning awakenings, use of hypnotics, mood disorders due to sleep deprivation and excessive daytime somnolence compared with those not complaining RLS symptoms [8]. Similarly, Winkelman et al. found that the presence of RLS was associated with poor sleep measures including lengthening of sleep onset, increased number of nocturnal awakenings, and total sleep reduction, as well as a significantly increased mortality risk (a lengthening of sleep onset, an increased number of nocturnal awakenings and a reduction in total sleep time were all directly correlated with the RLS symptom score) [56].

Mucsi et al., in a sample of 333 patients on dialysis, reported that RLS patients (13.5%) were twice as likely to have significant insomnia as patients without RLS (35 vs. 16%; $p < 0.05$). In multivariate regression models, the presence of RLS was the strongest significant independent predictor of the AIS (Athens Insomnia Scale) score or the presence of insomnia [53]. The same findings regarding sleep problems were found by Molnar et al. in a sample of 1067 kidney transplanted patients. Even if the prevalence of RLS in kidney transplanted patients seems to be similar to that of the general population, patients complaining RLS symptoms were more than three times more likely to have insomnia and had significantly higher AIS scores than patients without RLS. Patients with RLS reported more frequently problems with sleep initiation, sleep fragmentation, early awakening, and daytime consequences of poor sleep [57].

Szentkiralyi et al. found a stronger association between RLS symptoms and depression in waitlisted patients than in transplanted patients. They did not exclude the possibility that the more pronounced renal failure in the waitlisted group could somehow account for this observation. However, the dialysis sessions impose a 4-h immobilization test three times a week on waitlisted patients, which may provoke and exacerbate RLS symptoms. These can also explain the higher prevalence compared with kidney transplanted patients [58].

Regarding the type of dialysis, different studies have reported a similar prevalence of RLS symptoms between peritoneal and hemodialysis patients [8, 15, 46].

Jaber et al. demonstrated that home short daily hemodialysis (SDHD) is associated with long-term improvement in the prevalence and severity of RLS, sleep disturbances, and depressive symptoms. They affirmed that these favorable changes

might be due in part to the location of the therapy in the home setting and self-care dialysis [59].

Different studies have showed the negative impact of RLS on the quality of life. RLS interferes with sleep, resulting in impaired daytime well-being, increased daytime sleepiness and reduced mental and physical functioning capacity. Unruh et al. (2004), in a large dialysis cohort, described that patients with severe RLS had lower QoL indicators, including lower physical and mental component summary scores, lower vitality, higher bodily pain, and lower sleep quality, and had a 39% risk increase in all-cause mortality [15]. Similarly, Molnar et al. in a sample of kidney transplanted patients, described a worse QoL in patients with RLS for both the general domains assessing physical health status and also for the mental aspects of QoL [57].

Giannaki et al., in a sample on 70 patients on hemodialysis, found that 30 of them (42%) had RLS symptoms. In RLS patients, they found an higher level of muscle atrophy [60]. One explanation was that RLS is associated with sleep deprivation, which in turn could evoke alterations in anabolic hormones secretion and circulation such as in growth hormone (GH) and insulin-like growth factor I (IGF-I) [61] eventually affecting the patient's anabolism and muscle mass. However in this study, the lower level of QoL reported by the RLS patients on hemodialysis seems to be due mainly to mental health- and sleep-related aspects rather than the physical aspects. (In this study RLS patients had an impaired QoL; however, the differences with patients not complaining RLS symptoms was better explained by their diminished mental rather than their physical aspects).

Rijsman et al. (2004) found that almost 90% of all dialysis patients with RLS also have PLM. RLS appears to be the most important factor for PLM and is associated with low quality sleep and emotional distress. Patients without RLS may still have severe PLM; therefore, this disorder can have clinical relevance on sleep quality [13]. Beecroft et al. found that kidney transplantation was associated with a significant reduction in periodic limb movement index in all patients [62].

Conclusion

RLS in uremic patients appears to develop markedly more severe symptoms within a short period of time after starting dialysis. In this population, RLS is associated with a higher frequency of the indicators of insomnia and a higher prevalence of symptoms suggesting other sleep disorders. It is also associated with significantly impaired QoL and increased risk of cardio- and cerebrovascular disease and mortality. Therefore, clinicians should make every effort to diagnose and treat symptoms of restless legs in this at-risk population.

References

1. Allen RP, Picchietti D, Hening WA, Trenkwalder C, Walters AS, Montplaisi J. Restless legs syndrome diagnosis and epidemiology workshop at the national institute of health; international restless legs syndrome study group. 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.
2. Ohayon MM, O'Hara R, Vitiello MV. Epidemiology of restless legs syndrome: a synthesis of the literature. Sleep Med Rev. 2012;16(4):283–95.
3. 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 (8):1698–700.
4. Ulfberg J, Nyström B. Restless legs syndrome in blood donors. Sleep Med. 2004;5(2):115–8.
5. Manconi M, Govoni V, De Vito A, Economou NT, Cesnik E, Casetta I, et al. Restless legs syndrome and pregnancy. Neurology. 2004;63(6):1065–9.
6. Merlino G, Fratticci L, Valente M, Del Giudice A, Noacco C, Dolso P, et al. Association of restless legs syndrome in type 2 diabetes: a case-control study. Sleep. 2007;30(7):866–71.
7. Happe S, Treptau N, Ziegler R, Harms E. Restless legs syndrome and sleep problems in children and adolescents with insulin-dependent diabetes mellitus type 1. Neuropediatrics. 2005;36(2):98–103.
8. Gigli GL, Adorati M, Dolso P, Piani A, Valente M, Brotini S, et al. Restless legs syndrome in end-stage renal disease. Sleep Med. 2004;5:309–15.
9. Bhowmik D, Bhatia M, Gupta S, Agarwal SK, Tiwari SC, Dash SC. Restless legs syndrome in hemodialysis patients in India: a case controlled study. Sleep Med. 2003;4(2):143–6.
10. Walters AS, Rye DB. Review of the relationship of restless legs syndrome and periodic limb movements in sleep to hypertension, heart disease, and stroke. Sleep. 2009;32:589–97.
11. 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.
12. 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.
13. Rijsman RM, de Weerd AW, Stam CJ, Kerkhof GA, Rosman JB. Periodic limb movement disorder and restless legs syndrome in dialysis patients. Nephrology (Carlton). 2004;9: 353–61.
14. Enomoto M, Inoue Y, Namba K, Munezawa M, Matsuura T. Clinical characteristics of restless legs syndrome in end-stage renal failure and idiopathic RLS patients. Mov Disord. 2008;6:811–6.
15. Unruh ML, Levey AS, D'Ambrosio C, Fink NE, Powe NR, Meyer KB. Choices for healthy outcomes in caring for end-stage renal disease (CHOICE) study. Restless legs symptoms among incident dialysis patients: association with lower quality of life and shorter survival. Am J Kidney Dis. 2004;43:900–9.
16. De Santo, Bartiromo M, Cesare CM, Cirillo M. Sleep disorders occur very early in chronic kidney disease. J Nephrol 2008;21 suppl 13: s59–65.
17. Sabbatini M, Pisani A, Crispo A, Ragosta A, Gallo R, Pota A, et al. Sleep quality in patients with chronic renal failure: a 3-year longitudinal study. Sleep Med. 2008;9:240–6.
18. Merlino G, Lorenzut S, Gigli GL, Romano G, Montanaro D, Moro A, et al. A case-control study on restless legs syndrome in nondialyzed Patients with Chronic Renal Failure. Mov Disord. 2010;25(8):1019–25.
19. Applebee GA, Guillot AP, Schuman CC, Teddy S, Attarian HP. Restless legs syndrome in pediatric patients with chronic kidney disease. Pediatr Nephrol. 2009;24(3):545–8.
20. Roger SD, Harris DC, Stewart JH. Possible relation between restless legs and anaemia in renal dialysis patients. Lancet. 1991;337(8756):1551.

21. Collado-Seidel V, Kohnen R, Samtleben W, Hillebrand GF, Oertel WH, Trenkwalder C. Clinical and biochemical findings in uremic patients with and without restless legs syndrome. Am J Kidney Dis. 1998;31:324–8.
22. Winkelmann J, Stautner A, Samtleben W, Trenkwalder C. Long-term course of restless legs syndrome in dialysis patients after kidney transplantation. Mov Disord. 2002;17:1072–6.
23. Molnar AZ, 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.
24. Huiqi Q, Shan L, Minqcai Q. Restless legs syndrome (RLS) in uremic patients is related to the frequency of hemodialysis sessions. Nephron. 2000;86:540.
25. Iannaccone S, Quattrini A, Sferrazza B, Ferini-Strambi L, Gemignani F, Marbini A, et al. Charcot-Marie-Tooth disease type 2 with restless legs syndrome. Neurology. 2000;54: 1013–4.
26. Pennestri MH, Montplaisir J, Colombo R, Lavigne G, Lanfranchi PA. Nocturnal blood pressure changes in patients with restless legs syndrome. Neurology. 2007;68(15):1213–8.
27. 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. Feb 2007;118(2):438–48.
28. Coleman RM, Pollak CP, Weitzman ED. Periodic movements in sleep (nocturnal myoclonus): relation to sleep disorders. Ann. Neurol. 1980;8:416–21.
29. Trenkwalder C, Hening WA, Montagna P, Oertel WH, Allen RP, Walters AS, et al. Treatment of restless legs syndrome: an evidence-based review and implications for clinical practice. Mov Disord. 2008;23(16):2267–302.
30. Tan EK, Ondo W. Restless legs syndrome: clinical features and treatment. Am J Med Sci. 2000;319(6):397–403.
31. Schilling C, Schredl M, Strobl P, Deuschle M. Restless legs syndrome: evidence for nocturnal hypothalamic-pituitary-adrenal system activation. Mov Disord. 2010;25(8):1047e52.
32. Egan BM. Insulin resistance and the sympathetic nervous system. Curr Hypertens Rep. Jun 2003;5(3):247–54.
33. Rosmond R. Stress induced disturbances of the HPA axis: a pathway to type 2 diabetes? Med Sci Monit. Feb 2003;9(2):RA35–39.
34. Miller MA, Cappuccio FP. Inflammation, sleep, obesity and cardiovascular disease. Curr Vasc Pharmacol. Apr 2007;5(2):93–102.
35. McEwen BS. Sleep deprivation as a neurobiologic and physiologic stressor: allostasis and allostatic load. Metabolism. 2006;55(10 Suppl):S20–3.
36. Nilsson PM, Roost M, Engstrom G, Hedblad B, Berglund G. Incidence of diabetes in middle-aged men is related to sleep disturbances. Diab Care. 2004;27(10):2464–9.
37. Quan SF. Sleep disturbances and their relationship to cardiovascular disease. Am J Lifestyle Med. 2010;3(Suppl 1):55–9.
38. Meisinger C, Heier M, Loewel H, Study MKAC. Sleep disturbance as a predictor of type 2 diabetes mellitus in men and women from the general population. Diabetologia. 2005;48 (2):235–41.
39. Go AS, Chertow GM, Fan D, McCulloch CE, Hsu CY. Chronic kidney disease and the risks of death, cardiovascular events, and hospitalization. N Engl J Med. 2004;351(13):1296–305.
40. Shastri S, Sarnak MJ. Cardiovascular disease and CKD: core curriculum 2010. Am J Kidney Dis. 2010;56(2):399–417.
41. La Manna G, Pizza F, Persici E, Baraldi O, Comai G, Cappuccilli ML, et al. Restless legs syndrome enhances cardiovascular risk and mortality in patients with end-stage kidney disease undergoing long-term haemodialysis treatment. Nephrol Dial Transplant. 2011;26 (6):1976–83.
42. Stenvinkel P. Malnutrition and chronic inflammation as risk factors for cardiovascular disease in chronic renal failure. Blood Purif. 2001;19:143–51.
43. Zimmermann J, Herrlinger S, Pruy A, Metzger T, Wanner C. Inflammation enhances cardiovascular risk and mortality in hemodialysis patients. Kidney Int. 1999;55:648–58.

44. Simpsom N, Dinges DF. Sleep and inflammation. Nutr Rev. 2007;65:S244–52.
45. Chiu YL, Chuang YF, Fang KC, et al. Higher systemic inflammation is associated with poorer sleep quality in stable haemodialysis patients. Nephrol Dial Transplant. 2009;24:247–51.
46. Merlino G, Lorenzut S, Romano G, Sommaro M, Fontana A, Montanaro D, et al. Restless legs syndrome in dialysis patients: a comparison between hemodialysis and continuous ambulatory peritoneal dialysis. Neurol Sci. 2012;33:1311–8.
47. Quinn C, Uzbeck M, Saleem I, Cotter P, Ali J, O'Malley G, et al. Iron status and chronic kidney disease predict restless legs syndrome in an older hospital population. Sleep Med. 2011;12(3):295–301.
48. Mallon L, Broman JE, 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(4):457–63.
49. Szentkirályi A, Winter AC, Schürks M, Völzke H, Hoffmann W, E Buring J, et al. Restless legs syndrome and all-cause mortality in four prospective cohort studies. BMJ Open. 2012 Nov 5;2(6).
50. Parker KP. Sleep disturbances in dialysis patients. Sleep Med Rev. 2003;7:131–43.
51. Kosmadakis GC, Medcalf JF. Sleep disorders in dialysis patients. Int J Artif Organs. 2008;31:919–27.
52. 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.
53. Mucsi I, Molnar MZ, Ambrus C, Szeifert L, Kovacs AZ, Zoller R, et al. Restless legs syndrome, insomnia and quality of life in patients on maintenance dialysis. Nephrol Dial Transplant. 2005;20(3):571–7.
54. Chilcot J, Wellsted D, Da Silva-Gane M, Farrington K. Depression on dialysis. Nephron Clin Pract. 2008;108:256–64.
55. Lopes AA, Albert JM, Young EW, Satayathum S, Pisoni RL, Andreucci VE, et al. Screening for depression in hemodialysis patients: associations with diagnosis, treatment, and outcomes in the DOPPS. Kidney Int. 2004;66:2047–53.
56. Winkelman JW, Chertow GM, Lazarus JM. Restless legs syndrome in end-stage renal disease. Am J Kidney Dis. 1996;28:372–8.
57. Molnar MZ, Novak M, Szeifert L, Ambrus C, Keszei A, Koczy A, et al. Restless legs syndrome, insomnia, and quality of life after renal transplantation. J Psychosom Res. 2007;63:591–7.
58. Szentkiralyi A, Molnar MZ, Czira ME, Deak G, Lindner AV, Szeifert L, et al. Association between restless legs syndrome and depression in patients with chronic kidney disease. J Psychosom Res. 2009;2:173–80.
59. Jaber BL, Schiller B, Burkart JM, Daoui R, Kraus MA, Lee Y, et al. FREEDOM study group. Impact of short daily hemodialysis on restless legs symptoms and sleep disturbances. Clin J Am Soc Nephrol. 2011;6:1049–56.
60. Giannaki CD, Sakkas GK, Karatzaferi C, Hadjigeorgiou GM, Lavdas E, Liakopoulos V, et al. Evidence of increased muscle atrophy and impaired quality of life parameters in patients with uremic restless legs syndrome. PLoS ONE. 2011;6:e25180.
61. Van Cauter E, Spiegel K, Tasali E, Leproult R. Metabolic consequences of sleep and sleep loss. Sleep Med. 2008;9(Suppl 1):S23–8.
62. Beecroft JM, Zaltzman J, Prasad GV, Meliton G, Hanly PJ. Improvement of periodic limb movements following kidney transplantation. Nephron Clin Pract. 2008;109:c133–9.

Suggested Reading

63. Aritake-Okada S, Nakao T, Komada Y, Asaoka S, Sakuta K, et al. Prevalence and clinical characteristics of restless legs syndrome in chronic kidney disease patients. Sleep Med. 2011;12:1031–3.
64. Merlino G, Piani A, Dolso P, Adorati M, Cancelli I, Valente M, et al. Sleep disorders in patients with end stage renal disease undergoing dialysis therapy. Nephrol Dial Transplant. 2006;21:184–90.
65. Molnar MZ, Novak M, Mucsi I. Sleep disorders and quality of life in renal transplant recipients. Int Urol Nephrol. 2009;41:373–82.
66. Takakaki J, Nishi T, Nangaku M, Shimoyama H, Inada T, Matsuyama N, et al. Clinical and psychological aspects of restless legs syndrome in uremic patients on hemodialysis. Am J Kidney Dis. 2003;41:833–9.

Part II
Long Term Management of Restless Legs Syndrome/Willis-Ekbom Disease

Long-Term Efficacy of Pharmacological Treatment

11

Pietro-Luca Ratti

General Considerations

Restless Legs Syndrome-Willis–Ekbom Disease (RLS/WED) is in most cases a chronic, life-long disease with periods of recrudescence and intermission [1]. The age of onset of the disease picks at around 20 and around 40 years-old, with a biphasic distribution [2]. Early age-at-onset forms seem to associate with severer disease compared to late onset forms of the disease [3, 4]. Familiar cases tend to show an earlier age-at-onset, even in childhood [3, 5]. WED/RLS can cause important distress for the patients and negatively impact nocturnal sleep, daytime performance and quality of life [6]. Thus, patients affected by WED/RLS frequently necessitate pharmacological treatment for symptomatic relief for several years and even at elderly age.

On the other hand, many medications employed for WED/RLS bear long-term side effects that impose a cautious use of these agents, especially when higher doses are required. For instance, dopaminergic agents can provoke augmentation [7] or impulse control disorder [8, 9] and opioids are subjected to tolerance and risk of abuse [10].

Although the long-term treatment of WED/RLS represent a challenging task for the clinicians, very few clinical pharmacological studies focused on this topic. In fact, very limited evidence is available on the efficacy of drugs in WED/RLS for follow-up longer than six months [11, 12]. In particular, only one long-term study has been conducted with a double-blind randomized controlled trial (RCT) design [7].

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Several methodological issues preclude generalization of the results of the studies in the literature for routine clinical practice. First, the definition and clinical characterization of WED/RLS is not univocal among the different studies. Second, any placebo-controlled randomized clinical trial is available for the long-term period (i.e., one year or more). Third, most long-term studies were conceived as open-label, uncontrolled extension of short-term RCT, only in the active treatment patients' subgroup. This results in a selection bias of responders, as only these latter are included in the open-label extension. Fourth, as WED/RLS is a chronic disease, the long-term efficacy was ascertained in most studies on the basis of the non-progression of symptoms rather than of their improvement. Fifth, the natural course of the disease can vary from rapidly or slowly progressive forms, on one side, to relatively stable, self-improving and even spontaneously recovering forms, on the other. Thus, it is very hard to ascertain if non-progression or improvement is due to the natural history of the disease or rather to the therapeutic effect of medications, especially in observational studies in which flexible doses of the active treatment are employed [13]. Finally, efficacy outcomes are quite heterogeneous among the studies. As the International Restless Legs Syndrome Severity Scale (IRLSSG-SS) has only been recently validated [14], previous studies employed arbitrary subjective parameters (such as "subjective improvement of RLS symptoms") to assess the long-term efficacy of the different compounds.

More recent studies employed as efficacy outcome the reduction in IRLSSG-SS score from baseline [14]. The Clinical Global Impression scale (CGI), a standard method for making a global assessment of illness, based on physician's impression [15] has also been employed. Other indirect parameters which were employed are the improvement in nocturnal subjective sleep quality, diurnal sleepiness, or quality of life. As indirect parameters, dropout rate for inefficacy and augmentation have also been used in several studies. Augmentation is a serious adverse event developing during long-term dopaminergic medication characterized by an earlier onset of symptoms during the day, faster onset of symptoms when at rest, spreading of symptoms to the upper limbs and trunk, and shorter duration of the treatment effect [7].

These two parameters seem not to be adequate as efficacy measures, in particular for the studies employing drugs at flexible doses. In fact, in these latter, drug doses were adapted case by case by clinicians according to the subjective perceived efficacy and to adverse events.

Recommendations for the long-term treatment of WED/RLS have been published in 2013 by the International RLS Study Group (IRLSSG) [16].

Based on the evidence in the literature (class I and II studies [17, 18], the IRLSSG task force concluded that

- the dopamine agonists pramipexole, ropinirole, and rotigotine are "effective" up to 6 months (grade A recommendation);
- from them, pramipexole and ropinirole are also "probably effective" at 1 year and rotigotine at 5 years (grade B recommendation);

– levodopa is "probably effective" at 2 years (grade B recommendation);
– among the A2δ ligands, pregabalin is "effective" at 1 year (grade A recommendation), and gabapentin enacarbil "probably effective" (grade B recommendation).

A recent study was published after the issue of these guidelines, providing some evidence for the use of prolonged-release oxycodone-naloxone for up to one year [19]. In this chapter, we will focus on drugs employed in WED/RLS based on the evidence from studies including at least 25 patients with WED/RLS and a follow-up of one year or more (Table 11.1).

Dopaminergic Agents

Dopamine Agonists

Among dopamine agonists, the most studied compounds for the long-term treatment of WED/RLS are pramipexole, ropinirole, and rotigotine.

Pramipexole

Pramipexole is a non-ergoline dopamine agonist binding with highest affinity the D_4 and the D_2 dopamine receptors, and with high affinity also for the D_3 receptors [20]. One RCT [21] and five observational longitudinal retrospective studies, on prospective [22–25] or retrospective cohorts [26], have evaluated the efficacy of pramipexole for at least 1 year in WED/RLS.

The only RCT [21] available on pramipexole evaluated the long-term efficacy of pregabalin 300 mg/day compared to pramipexole 0.25 or 0.50 mg/day for 52 weeks as secondary outcome (the primary outcome being the same comparison at 12 weeks and also including a placebo group) in a group of 540 patients. Efficacy was evaluated as a reduction of the IRLS Severity Scale (IRLSSG-SS) score and at the CGI from the baseline. Pramipexole 0.50 mg seems to at least as efficient as pregabalin at 1 year at CGI. As the analysis was conducted in order to assess the non-inferiority of pregabalin compared to pramipexole, any formal conclusion can be driven on the efficacy of pramipexole 0.25 mg versus 0.50 mg at 1-year follow-up from this study. Moreover, the lack of a placebo group for the 52-week analysis represents a major limitation of the study. The augmentation rate was significantly higher in the pramipexole group versus pregabalin, in a dose-dependent fashion. The all-cause dropout rate was similar in the three groups (46% for pramipexole 0.25 mg, 49% for 0.50 mg), suggesting that the efficacy-tolerability rate of pramipexole at one year is still favorable for around half of the treated patients, with a slight dose-dependency.

In all the other five observational, open-label, uncontrolled studies on large case series (50–195 patients) [22, 23, 25–27], pramipexole dose was adjusted case by case according to routine clinical practice, with daily doses varying from 0.125 to 4.5 mg.

Table 11.1 Studies of drugs employed in WED/RLS including at least 25 patients and a follow-up of one year or more

Author, year	Design	Duration	Intervention[b]	N. patients F:M	Age[a]	IRLSG score[a]	Disease duration[a]	Outcome	Results
Allen 2014	RCT	52 weeks	Pregabalin 300 mg versus pramipexole 0.25 mg versus pramipexole 0.50 mg	540, ITT 1.6:1	55.0		4.6	IRLS SS improvement (non-inferiority)	Pregabalin > pramipexole 0.25 mg pregabalin > pramipexole 0.50 mg
								CGI improvement (non-inferiority)	Pregabalin = pramipexole 0.50 mg > pramipexole 0.25 mg
								Drop out	Pregabalin 51% pramipexole 0.25 46% pramipexole 0.50 49%
								Augmentation	Pregabalin 1.7% pramipexole 0.25 mg 6.6% pramipexole 0.50 mg 9.0%
Inoue 2010	ObsLRS	52 weeks	Pramipexole 0.125–0.75 mg, flexible doses 0.31 ± 0.27 mg	140 1.3:1	52.6 ± 14.0	10.1 ± 7.8	0.1 ± 0.4	IRLS SS, CGI, PSQI, ESS	↓ Mean IRLSGSS ↓ Mean CGI ↓ Mean PSQI ↓ Mean ESS
Silber 2003	ObsLRS	27 months	Pramipexole 0.125–4.5 mg, flexible doses 0.38 mg	60 1.5:1	57.7 years (25–82 years)	–	–	Subjective RLS symptoms	67% completely effective 27% partially effective 7% ineffective
								Augmentation	33%
Lipford 2012	ObsLRS	7.96 ± 3.73 years (0.6–12 years)	Pramipexole 0.25–4.5 mg, flexible doses 0.63 mg	50 1.6:1	–	–	–	Subjective RLS symptoms	60% partially or totally effective 28% need to add another drug 12% ineffective
Winkelman 2004	ObsLRS	21.2 ± 11.4 months	Pramipexole 0.125–1.0 mg, flexible doses 0.47 ± 0.22 mg	59 1.4:1	60.8 ± 14.4	–	–	Augmentation Tolerance	32% 46%
Montplaisir 2006	ObsLRS	>1 year	Pramipexole (dose not specified)	195 1.3:1	55.1 ± 12.1	–	23.6	Discontinuation	22.1% 13.3% for inefficacy
		30.5 ± 10.5 months	Pramipexole 0.125–2.25 mg, flexible doses Median 0.59 ± 0.31 mg	152 1.2:1	53 ± 11.8	–	23.2	Subjective severity of RLS symptoms	Mean ↓ of 80.0% (±20.8) Severity ↓ of > 50% in 94.7% points
				130 (subgroup)	–	–	–	Subjective sleep measures	86.9% ↓ sleep latency 20.4% ↓ nocturnal awakenings 91.4% ↑ overall sleep quality

(continued)

Table 11.1 (continued)

Author, year	Design	Duration	Intervention[b]	N. patients F:M	Age[a]	IRLSG score[a]	Disease duration[a]	Outcome	Results
Garcia-Borreguero 2007	ObsLRS	52 weeks	Ropinirole 0.25–4.0 mg, flexible doses 1.64 ± 1.0 mg	309 1.5:1	56.5 ± 11.0	22.0 ± 8.7	–	Augmentation Discontinuation	11.7% 19.0% 3.5% for inefficacy
				233 (subgroup)	–	–	–	IRLS SS, CGI	↓ IRLS SS −10.0 points 71.9% CGI improvement
Ondo 2004	ObsLRS	39.2 ± 20.9 months	Pramipexole (n = 40) ropinirole (n = 19) pergolide (n = 12) flexible doses LDED: 0.79 ± 0.55 mg	83 1.6:1	56.8 ± 11.5	–	22.0	Subjective severity of RLS symptoms	19.3% need to add another drug 24.1% Shift among pramipexole, ropinirole, or pergolide
								Augmentation Discontinuation	28.9% 12% 2.4% for inefficacy
Oertel 2013	ObsLRS	5 years	Rotigotine stable dose after titration: 2.4 ± 1.2 mg end: 3.1 ± 1.1	295 2.0:1	58.3 ± 10.1	27.7 ± 6.0	11.0 (6.0–24.0)	IRLS SS, CGI, RLS-6, RLS-QoL	↓ IRLS SS −18.7 ± 9.5 points ↓ CGI item 1 −2.8 ± 1.1 96% much or very much improvement CGI item 2 ↓ RLS-6 scale ↓ RLS-QoL −18.4 ± 13.2
								Augmentation Discontinuation	13% 57% 11% for inefficacy
								Subjective severity of RLS symptoms	61% need dose adjustment (not say up or down)
VonScheele 1990	ObsLRS	2 years	Levodopa-carbidopa Start: 50–250 mg Median: 100 mg	30 responders 1:1	59 (10–81)	–		Subjective RLS symptoms	86.7 L-DOPA keep to be efficient 30.0% need dose increase 26.7% kept the same dose 30.0% a decreased dose was sufficient
								Discontinuation	13.3% 6.7% for inefficacy

(continued)

Table 11.1 (continued)

Author, year	Design	Duration	Intervention[b]	N. patients F:M	Age[a]	IRLSG score[a]	Disease duration[a]	Outcome	Results
Trenkwalder 2003	ObsLRS	12 months	Levodopa-benserazide (RR + SR, flexible doses) Final: 314 ± 133 mg (150–640) (n = 20)	23, ITT 2.7:1	56 ± 10 (31–72)		20	Subjective sleep measures	Satisfaction with sleep +3.5 ± 1.9 Sleep latency (min) 131±152 Wake periods during night (min) −234 ± 129 Total sleep time +190 ± 136
								Subjective RLS measures	Severity at time falling asleep −6.5 ± 3.4 Severity during the night −6.0 ± 3.5
								CGI	Item 2 change ↑ in 39% points Item 3 change ↑ in 56% points
								Augmentation Discontinuation	34.8% 56.5% 4.3% for inefficacy 21.3% for RLS severity increase
Ellenbogen 2012[c]	ObsLRS	52 weeks	Gabapentin enacarbil flexible doses Final: 1267.0 ± 409.8 mg (600–1800)	573 1.8:1	50.2 ± 11.9 (19–79)	10.4 ± 8.13		IRLS score	↓ IRLS SS −2.4 points (Mean ESS at end 8.0 ± 8.29)
	ObsLRS	52 weeks	Gabapentin enacarbil flexible doses Final: 1197.0 ± 426.4 mg (600–1800)	197 (subgroup) 1.5:1	49.5 ± 12.0 (19–77)	13.8 ± 7.9		IRLS score ESS Discontinuation	↓ IRLS SS 8.4 ± 7.7 (−5.4 points) −2.0 points 1.5% for inefficacy
	ObsLRS	64 weeks	Gabapentin enacarbil flexible doses Final: 1303.7 ± 396.5 mg (600–1800)	376 (subgroup) 1.4:1	50.6 ± 11.8 (20–79)	23.2 ± 5.1		IRLS score ESS Discontinuation	↓ IRLS SS 7.8 ± 8.9 (−15.2 ± 8.9 points) (not available) 2.3% for inefficacy
Inoue 2012	ObsLRS	52 weeks	Gabapentin enacarbil flexible doses Initial: 1150.3 ± 156.6 mg (600–1800) Final: not specified	181 1.1:1	54.9 ± 12.2	24.4 ± 0.4	10.6 ± 11.0	IRLS score PSQI SF-36 Discontinuation Dose adjustment	↓ IRLS SS -18.0 ± 0.6 points ↓ PSQI −3.6 points ↓ SF−36 0.6% for inefficacy Dose increase in 2.2%

(continued)

Table 11.1 (continued)

Author, year	Design	Duration	Intervention[b]	N. patients F:M	Age[a]	IRLSG score[a]	Disease duration[a]	Outcome	Results
									Dose decrease in 10.0%
Ondo 2005	ObsLRS	23 ± 12 months (4–44)	Methadone flexible doses Initial: 13.0 ± 5.9 mg (5–30) Final:15.5 ± 7.7 mg (5–40)	27 1.1:1	54.8 ± 14.4	23		Subjective efficacy Discontinuation	63% efficacy maintained 37% 7.4% for inefficacy
Silver 2011	ObsLRS	1year/10 years	Methadone At 6 months median dose 10 ± mg At 8–10 years median dose ≤ 20 ± (range 5–15)	76				Discontinuation 1st y Discontinuation 2nd–10th year	17% 0%/year
		1year/10 years	Pramipexole Median dose at discontinuation for augmentation: 1.3 ± 1.0 mg	174				Discontinuation 1st year Discontinuation 2nd–10th year	23% 9 ± 3.9%/year 7 ± 2.7%/year for augmentation
		1year/10 years	Pergolide Median dose at discontinuation for augmentation: 0.5 ± 0.5 mg	77				Discontinuation 1st year Discontinuation 2nd–10th year	15% 8 ± 3.4%/year 5 ± 2.7%/year for augmentation
Grote 2009	DB P-C RCT	12 months	Iron sucrose i.v. 200 mg each 3 weeks, 5 times	60 7.6:1 serum ferritin ≤ 45 μmol/L	46 ± 9	Iron sucrose: 24 (10–37) placebo: 26 (13–36)		Discontinuation rate for inefficacy	Iron sucrose < placebo (17.2 vs. 61.2%)

Only statistically significant results are reported for RCTs

[a]Values expressed as mean ± standard deviation, when available

[b]Drug doses are given the 24 h

[c]This study is composed of two sub-studies of 52-week follow-up, with a total of 573 patients. Of them, 197 were drug-naïve and 376 was non-drug-naïve (i.e. they were treated with gabapentin enacarbil for 12 additional weeks before entering the 52-week study)

Taken together, the data emerging from these studies on pramipexole seem to suggest a presumed subjective positive benefit/risk ratio at one year and up to eight years in 50–80% of middle-aged patients with WED/RLS in routine clinical settings. As a rule, with longer disease duration, higher doses of pramipexole are required for symptomatic relief of RLS, with mean doses around 0.3 and 0.6 mg/day. The large variability of the therapeutic schedules employed in the studies, which were also adapted according to patients' clinical needs during the studies themselves, prevents from taking further general considerations on the doses.

Ropinirole

Ropinirole is a non-ergoline D_2, D_3, and D_4 dopamine receptor agonist with highest affinity for D_3 [20]. Although ropinirole probably is the most widely used dopamine agonist in WED/RLS in routine clinical practice, together with pramipexole, evidence justifying its employment is limited. In particular, only one observational, open-label uncontrolled, retrospective study on a prospective cohort has evaluated its use at one-year follow-up on 309 patients with moderate WED/RLS [28]. In this study, 1-year efficacy was only indirectly assessed by augmentation rate (estimated at 12%) and discontinuation rate (19%), which only in few cases (3.5%) seemed to be due to lack of long-term efficacy of ropinirole. In this study, ropinirole was administered at flexible doses varying from 0.25 to 4.0 mg daily, (mean dose: 1.64 ± 1.0 mg/day).

Two other observational, uncontrolled studies seems also to corroborate the interest of ropinirole in the long-term [7, 29], but further studies are needed to assess its efficacy and safety for more than one year [16].

Rotigotine

Rotigotine is a more recently developed dopamine agonist showing an activity at all dopamine receptor subtypes (D1 to D5), with a highest affinity for the D3 receptor [30]. In addition, it acts as an α2-adrenergic receptor antagonist and as an agonist of the 5HT1A receptor [31]. It is conditioned in form of transdermal-release patch assuring 24-hour delivery.

Its long-term efficacy has been evaluated in a single-arm open-label observational retrospective study over in a prospective cohort of 295 patients with moderate-to-severe idiopathic RLS followed for 5 years [32]. The drug was administered at fixed doses after a case-by-case titration, with a mean dose after titration of 2.4 ± 1.2 mg and a mean dose at 5 years of 3.1 ± 1.1 (range: 0.5–4 mg/24 h). Although in more than a half of the patients, a dose increase was necessary over the observation period (as a result of disease progression and/or of augmentation), rotigotine seemed to keep its efficacy for symptomatic relief over 5 years, as documented by a 19 points at the IRLSSG-SS. Also subjective estimates of sleep latency, stability and quality and quality of life seemed to be improved at the end of the follow-up compared to the baseline. Augmentation and discontinuation rates were similar to the ones of other studies on the other dopamine agonists on shorter periods (1–2 years).

Levodopa

Very few data are available on the use of dopamine precursor levodopa in the long-term treatment of WED/RLS on small patients' groups. Only two observational uncontrolled retrospective studies with levodopa associated to a decarboxilase inhibitor (benserazide or carbidopa) are available, with a follow-up of 2- (30 patients) [33] and 1-year (23 patients) [34], respectively. Although levodopa could have a potential interest the treatment of RLS up to two years, evidence of efficacy is lacking.

Alpha-2 Δ Ligands

Gabapentin and pregabalin are two structurally related agents with similar spectra of antiepileptic and antinociceptive activity. The interest of these drugs for the treatment of WED/RLS comes from their efficacy in the treatment of neuropathic pain. Their putative pharmacodynamics are thought to be exerted by inhibition of calcium currents via high-voltage-activated channels containing the $\alpha_2\delta$-1 subunit, leading in turn to reduced neurotransmitter release and attenuation of postsynaptic excitability in central nervous system neurons [35].

Gabapentin Enacarbil

Gabapentin enacarbil is a pro-drug of gabapentin developed to overcome the variable and unpredictable biodisponibility of gabapentin due to the saturation of a low-capacity transporter in the upper small intestine in its absorption pathway [36]. Its use has been evaluated in two retrospective observational studies of 573 [37] and 181 patients [24] with severe WED/RLS, respectively. Gabapentin enacarbil seems to be effective in the reduction of IRLSSG-SS for up to 64 weeks and in improving sleep quality and quality of life of WED/RLS at 1 year. Both studies employed flexible doses between 600 and 1800 mg daily, with a modal dose of 1200 mg/day.

Pregabalin

Long-term efficacy of pregabalin at fixed high dose (300 mg) has been assessed in a single non-inferiority double-blind RCT without placebo [21]. At 1-year follow-up, pregabalin 300 mg seems to be more efficient than both pramipexole 0.25 and 0.50 mg in alleviating WED/RLS symptoms at IRLSSG-SS, more efficient than pramipexole 0.25 mg, but as efficient as pramipexole 0.50 mg in improving CGI score. In this study, the augmentation rate was also significantly lower for pregabalin. The dropout rate was not significantly different for pregabalin than for pramipexole. These data suggest that pregabalin could represent an alternative

treatment to dopamine agonists, with different tolerability. However, the long-term efficacy of this drug still need to be confirmed in placebo-controlled RCTs and its long-term efficacy should also be tested at lower doses.

Opioids

A few studies indicate a potential interest opioids in the long-term treatment of WED/RLS. Exogenous opioids are powerful analgesic drugs acting by modulating the transmission of sensory and painful information in the central nervous system, actins as agonists of the μ receptors. More recently, an open-label extension of a multicenter randomized placebo-controlled study of Trenkwalder et al. on showed an efficacy of oxycodone up to 40 weeks of follow-up in 197 patients with WED/RLS [19]. Anyway, only two other previous studies focused on methadone use for the treatment of this disease for one year or more.

Methadone

Methadone is a chemically synthesized opioid. Two long-term open-label observational retrospective studies on prospective cohorts seem to point at their subjectively-perceived efficacy of this compound for WED/RLS for periods of 23 months and even 10 years, on small populations of 27 and 76 patients, respectively [38, 39]. The outcome endpoint of both studies is the rate of patients keep taking the drug at mean of 23 months and one year and 10 years, respectively. Based on the results of these studies, a dose of 5–20 mg could be proposed. Interestingly, methadone seems to be rarely associated to augmentation in the long-term.

Other Drugs

Iron Sucrose

Intravenous iron sucrose 200 mg given five times every 3 weeks seemed to show a lower discontinuation rate from the study for augmentation at 12 months in patients with moderate WED/RLS with serum ferritin levels below 45 μmol/L in a double-blind RCT against placebo enrolling 60 patients, although it failed to demonstrate a significant reduction in IRLS severity score at this follow-up time [40].

Other Drugs

The long-term use of other drugs (clonazepam [41], tramadol [42], intrathecal morphine [43, 44], tetrabenazine [45] in WED/RLS has been reported in small-size open-label observational studies and case reports, but evidence for their use for one year or longer is still lacking.

Concluding Remarks

Lack of sufficient evidence for long-term use of these drugs in WED/RLS requires to be particularly cautious in their prescription and to be particularly vigilant on their side effects on the long term. The lowest efficacious dose case by case should be employed. The indication to continue the treatment and dose should also be assessed time by time, as the disease can present spontaneous remissions or recovery (although this latter is quite rare). Long-term pharmacologic treatment would virtually require posologic adaptations. No conclusive evidence is available in the literature on add-on therapies of shift among the different compounds, even though they might be beneficial in individual cases [16, 25, 29].

Although some results on the long-term efficacy of the recently-developed rotigotine and pregabalin seem promising, it should be kept in mind that rotigotine has not been tested in a double-blind RCT for more a use of more than 6 months and that pregabalin for more than 1 year. Opioids could virtually play a promising therapeutic role, especially in the long-term, but evidence is still too limited to recommend their routine clinical use.

References

1. Allen RP, Picchietti D, Hening WA, Trenkwalder C, Walters AS, Montplaisi J, Restless Legs Syndrome D., Epidemiology workshop at the National Institutes of H., International Restless Legs Syndrome Study G. 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(2):101–19.
2. Whittom S, Dauvilliers Y, Pennestri MH, Vercauteren F, Molinari N, Petit D, Montplaisir J. Age-at-onset in restless legs syndrome: a clinical and polysomnographic study. Sleep Med. 2007;9(1):54–9.
3. Allen RP, Earley CJ. Defining the phenotype of the restless legs syndrome (RLS) using age-of-symptom-onset. Sleep Med. 2000;1(1):11–9.
4. Hanson M, Honour M, Singleton A, Crawley A, Singleton A, Hardy J, Gwinn-Hardy K. Analysis of familial and sporadic restless legs syndrome in age of onset, gender, and severity features. J Neurol. 2004;251(11):1398–401.
5. Winkelmann J, Muller-Myhsok B, Wittchen HU, Hock B, Prager M, Pfister H, Strohle A, Eisensehr I, Dichgans M, Gasser T, Trenkwalder C. Complex segregation analysis of restless legs syndrome provides evidence for an autosomal dominant mode of inheritance in early age at onset families. Ann Neurol. 2002;52(3):297–302.

6. 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 (3):237–46.
7. Garcia-Borreguero D, Högl B, Ferini-Strambi L, Winkelman J, Hill-Zabala C, Asgharian A, Allen R. Systematic evaluation of augmentation during treatment with ropinirole in restless legs syndrome (Willis-Ekbom disease): results from a prospective, multicenter study over 66 weeks. Mov Disord. 2012;27(2):277–83.
8. Voon V, Schoerling A, Wenzel S, Ekanayake V, Reiff J, Trenkwalder C, Sixel-Doring F. Frequency of impulse control behaviours associated with dopaminergic therapy in restless legs syndrome. BMC Neurol. 2011;11:117.
9. Schreglmann SR, Gantenbein AR, Eisele G, Baumann CR. Transdermal rotigotine causes impulse control disorders in patients with restless legs syndrome. Parkinsonism Relat Disord. 2012;18(2):207–9.
10. Tjaderborn M, Jonsson AK, Ahlner J, Hagg S. Tramadol dependence: a survey of spontaneously reported cases in Sweden. Pharmacoepidemiol Drug Saf. 2009;18(12):1192–8.
11. Scholz H, Trenkwalder C, Kohnen R, Riemann D, Kriston L, Hornyak M. Dopamine agonists for restless legs syndrome. Cochrane Database Syst Rev. 2011;3:CD006009.
12. Scholz H, Trenkwalder C, Kohnen R, Riemann D, Kriston L, Hornyak M. Levodopa for restless legs syndrome. Cochrane Database Syst Rev. 2011;2:CD005504.
13. Fuhs A, Bentama D, Antkowiak R, Mathis J, Trenkwalder C, Berger K. Effects of short- and long-term variations in RLS severity on perceived health status—the COR-study. PLoS ONE. 2014;9(4):e94821.
14. Walters AS, LeBrocq C, Dhar A, Hening W, Rosen R, Allen RP, Trenkwalder C. Validation of the international restless legs syndrome study group rating scale for restless legs syndrome. Sleep Med. 2003;4(2):121–32.
15. Guy W. Clinical global impression. ECDEU Assessment Manual for Psychopharmacology, revised. National Insitute of Mental Health, Rockville, MI, U.S.A. 1976. p. 217–222.
16. Garcia-Borreguero D, Kohnen R, Silber MH, Winkelman JW, Earley CJ, Hogl B, Manconi M, Montplaisir J, Inoue Y, Allen RP. 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(7):675–84.
17. West S, King V, Carey TS, Lohr KN, McKoy N, Sutton SF, Lux L. Systems to rate the strength of scientific evidence. Evid Rep Technol Assess (Summ). 2002;47:1–11.
18. Brainin M, Barnes M, Baron JC, Gilhus NE, Hughes R, Selmaj K, Waldemar G, Guideline Standards Subcommittee of the E. S. C. Guidance for the preparation of neurological management guidelines by EFNS scientific task forces–revised recommendations 2004. Eur J Neurol. 2004;11(9):577–81.
19. Trenkwalder C. Benes H, Grote L, Garcia-Borreguero D, Hogl B, Hopp M, Bosse B, Oksche A, Reimer K, Winkelmann J, Allen RP, Kohnen R, Group RS. Prolonged release oxycodone-naloxone for treatment of severe restless legs syndrome after failure of previous treatment: a double-blind, randomised, placebo-controlled trial with an open-label extension. Lancet Neurol. 2013;12(12):1141–50.
20. Emilien G, Maloteaux JM, Geurts M, Hoogenberg K, Cragg S. Dopamine receptors–physiological understanding to therapeutic intervention potential. Pharmacol Ther. 1999;84 (2):133–56.
21. Allen RP, Chen C, Garcia-Borreguero D, Polo O, DuBrava S, Miceli J, Knapp L, Winkelman JW. Comparison of pregabalin with pramipexole for restless legs syndrome. N Engl J Med. 2014;370(7):621–31.
22. Silber MH, Girish M, Izurieta R. Pramipexole in the management of restless legs syndrome: an extended study. Sleep. 2003;26(7):819–21.

23. Winkelman JW, Johnston L. Augmentation and tolerance with long-term pramipexole treatment of restless legs syndrome (RLS). Sleep Med. 2004;5(1):9–14.
24. 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(2):251–7.
25. Lipford MC, Silber MH. Long-term use of pramipexole in the management of restless legs syndrome. Sleep Med. 2012;13(10):1280–5.
26. Montplaisir J, Fantini ML, Desautels A, Michaud M, Petit D, Filipini D. Long-term treatment with pramipexole in restless legs syndrome. Eur J Neurol. 2006;13(12):1306–11.
27. Inoue Y, Kuroda K, Hirata K, Uchimura N, Kagimura T, Shimizu T. Long-term open-label study of pramipexole in patients with primary restless legs syndrome. J Neurol Sci. 2010;294 (1–2):62–6.
28. Garcia-Borreguero D, Grunstein R, Sridhar G, Dreykluft T, Montagna P, Dom R, Lainey E, Moorat A, Roberts J. A 52-week open-label study of the long-term safety of ropinirole in patients with restless legs syndrome. Sleep Med. 2007;8(7–8):742–52.
29. Ondo W, Romanyshyn J, Vuong KD, Lai D. Long-term treatment of restless legs syndrome with dopamine agonists. Arch Neurol. 2004;61(9):1393–7.
30. Jenner P. A novel dopamine agonist for the transdermal treatment of Parkinson's disease. Neurology. 2005;65(2 Suppl 1):S3–5.
31. Scheller D, Ullmer C, Berkels R, Gwarek M, Lubbert H. The in vitro receptor profile of rotigotine: a new agent for the treatment of Parkinson's disease. Naunyn Schmiedebergs Arch Pharmacol. 2009;379(1):73–86.
32. Oertel W, Trenkwalder C, Benes H, Ferini-Strambi L, Hogl B, Poewe W, Stiasny-Kolster K, Fichtner A, Schollmayer E, Kohnen R, Garcia-Borreguero D, S. P. s. group. Long-term safety and efficacy of rotigotine transdermal patch for moderate-to-severe idiopathic restless legs syndrome: a 5-year open-label extension study. Lancet Neurol 2011;10(8):710–720.
33. 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(10):801–10.
34. Trenkwalder C, Collado Seidel V, Kazenwadel J, Wetter TC, Oertel W, Selzer R, Kohnen R. One-year treatment with standard and sustained-release levodopa: appropriate long-term treatment of restless legs syndrome? Mov Disord. 2003;18(10):1184–9.
35. Sills GJ. The mechanisms of action of gabapentin and pregabalin. Curr Opin Pharmacol. 2006;6(1):108–13.
36. Cundy KC, Sastry S, Luo W, Zou J, Moors TL, Canafax DM. Clinical pharmacokinetics of XP13512, a novel transported prodrug of gabapentin. J Clin Pharmacol. 2008;48(12):1378–88.
37. Ellenbogen AL, Thein SG, Winslow DH, Becker PM, Tolson JM, Lassauzet ML, Chen D. A 52-week study of gabapentin enacarbil in restless legs syndrome. Clin Neuropharmacol. 2011;34(1):8–16.
38. Ondo WG. Methadone for refractory restless legs syndrome. Mov Disord. 2005;20(3):345–8.
39. Silver N, Allen RP, Senerth J, Earley CJ. A 10-year, longitudinal assessment of dopamine agonists and methadone in the treatment of restless legs syndrome. Sleep Med. 2011;12 (5):440–4.
40. Grote L, Leissner L, Hedner J, Ulfberg J. A randomized, double-blind, placebo controlled, multi-center study of intravenous iron sucrose and placebo in the treatment of restless legs syndrome. Mov Disord. 2009;24(10):1445–52.
41. Schenck CH, Mahowald MW. Long-term, nightly benzodiazepine treatment of injurious parasomnias and other disorders of disrupted nocturnal sleep in 170 adults. Am J Med. 1996;100(3):333–7.
42. Lauerma H, Markkula J. Treatment of restless legs syndrome with tramadol: an open study. J Clin Psychiatry. 1999;60(4):241–4.

43. Jakobsson B, Ruuth K. Successful treatment of restless legs syndrome with an implanted pump for intrathecal drug delivery. Acta Anaesthesiol Scand. 2002;46(1):114–7.
44. Lindvall P, Ruuth K, Jakobsson B, Nilsson S. Intrathecal morphine as a treatment for refractory restless legs syndrome. Neurosurgery. 2008;63(6):E1209; author reply E1209.
45. Ondo WG, Jia JJ. Effect of tetrabenazine use on restless legs syndrome. Sleep Med. 2010;11 (9):958–9.

Augmentation: Criteria, Prevalence, and Differential Diagnosis

12

Diego García-Borreguero, Mauro Manconi and Luigi Ferini-Strambi

Introduction

Since the first studies of dopaminergic agents for the treatment of RLS/WED in the early 1980s [1], the overall long-term efficacy of these drugs has been well established by further clinical trials [2–4], and the reported adverse events have been generally mild. Furthermore, unlike in Parkinson's disease, no cases of dyskinesia have been ever reported [3]. In the ensuing years, the treatment of RLS/WED with dopaminergic drugs was widespread, until in 1996 when the first clinical description of augmentation was made. Allen and Earley [5] described augmentation in patients who had been treated with levodopa and characterized it as an earlier onset of symptoms in the afternoon, a faster onset of symptoms when at rest, a spreading of symptoms to the arms and trunk, an overall increase in severity, and a shorter medication effect. Augmentation was found to be common and frequently severe, occurring in 82% of patients being treated with levodopa, and was severe enough to require change of treatment in 50% of patients [5]. The most characteristic feature of augmentation was an increase in severity beyond that seen at baseline, a feature that differentiated it from rebound or tolerance (i.e., seen under benzodiazepines or opiates). This drug-induced worsening of RLS/WED symptom severity beyond that experienced before treatment initiation continues to be the most characteristic feature of dopaminergic augmentation.

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Clinical Definition

Comparison of augmentation rates among different drugs was previously impossible given the lack of a standardized clinical definition. The need to standardize diagnostic criteria for augmentation was, however, recognized by the National Institutes of Health (NIH), who, in 2002, sponsored a workshop on RLS/WED [6]. This consensus conference generated an operational definition of augmentation, the primary feature of which was defined as a drug-induced shifting of symptoms to two hours earlier than was the typical period of daily onset of symptoms before pharmacological intervention. Nevertheless, the 2002 definition was based exclusively on clinical experience rather than on empirical data. Neither did it include guidelines on how to assess the severity or clinical significance of augmentation. This task was tackled several years later, in 2006, by a European Restless Legs Syndrome Study Group (EURLSSG)-sponsored Consensus Conference at the Max Planck Institute in Munich, Germany, during which, based on empirical data from clinical studies, a better operational definition for the clinical identification of augmentation was sought. Studies indicated that the reliable detection of augmentation could be obtained based on a four-hour time advance of symptoms, or a smaller (two to four hours) advance of symptoms expressed along with other necessary clinical indications [7], such as a shorter latency of symptoms at rest, a spread of symptoms to other body parts in addition to the lower limbs, or a greater intensity of symptoms. Additionally, the paradoxical response to treatment, reflected by an increase in severity with increasing dose of medication, and an improvement following decreases in medication, was considered an alternative key feature for diagnosis (see Table 12.1).

Several studies have reported a correlation between the presence of augmentation during dopaminergic treatment with the severity of RLS/WED symptoms at baseline and with a higher medication dosage, but not with age or gender [8–10]. Clinical experience shows that when severe, augmentation can result in a weakening or even a loss of essential RLS/WED features. Thus, symptoms are no longer reduced during inactivity or movement, and there is virtually no circadian pattern. The clinical picture obtained during dopaminergic augmentation resembles the one obtained in severe RLS/WED, with severe symptoms occurring most of the day and affecting all limbs. None of the clinical features of dopaminergic augmentation are specific to this condition or can be differentiated from RLS/WED itself. In fact, RLS/WED augmentation reflects a worsening of RLS/WED severity during dopaminergic treatment. Recently published recommendations on the management of augmentation from the International RLS Study Group (IRLSSG) identified a number of screening questions that may be used in clinical practice to identify possible augmentation, but these have yet to be validated [11].

Table 12.1 MPI criteria [7]

Preamble Augmentation is a worsening of RLS symptom severity experienced by patients undergoing treatment for RLS. The RLS symptoms in general are more severe than those experienced at baseline
A. Basic features (all of which need to be met): 1. The increase in symptom severity was experienced on five out of seven days during the previous week 2. The increase in symptom severity is not accounted for by other factors such as a change in medical status, lifestyle, or the natural progression of the disorder 3. It is assumed that there has been a prior positive response to treatment In addition, either B or C or both have to be met
B. Persisting (although not immediate) paradoxical response to treatment: RLS symptom severity increases some time after a dose increase and improves some time after a dose decrease OR
C. Earlier onset of symptoms: 1. An earlier onset by at least four hours OR 2. An earlier onset (between two and four hours) occurs with one of the following compared to symptom status before treatment a. Shorter latency to symptoms when at rest b. Spreading of symptoms to other body parts c. Intensity of symptoms is greater (or increase in periodic limb movements [PLM] if measured by polysomnography [PSG] or the suggested immobilization test [SIT]) d. Duration of relief from treatment is shorter
Augmentation requires criteria A + B, A + C, or A + B + C to be met

Incidence of Augmentation Under Dopaminergic Agents

Dopaminergic augmentation is very common and mostly unidentified in everyday clinical practice. A community survey performed on 266 RLS/WED patients being treated by primary care physicians or neurologists in the USA, whose medical records were reviewed by independent experts, showed some degree of augmentation in 75% of patients (20% with definite augmentation and 55% had partial symptoms of augmentation) [12].

A number of studies claim to have evaluated the incidence of augmentation for different drugs either prospectively or retrospectively (See Table 12.2). However, several issues make it difficult to ascertain correct incident rates for the different treatments for RLS/WED: Firstly, as mentioned above, there was no operational definition for augmentation before 2002. Secondly, the estimation of augmentation rates has been performed retrospectively, using different diagnostic criteria, and frequently based on the evaluation of clinical cases. Studies were not specifically designed to measure augmentation and frequently lacked specific information on augmentation. Third, trials were frequently not long enough for augmentation to manifest: It is a long-term consequence of treatment, and therefore, trials need to be

Table 12.2 Incidences of augmentation with dopaminergic RLS/WED therapies (Ref taken from [20])

Study	Design	Duration	Sample size	Assessment	Incidence of augmentation
Levodopa					
Allen 1996 [5]	Prospective case series	N/A	30	Increase in appearance and severity of RLS/WED symptoms	73.3% (22/30 patients)
Trenkwalder 2007 [21]	Double-blind, randomized, active-controlled (cabergoline) trial	30 weeks	Levodopa: 183 Cabergoline: 178	ASRS $\geq$ 1 Augmentation defined according to NIH criteria	Augmentation (ASRS $\geq$ 1) Levodopa: 40.4% Cabergoline: 21.1% Discontinuations due to augmentation Levodopa: 9.8% (18/183 patients) Cabergoline: 4.0% (7/178 patients)
Hogl 2010 [22]	Open-label trial	6 months	60	Augmentation diagnosed by two experts using established criteria. Changes in ASRS, IRLS, and CGI were analyzed	Augmentation: 60% (36/60 patients) Discontinuations due to augmentation: 11.7% (7/60 patients)
Rotigotine					
Trenkwalder 2008 [23]	Double-blind, randomized, placebo-controlled trial	6 months	Rotigotine: 341 Placebo: 117	ASRS (4-item version)	No signs of augmentation noted
Hening 2010 [24]	Double-blind, randomized, placebo-controlled trial	6 months	Rotigotine: 405 Placebo: 100	ASRS (4-item version) Retrospective analysis of study data by an expert panel using the MPI criteria	Clinically relevant augmentation: 1.5% (6/404 patients) on rotigotine 1% (1/100 patients) on placebo

(continued)

Table 12.2 (continued)

Study	Design	Duration	Sample size	Assessment	Incidence of augmentation
Oertel 2011 [25]	Open-label, continuation of double-blind, randomized, placebo-controlled trial	5 years	295	ASRS Retrospective analysis of study data by an expert panel using the MPI criteria	Clinically significant augmentation: 5% (15/295 patients) on EMA-approved dose[a]
Benes 2012 [26]	Retrospective assessment of two double-blind studies [24, 27] and their respective open-label extensions	DB: 6 months OL: 12 months	DB: rotigotine, 745; placebo, 214. OL: 620	Expert review of study data (IRLS, RLS-6, CGI-1, ASRS) using the MPI criteria	Clinically relevant augmentation DB: 1.5% (11/745 patients) on rotigotine; 0.5% (1/214) patients on placebo OL: 2.9% (18/620 patients)
Cano 2013 [28]	Retrospective chart review	12 years	138 (112 received ≥ 1 RLS/WED medication)	Not specified	Rotigotine: 0% Clonazepam: 37.1% Ropinirole: 40.4%
Inoue 2013 [29]	Open-label continuation of a double-blind trial	1 year	185	ASRS $\geq$ 5 used to identify patients with possible augmentation. These patients were then assessed by expert panel using the MPI criteria	Clinically significant augmentation: 2.7% (5/185 patients)
Miranda 2013 [30]	Switching study	18 months	10	None described	None reported

(continued)

Table 12.2 (continued)

Study	Design	Duration	Sample size	Assessment	Incidence of augmentation
Ropinirole					
Montplaisir 2006 [31]	Single-blind phase followed by double-blind treatment	SB: 24 weeks DB: 12 weeks	202	Augmentation recorded as an adverse event (AE)	Possible augmentation Ropinirole: 1.5% (3/202 patients)
Garcia-Borreguero 2007 [9]	Open-label, continuation of double-blind, randomized, placebo-controlled trial	52 weeks	310	Retrospective assessment of AEs	9.1% (28/309) had AEs coded to RLS 2.3% (7/30) had AEs recorded as augmentation[b]
Garcia-Borreguero 2012 [32]	Double-blind, randomized, placebo-controlled trial followed by open-label continuation	DB: 26 weeks OL: 40 weeks	DB: 404 OL: 269	ASRS Potential cases prospectively identified by a structured diagnostic interview and by reporting of AEs, and then evaluated by an expert panel based on the NIH criteria	Clinically significant augmentation DB: 3% (5/197) patients on rotigotine; 0.48% (1/207) patients on placebo OL: 2% (5/269 patients)[c]
Pramipexole					
Montplaisir 2000 [33]	Open-label continuation of double-blind study	Mean: 7.8 months	7	Not specified	None reported
Ferini-Strambi 2002 [16]	Open-label trial	$\geq$6 months	60	Not specified	8.3% (5/60 patients)

(continued)

Table 12.2 (continued)

Study	Design	Duration	Sample size	Assessment	Incidence of augmentation
Silber 2003 [34]	Retrospective chart review	30 months	60	New development or increase in severity, duration, or anatomic distribution of RLS/WED earlier in the day than the time a medication for RLS/WED was taken	33% (16/49 patients)
Winkelman 2004 [15]	Retrospective chart review	Average of 21.2 ± 11.4 months; range: 6–60 months	59	Earlier RLS/WED symptom appearance ($\geq$ 5 times/week) requiring earlier administration of medications (>2 h) Extension of symptoms beyond legs	32% (19/59) of patients
Trenkwalder 2006 [35]	Double-blind, randomized, placebo-controlled withdrawal study	3 months (following 6 months OL treatment)	Pramipexole: 78 Placebo: 72	ASRS	None reported
Inoue 2010 [36]	Open-label, continuation of double-blind, randomized, placebo-controlled trial	52 weeks	141 (Japanese pts)	Patient diary Defined as symptom appearance $\geq$ 2 h earlier than usual for $\geq$ 5 days/week	Possible augmentation: 4.3% (6/141 patients)
Montagna 2011 [37]	Double-blind, randomized, placebo-controlled trial	12 weeks	Pramipexole: 203 Placebo: 201	None described	None reported
Hogl 2011 [38]	Double-blind, randomized, placebo-controlled trial	26 weeks	Pramipexole: 166 Placebo: 163	RLS/WED symptom diary and augmentation questionnaire (based on NIH and MPI criteria and an ASRS score $\geq$ 5). All potential cases reviewed by an expert panel	Confirmed augmentation Pramipexole: 9.2% (14/152 patients) Placebo: 6.0% (9/149 patients)

(continued)

Table 12.2 (continued)

Study	Design	Duration	Sample size	Assessment	Incidence of augmentation
Lipford 2012 [39]	Retrospective chart review	Mean treatment duration: 8 years	50	Earlier onset, increased severity, duration, or new anatomical distribution of symptoms	42% (21/50 patients)
Allen 2014 [4]	Double-blind, randomized, placebo and active (pregabalin) controlled trial	40 or 52 weeks[d]	719	SIDA based on the NIH criteria, ASRS, and IRLS. Cases of possible augmentation (+ve SIDA score, ASRS $\geq$ 5, or clinical judgment) referred to expert panel for review	Pramipexole 0.5 mg: 7.7% (18/235 patients) Pramipexole 0.25 mg: 5.3% (12/225 patients) Pregabalin: 2.1% (5/235 patients)

[a]The European Medicines Agency approved doses for rotigotine were 1–3 mg/24 h

[b]The term "augmentation" was recorded only when specifically used by the investigator; otherwise, augmentation-like symptoms were recorded as an adverse event under "restless legs syndrome"

[c]Patients randomized to placebo were offered open-label ropinirole at the end of the double-blind phase

[d]Patients were randomized to 52 weeks of active treatment (pramipexole 0.5 mg/pramipexole 0.25 mg/pregabalin 300 mg) or to 12 weeks of placebo followed by 40 weeks of randomized active treatment

ASRS Augmentation severity rating scale; *CGI* Clinical global impression; *DB* Double-blind; *EMA* European Medicines Agency; *IRLS* International restless legs scale; *MPI* Max Planck Institute; *NIH* National Institutes of Health Guidelines; *OL* Open-label; *RLS* Restless legs syndrome; *SIDA* Structured interview for the diagnosis of augmentation; *WED* Willis-Ekbom disease

longer than 6 months for augmentation to be seen. Finally, there is a lack of comparative trials with one single exception [4].

Some degree of augmentation has been reported with the use of all investigated dopaminergic drugs [8, 13–16] and also for tramadol [17]. In the virtual absence of direct comparative studies, the incidence rates seem to be the highest during treatment with levodopa and for shorter-acting (pramipexole, ropinirole) than longer-acting (rotigotine) dopamine-receptor agonists. However, this is still controversial since it is unclear whether this finding is related to the masking of earlier symptom onset by the longer-acting dopaminergic agents or whether it is truly an augmentation-sparing effect.

In comparison with dopaminergic agents, less emphasis has been placed on the performance of systematic long-term treatment with non-dopaminergic agents. A recent and probably the best-designed study performed on augmentation so far is a prospective double-blind comparison on two different doses of pramipexole (0.25 and 0.5 mg/day) with 300 mg/day of pregabalin for over a year [4]. While the therapeutic efficacy of pregabalin was similar to the higher dose of pramipexole, the one-year incidence rate of augmentation was clearly lower (2.1 vs. 7.7%) and not different from what has been observed for placebo [4]. Another recent large study reported no cases of augmentation during a one-year treatment with oxycodone prolonged release combined with naloxone [18]. In summary, augmentation seems to occur specifically during dopaminergic treatment.

Differential Diagnosis of Augmentation

It is important to be able to distinguish augmentation from tolerance, early morning rebound and from the natural progression of RLS/WED, or fluctuations in disease severity (see Table 12.3). It is also important to ask the patient about any lifestyle changes, changes in medical factors (use of dopamine antagonists or antidepressants), or other extrinsic factors (sleep deprivation, blood loss, alcohol use) that might have led to the earlier onset or increased severity.

Early morning rebound is characterized by the development of RLS/WED in the early morning during the falling phase of plasma levels of the drug being administered. Following rebound in the morning, there is usually a symptom-free period of time until symptoms reappear again in the afternoon or evening. In contrast, under augmentation, there is an earlier onset of symptoms in the evening. However, in some cases of severe augmentation, particularly when patients suffer symptoms throughout the day, it might be difficult to differentiate from rebound. Rebound is considered to be an end-of-dose effect, related to the half-life of the therapeutic agent. No correlation has been found between the occurrence of augmentation and rebound, supporting the general view that both phenomena reflect separate problems.

Table 12.3 Differentiating augmentation from other conditions [19]

Augmentation	Tolerance
Additional features (symptoms spread to other body parts, shorter latency to symptoms at rest, increased intensity of symptoms)	No additional features
Increase severity beyond baseline levels	Never worse than baseline

Augmentation	Early morning rebound
Symptom onset in afternoon or evening	Symptom onset in early morning
Anticipation of time of onset	Delayed onset of symptoms
Followed by usual course of symptoms	Followed by symptom-free interval in the morning/noon
Related to total daily dosage/severity of symptoms at baseline	Related to half-life. Occurs during the declining phase of plasma concentrations
Additional features (symptoms spread to other body parts, shorter latency to symptoms at rest, increased intensity of symptoms)	No additional features

Augmentation	Natural progression of RLS
Additional features (symptoms spread to other body parts, shorter latency to symptoms at rest, increased intensity of symptoms)	Additional features
Progresses within weeks/months	Natural progression of RLS is usually slow (years)
A reduction in the dose leads ultimately to a *decrease* in symptoms. An increase in the dose ultimately leads to an increase in symptoms	A reduction in the dose leads to an *increase* in symptoms
Increase beyond baseline severity	Increase beyond baseline severity

In contrast to the former, distinguishing augmentation from tolerance might be more difficult from a clinical point of view. Tolerance results when the effectiveness of a medication decreases over a period of time, thereby necessitating an increase in medication to maintain the initial relief of symptoms that was seen at therapy initiation. Strictly speaking, even in the worst case of tolerance, severity of symptoms would not be expected to increase beyond the level of severity occurring without treatment. In contrast, during augmentation, the severity of symptoms might well increase beyond the preexisting baseline level. This differentiation might prove to be of more theoretical than practical value in clinical practice, as most patients cannot assess the severity of their symptoms with such precision. Furthermore, the absence of specific rating instruments for augmentation as well as the lack of prospective studies to assess the long-term course of the different features of augmentation makes the differentiation between both processes particularly difficult.

Another situation that needs to be differentiated from augmentation is a progressive worsening of the clinical course of RLS/WED over time. Although data on the long-term spontaneous course of untreated RLS/WED patients are scarce and usually not well controlled, it is believed that progression is slow. However, this

could be in fact confounded with a slowly progressive, mild process of augmentation. In this case, however, a time off-treatment produces opposite effects, that is, a full expression of the progressive worsening of symptoms, while in augmentation symptoms would be reduced.

Conclusion

Today, augmentation represents the main challenge in the long-term treatment of RLS/WED. It is not only the main cause of non-response to dopaminergic drugs, but is also the main reason for discontinuation of treatment. Thus, its early identification becomes crucial in order to prevent the collapse of the therapeutic strategy.

References

1. Akpinar S. Treatment of restless legs syndrome with levodopa plus benserazide. Arch Neurol. 1982;39:739.
2. Garcia-Borreguero D, Ferini-Strambi L, Kohnen R, 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.
3. Garcia-Borreguero D, Kohnen R, Silber MH, 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.
4. Allen RP, Chen C, Garcia-Borreguero D, et al. Comparison of pregabalin with pramipexole for restless legs syndrome. N Engl J Med. 2014;370:621–31.
5. Allen RP, Earley CJ. Augmentation of the restless legs syndrome with carbidopa/levodopa. Sleep. 1996;19:205–13.
6. Allen RP, Picchietti D, Hening WA, Trenkwalder C, Walters AS, Montplaisi 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.
7. Garcia-Borreguero D, Allen RP, Kohnen R, et al. Diagnostic standards for dopaminergic augmentation of restless legs syndrome: report from a World Association of Sleep Medicine-International Restless Legs Syndrome Study Group consensus conference at the Max Planck Institute. Sleep Med. 2007;8:520–30.
8. Oertel W, Trenkwalder C, Benes H, et al. Long-term safety and efficacy of rotigotine transdermal patch for moderate-to-severe idiopathic restless legs syndrome: a 5-year open-label extension study. Lancet Neurol. 2011;10:710–20.
9. Garcia-Borreguero D, Grunstein R, Sridhar G, et al. A 52-week open-label study of the long-term safety of ropinirole in patients with restless legs syndrome. Sleep Med. 2007;8:742–52.
10. Allen RP. Pregabalin versus pramipexole for restless legs syndrome. N Engl J Med. 2014;370:2050–1.
11. Garcia-Borreguero D, Silber MH, Winkelman JW, et al. Guidelines for the first-line treatment of restless legs syndrome/Willis-Ekbom disease, prevention and treatment of dopaminergic

augmentation: a combined task force of the IRLSSG, EURLSSG, and the RLS-foundation. Sleep Med. 2016;21:1–11.
12. Allen RP, Ondo WG, Ball E, et al. Restless legs syndrome (RLS) augmentation associated with dopamine agonist and levodopa usage in a community sample. Sleep Med. 2011;12: 431–9.
13. Garcia-Borreguero D, Högl B, Ferini Strambi L, et al. Systematic evaluation of augmentation during treatment with ropinirole in Restless Legs Syndrome: Results from a prospective, multicenter study over sixty-six weeks. Mov Disord. 2011, in press.
14. Benes H, Heinrich CR, Ueberall MA, Kohnen R. Long-term safety and efficacy of cabergoline for the treatment of idiopathic restless legs syndrome: results from an open-label 6-month clinical trial. Sleep. 2004;27:674–82.
15. Winkelman JW, Johnston L. Augmentation and tolerance with long-term pramipexole treatment of restless legs syndrome (RLS). Sleep Med. 2004;5:9–14.
16. Ferini-Strambi L. Restless legs syndrome augmentation and pramipexole treatment. Sleep Med. 2002;3(Suppl):S23–5.
17. Vetrugno R, La Morgia C, D'Angelo R, et al. Augmentation of restless legs syndrome with long-term tramadol treatment. Mov Disord. 2007;22:424–7.
18. Trenkwalder C, Benes H, Grote L, et al. Prolonged release oxycodone-naloxone for treatment of severe restless legs syndrome after failure of previous treatment: a double-blind, randomised, placebo-controlled trial with an open-label extension. Lancet Neurol. 2013;12:1141–50.
19. Garcia-Borreguero D, Williams AM. Dopaminergic augmentation of restless legs syndrome: the scope of the problem. Sleep Med. 2011;12:425–6.
20. Garcia-Borreguero D, Benitez A, Kohnen R, Allen R. Augmentation of restless leg syndrome (Willis-Ekbom disease) during long-term dopaminergic treatment. Postgrad Med. 2015;127:716–25.
21. Trenkwalder C, Benes H, Grote L, et al. Cabergoline compared to levodopa in the treatment of patients with severe restless legs syndrome: results from a multi-center, randomized, active controlled trial. Mov Disord. 2007;22:696–703.
22. Högl B, Garcia-Borreguero D, Kohnen R, et al. Progressive development of augmentation during long-term treatment with levodopa in restless legs syndrome: results of a prospective multi-center study. J Neurol. 2010;257:230–7.
23. Trenkwalder C, Benes H, Poewe W, 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.
24. Hening WA, Allen RP, Ondo WG, et al. Rotigotine improves restless legs syndrome: a 6-month randomized, double-blind, placebo-controlled trial in the United States. Mov Disord. 2010;25:1675–83.
25. Oertel W, Trenkwalder C, Benes H, et al. Long-term safety and efficacy of rotigotine transdermal patch for moderate-to-severe idiopathic restless legs syndrome: a 5-year open-label extension study. Lancet Neurol. 2011;10:710–20.
26. Benes H, Garcia-Borreguero D, Ferini-Strambi L, Schollmayer E, Fichtner A, Kohnen R. Augmentation in the treatment of restless legs syndrome with transdermal rotigotine. Sleep Med. 2012;13:589–97.
27. Trenkwalder C, Hogl B, Benes H, Kohnen R. Augmentation in restless legs syndrome is associated with low ferritin. Sleep Med. 2008;9:572–4.
28. Cano N, Bayarri P, Chilet R, Plaza G, Carrasco A, Ibanez J. Evolution of safety profile of different therapeutic alternatives in restless legs syndrome (rls). Sleep Med 2013;14S:e88 (abstract).
29. Inoue Y, Hirata K, Hayashida K, Hattori N, Tomida T, Garcia-Borreguero D. Efficacy, safety and risk of augmentation of rotigotine for treating restless legs syndrome. Prog Neuropsychopharmacol Biol Psychiatry. 2013;40:326–33.

30. Miranda C. Transdermal Rotigotine in the treatment of restless legs patients who develop augmentation of symptoms. Rev Méd Chile. 2013;141:407–8.
31. Montplaisir J, Karrasch J, Haan J, Volc D. Ropinirole is effective in the long-term management of restless legs syndrome: a randomized controlled trial. Mov Disord. 2006;21:1627–35.
32. Garcia-Borreguero D, Hogl B, Ferini-Strambi L, et al. Systematic evaluation of augmentation during treatment with ropinirole in restless legs syndrome (Willis-Ekbom disease): results from a prospective, multicenter study over 66 weeks. Mov Disord. 2012;27:277–83.
33. Montplaisir J, Denesle R, Petit D. Pramipexole in the treatment of restless legs syndrome: a follow-up study. Eur J Neurol. 2000;7(Suppl 1):27–31.
34. Silber MH, Girish M, Izurieta R. Pramipexole in the management of restless legs syndrome: an extended study. Sleep. 2003;26:819–21.
35. Trenkwalder C, Stiasny-Kolster K, Kupsch A, Oertel WH, Koester J, Reess J. Controlled withdrawal of pramipexole after 6 months of open-label treatment in patients with restless legs syndrome. Mov Disord. 2006;21:1404–10.
36. Inoue Y, Kuroda K, Hirata K, Uchimura N, Kagimura T, Shimizu T. Long-term open-label study of pramipexole in patients with primary restless legs syndrome. J Neurol Sci. 2010;294:62–6.
37. Montagna P, Hornyak M, Ulfberg J, 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.
38. Högl B, Garcia-Borreguero D, Trenkwalder C, et al. Efficacy and augmentation during 6 months of double-blind pramipexole for restless legs syndrome. Sleep Med. 2011;12: 351–60.
39. Lipford MC, Silber MH. Long-term use of pramipexole in the management of restless legs syndrome. Sleep Med. 2012;13:1280–5.

13 Treatment Options When Short-Acting Dopamine Agonists Fail or Cause Augmentation: Switching or Adding Medications

Mark Buchfuhrer

In 1982, levodopa was the first of the drugs that act upon the dopamine system to be found as an effective treatment for RLS symptoms [1]. However, despite providing initial dramatic relief of symptoms, frequent problems with augmentation of RLS symptoms limited the daily use of levodopa [2]. After an influx of patients presented with severe augmentation symptoms from levodopa, RLS experts found that the ergot-derived dopamine agonists (DAs), bromocriptine [3] and pergolide [4–7] were effective alternatives. However, the ergot-derived DAs were often limited by side effects and were ultimately found to be associated with fibrotic heart valve damage [8, 9]. When the short-acting non-ergot-derived DAs pramipexole and ropinirole were approved by the FDA in 1997 for idiopathic Parkinson's disease, they were quickly adopted as off-label treatment for RLS. Within a few years, they became the drugs of choice for treating RLS symptoms [10] which was further validated by the many studies that lead to their FDA approval for RLS (ropinirole in 2005 and pramipexole in 2006). Therefore, the vast majority of patients presenting with moderate to severe RLS have been treated with one of these two short-acting DAs and failure of RLS therapy has been generally synonymous with failure of one or both of these drugs. Despite new treatment guidelines [11, 12] and the recent availability of the FDA-approved long-acting rotigotine patch (2012) and the α2δ drug, gabapentin enacarbil (2011), the vast majority of physicians are still treating their RLS patients with the older short-acting dopamine drugs.

This chapter will discuss treatment choices for patients who have failed these short-acting DAs. Since few, if any, medical studies have been published for this

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subset of patients, the management plans outlined below are based mostly upon clinical experience. The various reasons for patients failing short-acting DAs are discussed with various management alternatives presented.

Inadequate Initial Response Despite Adequate Doses of Short-Acting DAs

The short-acting DAs should be started at their lowest available dose and increased slowly until RLS symptoms are relieved. Although some RLS specialists may start treatment at higher doses, it may be more prudent to initiate therapy with lower doses that may decrease the severity of side effects and enable patients to adapt to any adverse reactions. This will result in a longer latency before relief of symptoms is achieved, but most patients have already been suffering for months or years so the delay should be only a minor inconvenience. While over 90% of RLS patients will respond initially to dopamine agonist (DA) therapy [13], there is still a significant minority who do not benefit sufficiently or even worsen from those drugs.

What is the maximum dose of a short-acting DA before the drug trial is deemed to be unsuccessful? The answer to that question is essential to determine further management choices and often to obtain insurance authorization for more expensive brand-name drugs. While the FDA approved upper limit of dosing for ropinirole is 4 mg once daily and for pramipexole 0.5 mg once daily, some experts [11] believe that significantly lower limits (1 mg for ropinirole and 0.25 mg for pramipexole) are more prudent. Although currently evidence exists only for a dose relationship of increasing augmentation for levodopa, this is thought to occur similarly with DAs [14, 15] and the authors of those articles have also advocated lower dose limits of these drugs. Unless factors such as cost, availability, or adverse effects restrict the use of alternative drugs, physicians should try to limit the doses of DAs to the lower amounts suggested above.

Failure of the short-acting DAs may be partial or complete. When adequate doses of one short-acting DA have been tried without any significant relief, several choices are available. Another short-acting DA may be effective but once two short-acting DAs proof ineffective, it is very unlikely that short- or long-acting DAs will be helpful. Typically, α2δ drugs (gabapentin, pregabalin, or gabapentin enacarbil) are the first choice in this situation [11]. Gabapentin enacarbil (currently only available in the USA and Japan) is the preferred option as it has been extensively studied for effectiveness and safety [16–20] and is FDA approved for treating RLS. Outside the USA and Japan, pregabalin and gabapentin are the alternative choices. Pregabalin has been demonstrated to be effective and safe for RLS [21, 22], which has been corroborated by clinical experience. When neither of the above α2δ drugs are available or affordable, then gabapentin may prove beneficial as several studies have demonstrated its effectiveness [23–26]. However, gabapentin has dose-dependant absorption [27, 28] so that lower percentages of the drug are absorbed with increases in the dose and this problem varies considerably

from patient to patient [29]. This issue is reflected in the wide effective dose ranges (200–3600 mg/day) in the literature and in clinical practice. Despite these limitations, gabapentin may provide relief when the other α2δ drugs are not options. If the α2δ drugs are unsuccessful, then treatment with opioids should be considered. Tramadol and the opioids such as methadone or oxycodone that are not combined with acetaminophen or ibuprofen (which do not help RLS symptoms) are preferred. There is support in the literature for the use of oxycodone [30, 31] and methadone [32, 33] for treating RLS that is confirmed by the many RLS experts, who use these opioids regularly. Based upon clinical experience of many RLS specialists in the USA (personal communication), methadone is the opioid of choice as it tends to relieve RLS symptoms more effectively, lasts longer (8–10 h compared to about 4–6 h with oxycodone) and causes fewer adverse reactions than the other opioids. Furthermore, with proper patient selection (avoid patients with a history of substance abuse), appropriate dosing and close monitoring, tolerance, dependence, and dose escalation occur infrequently [30–33].

Somewhat different options present when patients have a partial response to short-acting DAs. When the short-acting DAs provide inadequate improvement once the maximum dose is achieved then an α2δ drug may be added to provide further relief. If the α2δ drugs are not helpful or cause side effects, opioids are the next choice. When patients do respond to the addition of α2δ drugs or opioids (or both), physicians might consider discontinuing the DA and see if the patient may sustain their relief with less medication. If patients do not respond adequately to the addition of both the α2δ drugs and opioids then increasing the dosage of the short-acting DA may be considered realizing that this raises the risk of augmentation.

The other common situation that occurs is that the short-acting DA relieves the RLS, but is not long acting enough to cover all of the RLS symptoms. Most physicians would simply add an additional earlier or later dose or two to cover those symptoms. However, it may be better to change to a long-acting DA that may present less of a risk for subsequent augmentation.

Response That Has Become Inadequate with Time

As stated above, the vast majority of RLS patients respond initially to short-acting DA treatment. However, with time, this response may wane for several reasons.

Disease Progression

Although RLS typically worsens slowly over many years to decades, the increase in symptoms may evolve in a smooth linear fashion but often occurs in a step-like manner. Patients typically notice that their DA dose is not sufficient to control symptoms, earlier onset of symptoms or extension of symptoms to the arms or other body parts. This is similar to other causes of disease worsening discussed below and may be very difficult to differentiate.

When disease progression occurs, increasing the DA dose will generally improve the RLS symptoms. However, when the upper limits of the DA dose is reached, other options as discussed above should be considered. Although adding an earlier dose for symptoms that occur in the daytime may be effective, changing to a long-acting DA may be a better alternative.

Triggers

There is a long list of prescription and over-the-counter drugs that exacerbate RLS. These include sedating antihistamines, anti-nausea/antiemetic drugs, antidepressants [34–41], neuroleptics [42–44], and other dopamine blockers/antagonists. This can be very tricky to uncover as patients often forget to mention or do not know the new drugs (or increased dose of an existing drug) that have been added between office visits. Even more intensive interrogation is usually necessary to discover the over-the-counter drugs worsening RLS as they are typically not part of the medical or pharmacy record and patients may not think these as relevant medications. Once the offending drug has been unearthed, it should be changed to a comparable "RLS friendly" medication (Table 13.1) if possible. If the drug is essential and no viable alternative exists, then the RLS treatment may need to be ramped up as discussed above.

Table 13.1 Max Planck Institute criteria for diagnosing RLS augmentation

A. Basic features (all of which need to be met) 1. The increase in symptom severity was experiences on five out of seven days during the previous week 2. The increase in symptom severity is not accounted for by other factors such as a change in medical status, lifestyle, or the natural progression of the disorder 3. It is assumed that there has been a prior positive response to treatment
In addition, either B or C or both have to be met
B. Persisting (although not immediate) paradoxical response to treatment: RLS symptom severity increases some time after a dose increase, and improves some time after a dose decrease
C. Earlier onset of symptoms 1. An earlier onset by at least 4 h OR 2. An earlier onset (between 2 and 4 h) occurs with one of the following compared to symptom status before treatment 3. (A) Shorter latency to symptoms when at rest 4. (B) Spreading of symptoms to other body parts 5. (C) Intensity of symptoms is greater [or increase in periodic limb movements (PLM) if measured by polysomnography (PSG) or the suggested immobilization test (SIT); suggested immobilization test (SIT)] 6. (D) Duration of relief from treatment is shorter

Adapted from García-Borreguero [57]. Epub 2007 Jun 1, with permission

Other triggers include alcohol, dietary products, inadequate sleep, stress, comorbid diseases, lifestyle changes, and exercise. Despite the only study that evaluated the relationship between RLS and alcohol [45] having found an epidemiological association between RLS and low alcohol consumption, many patients report worsening of their RLS shortly after drinking alcoholic beverages. This study also found a link between lack of exercise and RLS. Moderate exercise has been demonstrated in one study to improve RLS symptoms with a 12-week conditioning program of aerobic and lower body resistance training 3 days per week [46]. However, there is anecdotal evidence that vigorous exercise may exacerbate RLS, sometimes even markedly. There is also anecdotal evidence for anxiety and stress worsening RLS, and the epidemiological study above [45] found a relationship between RLS and poor mental health status. Comorbid disease may result in worsening RLS symptoms. In clinical practice, patients with pain or discomfort from conditions such as back pain or neuropathy find that their RLS has worsened. This relationship may not be immediately apparent and may require extensive questioning to determine the temporal relationship between the comorbid condition and the exacerbation of RLS symptoms. Patients often report worsening of RLS symptoms after surgical procedures or trauma even well after full healing has occurred. There are no studies to support any foods worsening RLS but patients often report that refined carbohydrates, gluten, and ice cream may exacerbate their symptoms. Instituting proper sleep hygiene has been recommended for RLS patients by a few review articles [47–49], but there are no studies to support this advice. However, since it is thought that RLS symptoms increase with sleepiness, inadequate sleep may be a significant factor that could worsen RLS symptoms. Increases in RLS symptoms may also occur with lifestyle changes that result in decreased activity such as retirement or changing to a deskbound job. Patients may not realize that the increased sedentary time may be the cause of their increased RLS symptoms.

Low iron levels have been associated with RLS and treating with oral iron has been found to improve RLS symptoms [50, 51]. Any RLS patient who experiences worsening of RLS symptoms should have a serum ferritin level and if below 50–75 mcg/l, further blood testing should be performed (serum iron, iron binding capacity, and CBC) and treatment with iron therapy should be considered. Additionally, underlying etiologies of decreased iron such as gastrointestinal bleeding or cancer should be investigated although many RLS patients have low iron levels that cannot be explained.

Tolerance

Drug tolerance is defined as a diminution in the response to a drug after prolonged exposure requiring an increased dose to produce the previous response. Tolerance to DAs is thought to be an early stage of augmentation (discussed below) and has been documented in the medical literature [52] and is seen often clinically. It usually develops after several months or years of drug usage.

Once all the above triggers that might worsen RLS have been ruled out, tolerance may be difficult to differentiate from progression of disease and augmentation

(which is discussed below). Since tolerance is reversible, stopping the drug for a short time (typically a few weeks or more) will reestablish the effectiveness of the drug which does not occur with disease progression.

There are several actions available when tolerance to DAs occurs. If the DA dose is relatively low, its dose may be increased to the upper limits defined above. If further tolerance develops, care should be taken with further increases of the drug to avoid the emergence of augmentation. Another DA may be substituted but it is quite likely that cross-tolerance may develop. If that occurs, then treatment with α2δ drug and/or opioids as discussed above may be instituted. For patients who prefer the DAs to those other treatments, rotation drug therapy may be helpful. The α2δ drug and/or opioid can be taken for a few weeks then the DA resumed for weeks or months until significant tolerance develops again.

Intolerable Side Effects

Early Treatment Adverse Reactions

The short-acting DAs tend to share similar side effects. The most common one that occurs with the initiation of therapy is nausea. This typically manifests about 1–3 h after the medications are taken and corresponds to the peak of dopamine agonist blood levels. The nausea may be self-limiting and diminish with time but some patients have persistent severe symptoms that lead to discontinuation of the drug. There are several strategies for dealing with the nausea. The medication can be taken with food which often blunts or eliminates this issue but results in about an hour delay of the onset of action. Anti-nausea medications may prevent the nausea but most of these make RLS worse. The "RLS friendly" anti-nausea drugs (Table 13.1) may be taken prior to the DAs but adding a drug on a regular basis should only be considered when other treatment options are not available. Switching from one DA to another may reduce or eliminate the nausea.

Other common early treatment-emergent side effects include fatigue, sleepiness, dizziness, insomnia, nasopharyngitis, and headache. These early problems may resolve with time but if they are severe enough and do not resolve then the DA should likely be stopped. As with nausea, changing to another DA may be helpful. Otherwise, the patient should be changed to a different class of RLS drugs (α2δ drugs or opioids).

Late Treatment Adverse Reactions

The most common late treatment-emergent side effect other than augmentation is ICD (Impulse Control Disorders), which occurs in 6–17% of RLS patients taking dopamine agonists [53]. The ICDs constitute a group of psychiatric disorders in DSM-IV, their essential feature being a failure to resist an impulse, drive, or

temptation to perform an act that is harmful to the person or to others [54]. The behaviors that are typically manifested include pathologic gambling, hypersexuality, compulsive shopping, compulsive eating, compulsive medication use and punding. It is often difficult to diagnose the ICD in its early stages as patients are generally very secretive about their abnormal behavior and will not acknowledge their problem until it is exposed by family members or close friends. Treatments of the ICD include changing to another dopamine agonist, reducing the dose of the dopamine or eliminating dopamine agonists completely. When the dopamine agonist dose is reduced or eliminated, other classes of medication (α2δ drugs or opioids) typically need to be added or substituted.

Augmentation

After Akpinar described the use of levodopa for treating RLS in 1982 [1], this drug was widely prescribed and dramatically helped many RLS sufferers. However, after an initial period of relief, most patients developed very increased RLS symptoms that required higher and higher doses to obtain a therapeutic response, symptoms started occurring earlier in the day and expanded to the arms and other body parts. This phenomenon was quite puzzling until the term augmentation was first described in 1996 [2]. Augmentation was further defined with the development of criteria for its diagnosis by an NIH workshop in 2003 [55] (Fig. 13.1) [56] and subsequently by a consensus conference at the Max Planck Institute (called the MPI criteria) in 2007 [57] (Table 13.1). When it became apparent that the majority of

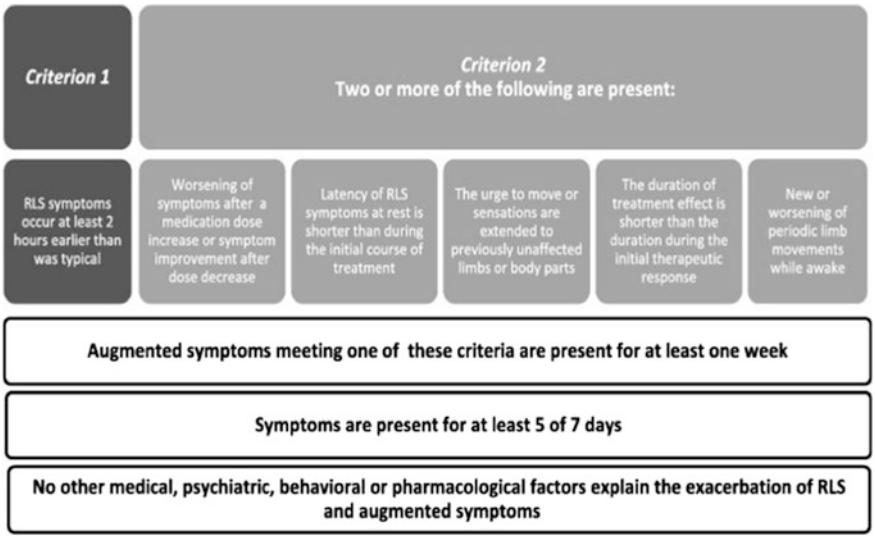

Fig. 13.1 NIH diagnostic criteria for diagnosing RLS augmentation

patients taking levodopa for RLS were developing augmentation [2], physicians switched the treatment to a dopamine agonist. Pergolide was one of the first DAs used to treat RLS. It worked quite well to treat the RLS symptoms of those augmented patients but its use was often limited by its side effects. Therefore, most physicians treating RLS with or without augmentation switched to ropinirole and pramipexole when they became available in 1997 for Parkinson's disease and especially after they were FDA approved for RLS in 2005 and 2006 respectively. The majority of these patients seemed to do very well with short-acting DA treatment and there appeared to be only minor concerns about augmentation. However, more recent studies using the more current NIH or MPI criteria for diagnosing RLS have found much higher rates of augmentation; up to 8% per year in a community sample study [55] and 5–7% per year in 10-year long retrospective study [33]. Augmentation symptoms from DAs tends to be severe often resulting in discontinuation of the DA [57]. Since the augmentation problem may develop at any time during 10 or more years of treatment, it is not often identified as such by most primary care physicians or even many specialists who are the local consultants for difficult RLS cases. These patients are thought to have gradual progression of their disease and are most often treated with escalating doses of DAs, frequently even into the high Parkinson's disease ranges. This has resulted in patients with augmentation making up the majority of RLS referrals to doctors, who have greater expertise with RLS such as movement disorder specialists [58].

As discussed above, one of the most important aspects of treating the augmentation caused by short-acting DAs is the recognition of the problem. Although the diagnostic criteria for augmentation are well defined [54, 56], there is considerable overlap of its features with other conditions that may confuse the diagnosis. The most common misdiagnosis of augmentation is the natural progression of the disease. This misunderstanding may have been further propagated by earlier studies, which found that augmentation occurred no later than 4 months [59] or 2.5 years [60] after the initiation of short-acting DA therapy. It is now clear that augmentation can occur for up to 10 years [57] or longer. When the augmentation symptoms onset within a few months of treatment, the diagnosis is much more obvious (patients will typically complain about the relative sudden worsening after the short period of symptom relief). However, as discussed above, when augmentation arises after several years of treatment, most physicians will assume it is due to progression of the disease. The only definite way to differentiate between these two issues is to stop the short-acting DA. Patients with augmentation will show improvement of their symptoms within a few weeks or months (after an initial period of marked worsening) while those with natural progression of the disease will not. However, since the cessation of treatment in augmentation cases causes a temporary dramatic increase of RLS symptoms resulting in significant suffering, this is usually not a very practical approach. Therefore, physicians should be very suspicious of augmentation whenever the dose of a short-acting DA must be increased. With augmentation, there will be further dose increases after shorter and shorter intervals while natural progression requires dose increases over prolonged intervals (personal observation).

Before augmentation is diagnosed, triggers that may impact RLS should be ruled out [56]. As discussed above, a thorough review of the patient's medications, lifestyle, and iron status should be performed. Removing the trigger may improve the RLS and obviate the need for additional RLS medication or concerns of augmentation. Rebound should not be confused with augmentation. Since rebound is an end of the dose effect of a short-acting DA, symptoms will occur as the drug's action is waning which typically occurs about 6–8 h after the medication is taken. Therefore, the clinical presentation of rebound is a worsening of RLS symptoms several hours after taking the DA rather than a few hours prior to taking the DA as with augmentation. Tolerance to the DAs also shares features of augmentation and may even be an early stage or subtype of augmentation [52]. However, despite tolerance producing a decreased effectiveness of a given DA dose with time that requires higher doses of that DA, it does not cause an earlier onset of symptoms or expansion of symptoms to other body parts.

Treatment of Augmentation from Short-Acting Dopamine Agonists

Prevention

Since the pathophysiology of augmentation is not fully understood, schemes to prevent it must rely on observational data. Increased augmentation rates have been associated with lower serum ferritin levels [61, 62]. However, there are no guidelines for the ideal serum ferritin levels that would prevent augmentation. Until further studies are performed, it would seem reasonable to suggest that the previous ferritin goal of >50–75 mcg/l [50, 51] discussed above (in the Triggers section) is a suitable target range that might forestall the development of augmentation for patients on short-acting DAs. Keeping the dose of the DA as low as possible has also been recommended to prevent augmentation as higher doses have been thought to be associated with increased risk of augmentation [14, 52, 56, 63, 64]. As such, recommendations to limit the daily dose of ropinirole to as low as 1 mg and pramipexole to 0.25 mg have been suggested to decrease the development of augmentation [11, 65]. However, it should be noted that augmentation may occur at even the lowest available doses of these short-acting DAs. In fact, one article [66] has gone so far as to suggest that perhaps dopaminergics should not be used at all to treat RLS due to the augmentation issue. The authors of this article use rotation therapy (alternating a short-acting DA with clonazepam and low-potency opioids) to avoid the sustained use of a DA which they believe may heighten the risk of augmentation. It has been suggested that the risk of augmentation is inversely related to half-life of the DA [4, 67, 68]. Although this phenomenon has not been proven, it appears that augmentation rates are lower with the long-acting cabergoline (5.6%) [69] and the rotigotine patch (5% with the 1–3 mg/day FDA approved doses) [70]. Therefore, it may be prudent to consider using a long-acting

DA instead of a short-acting one when this class of medication is being considered for treating RLS. However, issues with fibrotic heart valve formation should limit the use of cabergoline [71]. One of the concerns with the decreased augmentation seen with long-acting DAs is that their long duration of action may obscure the diagnosis of augmentation by treating the earlier onset of RLS symptoms, which is one of the cardinal symptoms for identifying augmentation.

Management of Augmentation

So far there are only a few articles [4, 12, 15, 56, 58, 64, 65, 72] in the medical literature that discuss the treatment of augmentation. One of the articles published in 2007 [70], is authored by several experts in the field and is still quite clinically relevant. This article contains the first and only algorithm written so far on how to manage augmentation (Fig. 13.2). This algorithm is discussed below with further suggestions based on additional knowledge and drugs that that have become available since the algorithm's creation in 2007.

When augmentation is suspected, physicians should search for possible triggers that may have worsened the RLS symptoms (see Triggers above). A serum ferritin level should be checked and patients should be questioned about drug and lifestyle changes that may affect their RLS symptoms [12, 15].

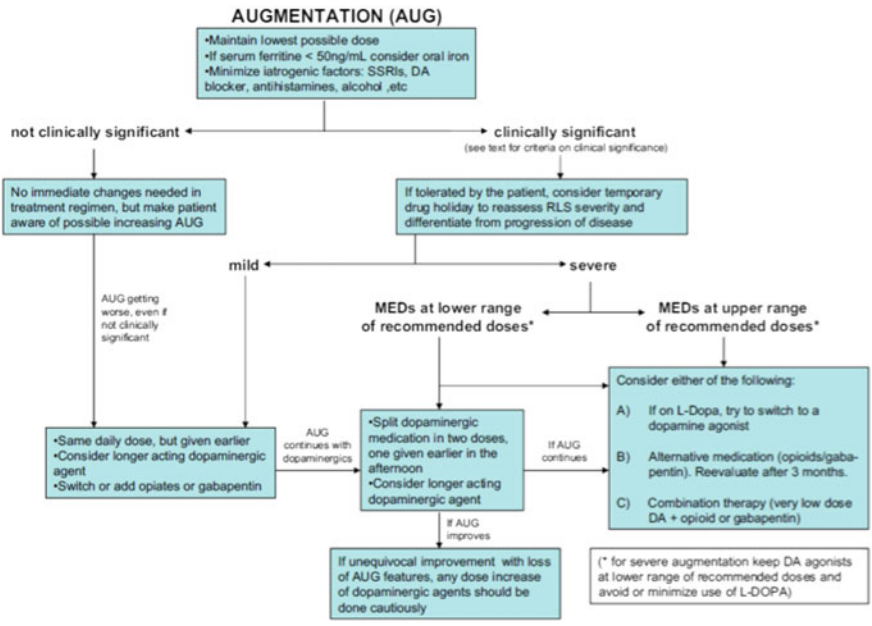

Fig. 13.2 RLS augmentation treatment algorithm

Management of RLS that Is Not Clinically Significant

Augmentation symptoms may range from minimal and barely bothersome to extremely severe and disruptive. Physicians have to decide at what point in the continuum that they must intervene. Mild augmentation with symptoms that are not disruptive may not need any action. Based on the MPI Consensus Conference [56], the algorithm suggests that augmentation does not need to be treated until the symptoms become clinically significant as defined below:

Any One of More of a–e Below

a. Change in daily activities and/or behavior (e.g., the patient stops riding in cars in the afternoon) due to augmentation.
b. Negative impact on the patient's quality of life (sleep, mood, etc.) due to augmentation.
c. Need to change the treatment dose or the patient needs to take the dose earlier in the day (e.g., dividing the dose).
d. Adjustments in concomitant medication are made to compensate for augmented RLS symptoms (e.g., an increased intake of analgesics or hypnotics to cover an increase in symptom intensity).
e. Any other aspect as judged by the evaluator (should be specified).

Patients without clinically significant symptoms can simply be watched closely for any further development of augmentation symptoms without altering their therapy. The percentage of patients with this clinically insignificant augmentation that progress to more severe augmentation is unknown. However, based upon clinical experience, these patients are clearly at higher risk of developing worsening augmentation problems over the next several years. Since it is much easier to modify therapy earlier in the augmentation process when symptoms are less severe, this may be an opportune time to intervene and change treatment. Although the augmentation algorithm (Fig. 13.2) indicates that no treatment adjustments are necessary for these milder augmented patients, several treatment options are presented below.

Options for Changing Current Short-Acting DA Therapy

Changing to Another Short-Acting DA

There have been some suggestions that augmentation that has developed with one short-acting dopamine may not occur when substituting another [4, 64]. However, there is really no evidence in the medical literature that substantiates this supposition and based upon clinical experience many experts believe that it is better to reduce or eliminate all short-acting DAs [70] when deciding to treat augmented patients. Nevertheless, if no other options exist, it may be worth trying this substitution.

Reducing the Dose of the Short-Acting DA

There is no clinical research that validates the approach to decrease dose of the short-acting DA to treat augmentation but physicians have used this technique with some success. This approach may also be easier with milder cases of augmentation as the temporary increase in RLS symptom intensity and duration upon reducing the DA dose is significantly less than with severely augmented patients. There are no clear guidelines on how much to decrease the dose but most physicians reduce the current dose by at least 50% with a possible goal of reaching the lowest available dose. Leaving the patient with some DA medication may prevent the more intense and prolonged dopamine withdrawal increase in RLS symptoms when completely eliminating the DA. Some patients may adjust to lower levels of short-acting DA therapy with a very significant decrease in RLS symptoms/augmentation and need no additional therapy. However, many of these patients will require additional therapy (but perhaps less than those who completely eliminate the DA) with either an α2δ drug or an opioid. It is not known whether leaving a low dose of the DA that caused the augmentation may result in a reemergence of the augmentation with time so these patients should be watched closely for any signs of this problem.

Elimination of the Short-Acting DA

As noted above, this approach is easier to accomplish with patients with milder augmentation symptoms. When DAs are discontinued abruptly, a marked increase in RLS symptoms should be expected for a few days to weeks or even months [58]. After this interval, the RLS symptoms typically abate to pre-DA treatment levels and the RLS is much easier to control. In that interval period, higher doses of the replacement therapy (α2δ drugs or opioids) may be needed and can be significantly reduced when symptoms diminish at the end of the interval. The short-acting DA may be slowly tapered off while gradually titrating up the replacement α2δ drug or opioid but there still may be a significant intensification of RLS symptoms when the DA is completely eliminated. Eliminating the short-acting DA completely is the preferred approach of most RLS specialists for patients with severe augmentation and often even for milder cases.

Replacement with a Long-Acting DA

Since longer acting dopamine agonists are thought to cause fewer problems with augmentation, they might be a suitable choice to replace a short-acting DA once augmentation occurs. However, there are no studies examining the use of long-acting DAs in this situation. There is some limited clinical experience with the use of cabergoline, transdermal rotigotine and extended release ropinirole and pramipexole which has had some success in resolving early and mild augmentation symptoms. Since these medications act for 24 h or more, they typically eliminate the augmentation symptoms that occur earlier in the day. Further clinical experience and medical studies evaluating 5–10 years (or longer) of treatment may determine the validity of using the longer acting DAs in this context. Cabergoline should be used with caution if at all [12] as it may cause heart valvular fibrosis. There is less

clinical experience available supporting the use of extended release pramipexole and ropinirole due to the short time they have been available and the difficulty prescribing branded drugs off-label for RLS.

Rotation Therapy/Drug Holidays

Drug holidays and rotation therapy have been mentioned in the literature [4, 65] as possible management or prevention of augmentation. The process of augmentation requires the sustained use of dopaminergic drugs. Even levodopa, which has the highest incidence of augmentation [2], can be taken on an intermittent basis (up to 3–5 days per week based on personal experience) without ever causing augmentation. There are patients who rotate levodopa or short-acting DAs with other drugs (α2δ drugs or opioids) or no drugs on a weekly basis successfully for many years. However, it is more convenient for most patients to rotate drugs at longer intervals such as several weeks or months. The two articles above [4, 65] suggest a 3-month hiatus off the DA for drug holidays or rotation therapy. However, although the initial onset of augmentation with DAs typically takes a few months or much longer, when reintroducing the DA, the reoccurrence of augmentation may occur within a few weeks or even days. Therefore, the DA portion of the rotation therapy should continue for up to 3 months only if no symptoms of augmentation appear.

Management of Clinically Significant Augmentation

Mild Augmentation

The augmentation algorithm (Fig. 13.2) suggests that the first step is to have the patient take a temporary drug holiday to reassess RLS severity to help differentiate augmentation from progression of disease. Patients who improve with time have augmentation while those who remain worse off treatment are likely experiencing disease progression. This may be feasible for some patients with very mild augmentation but those with more significant augmentation will undergo a very severe exacerbation of RLS symptoms upon withdrawal of their DA that can last weeks to months. Therefore, this procedure will be very tough to accomplish in all but those with very mild augmentation and often even those patients experience a profound increase in RLS symptoms with cessation of DA therapy.

The next step for those with mild augmentation is to institute earlier dosing of the DA so as to treat the earlier onset of symptoms. This may be helpful for patients with very mild augmentation but many patients may need to split the dose into 2 doses (1/2 the previous dose taken 1–2 h before the earlier onset of symptoms and ½ the dose taken 1–2 h before bedtime) as the single earlier dose may not last long enough and cause rebound symptoms in the early morning hours. The augmentation algorithm also suggests the option of switching to longer acting DAs, opioids, or α2δ drugs (or adding opioids or α2δ drugs) at this step which is similar to the discussion above for Options 3 and 4.

Once the augmentation process has been identified, any increase in the DA dose should be done with extreme caution as this will most likely result in worsened augmentation symptoms after an initial improvement. Although it is very tempting

to raise the amount of short-acting DA to provide immediate relief, this should only be considered when the above alternative choices are not effective, tolerated, affordable, or available. Therefore, if patients do not respond to the above interventions, the short-acting DA should be changed to another therapy as described below for severe augmentation.

Severe Augmentation

For patients with severe augmentation, management choices are generally more limited. Option 1 above (changing to another short-acting DA) is seldom effective and many of these patients have already tried and failed all the other short-acting DAs. Option 4 (changing to a long-acting DA) is typically not an alternative as most patients with severe augmentation are already on very high doses and will need equivalent high doses of the long-acting DA. With the rotigotine patch, the higher doses (over 3 mg/24 h) are not FDA approved for RLS and have been associated with increased incidences of augmentation [69]. There is not a lot of clinical experience with long-acting ropinirole and pramipexole for treating RLS or especially for treating augmentation and they are not FDA approved for RLS making them very expensive for RLS patients. Therefore, they cannot be recommended for treating augmentation at this time. However, if they are used for treating severe augmentation, they should be limited to their lower doses.

Option 5 (Rotation therapy/Drug Holidays) may be difficult to institute due to concerns with DA withdrawal symptoms as discussed above. However, if potent opioids are alternated with the short-acting DA, this may be a viable choice since the opioids are a very effective treatment for the marked worsening of RLS symptoms when stopping DAs. The only other issue would occur when restarting the DA at its previous high dose which may cause side effects and thus may require a slow titration over a week or two. Rotation intervals may have to be quite short as augmentation can recur fairly quickly (days to weeks) in patients with a history of severe augmentation.

The two most common and effective courses of management for severe augmentation (based upon clinical experience) are Option 3 and 2. For Option 3 (discontinuing the short-acting DA which is the author's most common and preferred approach for severe augmentation), the short-acting DA may be reduced slowly or stopped abruptly. Either way, there will be a marked worsening of RLS symptoms that is typically only relieved by adequate doses of a potent opioid. Unlike treating mild augmentation, $\alpha 2\delta$ drugs will only modestly mute the severe DA withdrawal augmentation symptoms compared to the virtual complete relief typically afforded by opioids. Using drugs other than potent opioids (such as $\alpha 2\delta$ drugs, tramadol, propoxyphene, or clonazepam) will result in weeks to months of marked suffering from RLS symptoms and sleepless nights [58]. With DA cessation, potent opioids such as oxycodone or methadone at 5 mg, 1/2–2 tablets up to three times daily are typically necessary to control the RLS and will make the transition off the DA virtually painless. As noted above, methadone is often the preferred opioid by many RLS experts in the USA. Patients should be advised to determine the lowest dose necessary to quell their symptoms and may take less or

no medication when active during the daytime. The initial opioid dose can usually be significantly reduced after a few weeks to months as the augmentation process resolves and RLS symptoms returns to baseline. Once the RLS symptoms have stabilized, patients may stay on the opioid as solo therapy especially if only a very low dose is needed to control symptoms. However, if patients are uncomfortable taking opioids or when higher doses of opioids are required once RLS symptoms have stabilized (typically after 3–4 months off the DA), then α2δ drugs may be added. The α2δ drugs may help eliminate the use of opioids (for those on low dose therapy) or reduce the opioid dose (for those on higher doses). If the α2δ drugs are not effective or tolerated, adding a low dose of a long-acting DA such as the rotigotine transdermal patch may also help reduce the amount of opioid therapy. However, the long-acting DAs have only been available for a short while so there is not much clinical experience accumulated with their use in this setting. The little clinical experience available (personal experience) has found them effective in the short term, but more time is necessary to see if this is a durable response and does not result in the reemergence of augmentation.

Option 2 (Reducing the dose of the Short-acting DA) is the other more common approach to managing severe augmentation. It is similar to completely eliminating the DA but is thought to be easier to implement and may require lower doses of opioid therapy. However, it is not clear if maintaining a low dose of the DA will prevent the return of RLS symptoms to baseline that occurs with the complete

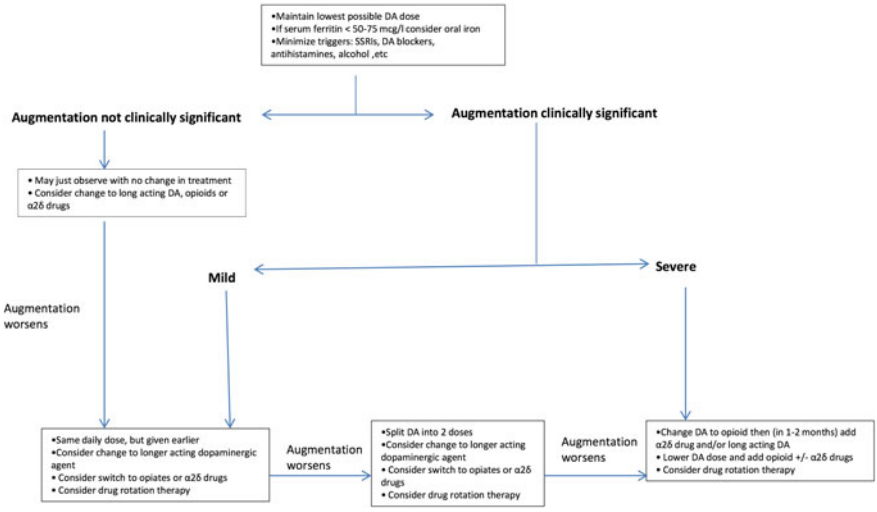

Fig. 13.3 Treatment of augmentation from short-acting DAs

cessation of the DA as in Option 3. Based on some clinical experience (and the opinion of those physicians who follow this management course), leaving a small dose of a DA is thought to decrease the dose of opioids needed to treat the RLS. As with option 3 above, α2δ drugs may be added to the combination of low dose DA and opioids to further reduce or eliminate the opioids.

Figure 13.3 is a simplified version of the Fig. 13.2 augmentation algorithm updated with the suggestions and comments discussed above. Physicians can use this revised algorithm as a guide for managing augmentation from short-acting DAs. Whichever plan is chosen to treat RLS augmentation, physicians must be flexible and try different drugs in every class. All of the safe or available long-acting DAs, α2δ drugs or opioids can be tried if problems occur with the initial or approved drugs. Different combinations of drugs and doses should be employed if necessary until the best tolerated and effective regimen is established. Following the treatment choices outlined above should enable most patients to achieve excellent control of their RLS symptoms. Physicians should avoid just increasing the short-acting DA dose over several months or years unless no other options are available or effective.

References

1. Akpinar S. Treatment of restless legs syndrome with levodopa plus benserazide. Arch Neurol. 1982;39:739.
2. Allen RP, Earley CJ. Augmentation of the restless legs syndrome with carbidopa/levodopa. Sleep. 1996;19:205–13.
3. Walters AS, Hening WA, Kavey N, Chokroverty S, Gidro-Frank S. A double-blind randomized crossover trial of bromocriptine and placebo in restless legs syndrome. Ann Neurol. 1988;24(3):455–8.
4. Silber MH, Shepard JW Jr, Wisbey JA. Pergolide in the management of restless legs syndrome: an extended study. Sleep. 1997;20(10):878–82.
5. Earley CJ, Yaffee JB, Allen RP. Randomized, double-blind, placebo-controlled trial of pergolide in restless legs syndrome. Neurology. 1998;51(6):1599–602.
6. Stiasny K, Wetter TC, Winkelmann J, Brandenburg U, Penzel T, Rubin M, Hundemer HP, Oertel WH, Trenkwalder C. Long-term effects of pergolide in the treatment of restless legs syndrome. Neurology. 2001;56(10):1399–402.
7. Trenkwalder C, Hundemer HP, Lledo A, Swieca J, Polo O, Wetter TC, Ferini-Strambi L, de Groen H, Quail D, Brandenburg U, PEARLS Study Group. Efficacy of pergolide in treatment of restless legs syndrome: the PEARLS Study. Neurology. 2004;62(8):1391–7.
8. Serratrice J, Disdier P, Habib G, Viallet F, Weiller PJ. Fibrotic valvular heart disease subsequent to bromocriptine treatment. Cardiol Rev. 2002;10(6):334–6.
9. Pritchett AM, Morrison JF, Edwards WD, Schaff HV, Connolly HM, Espinosa RE. Valvular heart disease in patients taking pergolide. Mayo Clin Proc. 2002;77(12):1280–6.
10. Silber MH, Ehrenberg BL, Allen RP, Buchfuhrer MJ, Earley CJ, Hening WA, Rye DB. An algorithm for the management of restless legs syndrome. Mayo Clin Proc. 2004;79(7):916–22.
11. Hochang BL, Buchfuhrer MJ, Allen RP, Hening WA. Clinical management of restless legs syndrome. West Islip, New York: Professional Communications Inc.; 2013.
12. Garcia-Borreguero D, Kohnen R, Silber MH, Winkelman JW, Earley CJ, Högl 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(7):675–84.
13. Allen RP, Picchietti D, Hening WA, Trenkwalder C, Walters AS, Montplaisi J, Restless Legs Syndrome Diagnosis, Epidemiology workshop at the National Institutes of Health, International Restless Legs Syndrome Study Group. 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 (2):101–19.
14. Paulus W, Trenkwalder C. Less is more: pathophysiology of dopaminergic-therapy-related augmentation in restless legs syndrome. Lancet Neurol. 2006;5(10):878–86.
15. García-Borreguero D, Williams AM. Dopaminergic augmentation of restless legs syndrome. Sleep Med Rev. 2010;14(5):339–46.
16. Kushida CA, Becker PM, Ellenbogen AL, Canafax DM, Barrett RW, XP052 Study Group. Randomized, double-blind, placebocontrolled study of XP13512/GSK1838262 in patients with RLS. Neurology. 2009;3,72(5):439–46.
17. Kushida CA, Walters AS, Becker P, Thein SG, Perkins AT, Roth T, Canafax D, Barrett RW, XP021 Study Group. A randomized, double-blind, placebo-controlled, crossover study of XP13512/GSK1838262 in the treatment of patients with primary restless legs syndrome. Sleep. 2009;1,32(2):159–68.
18. Bogan RK, Bornemann MA, Kushida CA, Trân PV, Barrett RW, XP060 Study Group. Long-term maintenance treatment of restless legs syndrome with gabapentin enacarbil: a randomized controlled study. Mayo Clin Proc. 2010;85(6):512–21.
19. Ellenbogen AL, Thein SG, Winslow DH, et al. A 52-week study of gabapentin enacarbil in restless legs syndrome. Clin Neuropharmacol. 2011;34(1):8–16.
20. Lee DO, Ziman RB, Perkins AT, Poceta JS, Wlaters AS, Barrett RW, XP053 Study Group. 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;15:282–92.
21. Garcia-Borreguero D, Larrosa O, Williams AM, et al. Treatment of restless legs syndrome with pregabalin: a double-blind, placebo-controlled study. Neurology. 2010;74(23): 1897–904.
22. Allen R, Chen C, Soaita A. A randomized, double-blind, 6-week, dose-ranging study of pregabalin in patients with restless legs syndrome. Sleep Med. 2010;11(6):512–9.
23. Mellick GA, Mellick LB. Management of restless legs syndrome with gabapentin (Neurontin). Sleep. 1996;19:224–6.
24. Happe S, Klosch G, Saletu B, Zeitlhofer J. Treatment of idiopathic restless legs syndrome (RLS) with gabapentin. Neurology. 2001;57:1717–9.
25. Garcia-Borreguero D, Larrosa O, de la Llave Y, Verger K, Masramon X, Hernandez G. Treatment of restless legs syndrome with gabapentin: a double-blind, cross-over study. Neurology. 2002;59:1573–9.
26. Happe S, Sauter C, Klosch G, Saletu B, Zeitlhofer J. Gabapentin versus ropinirole in the treatment of idiopathic restless legs syndrome. Neuropsychobiology. 2003;48:82–6.
27. Stewart BH, Kugler AR, Thompson PR, Bockbrader HN. A saturable transport mechanism in the intestinal absorption of gabapentin is the underlying cause of the lack of proportionality between increasing dose and drug levels in plasma. Pharm Res. 1993;10(2):276–81.
28. Bockbrader HN, Breslin EM, Underwood BA, Posvar EL, Sedman AI. Multiple-dose, dose-proportionality study of neurontin (gabapentin) in healthy volunteers. EPILE PSIA. 1996;37(Suppl 5):159.
29. Gidal BE, Radulovic LL, Kruger S, Rutecki P, Pitterle M, Bockbrader HN. Inter- and intra-subject variability in gabapentin absorption and absolute bioavailability. EPILE PSY RES. 2000;40(2–3):123–7.
30. Walters AS, Winkelmann J, Trenkwalder C, et al. Long-term follow-up on restless legs syndrome patients treated with opioids. Mov Disord. 2001;16:1105–9.

31. Walters AS, Wagner ML, Hening WA, et al. Successful treatment of the idiopathic restless legs syndrome in a randomized double-blind trial of oxycodone versus placebo. Sleep. 1993;16:327–32.
32. Ondo WG. Methadone for refractory restless legs syndrome. Mov Disord. 2005;20:345–8.
33. Silver N, Allen RP, Senerth J, Earley CJ. A 10-year, longitudinal assessment of dopamine agonists and methadone in the treatment of restless legs syndrome. Sleep Med. 2011;12 (5):440–4.
34. Sanz-Fuentenebro FJ, Huidobro A, Tejada-Rivas A. Restless legs syndrome and paroxetine. Ann Psychiatr Scand. 1996;P94:482–4.
35. Hargrave R, Beckley DJ. Restless leg syndrome exacerbated by sertraline. Psychosomatics. 1998;2:177–8.
36. Teive HA, de Quadros A, Barros FC, Werneck LC. Worsening of autosomal dominant restless legs syndrome after use of mirtazapine: case report. Arq Neuropsiquiatr. 2002;60 (4):1025–9.
37. Bahk WM, Pae CU, Chae JH, Kim KS. Mirtazapine may have the propensity for developing a restless legs syndrome? A case report. Psychiatry Clin Neurosci. 2002;56(2):209–10.
38. Salin-Pascual RJ, Galicia-Polo L, Drucker-Colin R. Sleep changes after 4 consecutive days of venlafaxine administration in normal volunteers. J Clin Psychiatry. 1997;58:248–350.
39. Rottach KG, Schaner BM, Kirch MH, et al. Restless legs syndrome as side effect of second generation antidepressants. J Psychiatr Res. 2008;43(1):70–5.
40. Hoque R, Chesson AL Jr. 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 (1):79–83.
41. Garvey MJ, Tolefson GD. Occurrence of myoclonus in patients treated with cyclic antidepressants. Arch Gen Psychiatr. 1987;44(2):9–474.
42. Kraus T, Schuld A, Pollmacher T. Perodic leg movements in sleep and restless legs syndrome probably caused olanzapine. J Clin Psychopharmocol. 1999;19(15):478–9.
43. Wetter TC, Brunner J, Bronisch T. Restless legs syndrome probably induced by risperidone treatment. Pharmacopsychiatry. 2002;35(3):109–11.
44. Terao T, Terao M, Yoshimura R, Kazuhiko A. Restless legs syndrome induced by lithium. Biol Psychiatry. 1991;30:1167–70.
45. Phillips B, Young T, Finn L, Asher K, Hening WA, Purvis C. Epidemiology of restless legs symptoms in adults. Arch Intern Med. 2000;160(14):2137–41.
46. Aukerman MM, Aukerman D, Bayard M, Tudiver F, Thorp L, Bailey B. Exercise and restless legs syndrome: a randomized controlled trial. J Am Board Fam Med. 2006;19:487–93.
47. Stiasny K, Oertel WH, Trenkwalder C. Clinical symptomatology and treatment of restless legs syndrome and periodic limb movement disorder. Sleep Med Rev. 2002;6:253–65.
48. Paulson GW. Restless legs syndrome. How to provide symptom relief with drug and nondrug therapies. Geriatrics. 2000;55:35–8.
49. Hening W, Allen R, Earley C, Kushida C, Picchietti D, Silber M. The treatment of restless legs syndrome and periodic limb movement disorder. An American Academy of Sleep Medicine Review. Sleep. 1999;22:970–99.
50. O'Keeffe ST, Gavin K, Lavan JN. Iron status and restless legs syndrome in the elderly. Age Ageing. 1994;23:200–3.
51. 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.
52. Winkelman JW, Johnston L. Augmentation and tolerance with long-term pramipexole treatment of restless legs syndrome (RLS). Sleep Med. 2004;5(1):9–14.
53. Cornelius JR, Tippmann-Peikert M, Slocumb NL, Frerichs CF, Silber MH. Impulse control disorders with the use of dopaminergic agents in restless legs syndrome: a case-control study. Sleep. 2010;33:81–7.

54. American Psychiatric Association. Diagnostic and statistical manual of mental disorders. Fourth Edition, Text Revision. Washington, DC: American Psychiatric Association; 2000.
55. Allen RP, Picchietti D, Hening WA, Trenkwalder C, Walters AS, Montplaisi J, Restless Legs Syndrome Diagnosis and Epidemiology workshop at the National Institutes of Health, International Restless Legs Syndrome Study Group. 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 (2):101–19.
56. Allen RP, Ondo WG, Ball E, Calloway MO, Manjunath R, Higbie RL, et al. Restless legs syndrome (RLS) augmentation associated with dopamine agonist and levodopa usage in a community sample. Sleep Med. 2011;12(5):431–9.
57. García-Borreguero D, Allen RP, Kohnen R, Högl B, Trenkwalder C, Oertel W, Hening WA, Paulus W, Rye D, Walters A, Winkelmann J, Earley CJ, International Restless Legs Syndrome Study Group. Diagnostic standards for dopaminergic augmentation of restless legs syndrome: report from a World Association of Sleep Medicine-International Restless Legs Syndrome Study Group consensus conference at the Max Planck Institute. Sleep Med. 2007;8 (5):520–30.
58. Kurlan R, Rabin M. Augmentation in restless legs syndrome: poor response to sudden withdrawal of dopaminergic therapy. J Parkinsonism Restless Legs Syndr. 2013;3:49–52.
59. Ferini-Strambi L. Restless legs syndrome augmentation and pramipexole treatment. Sleep Med. 2002;3(Suppl):S23–5.
60. Silber MH, Girish M, Izurieta R. Pramipexole in the management of restless legs syndrome: an extended study. Sleep. 2003;26(7):819–21.
61. Frauscher B, Gschliesser V, Brandauer E, 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.
62. Trenkwalder C, Hogl B, Benes H, Kohnen R. Augmentation in restless legs syndrome is associated with low ferritin. Sleep Med. 2008;9:572–4.
63. Garcia-Borreguero D, Odin P, Schwarz C. Restless legs syndrome: an overview of the current understanding and management. Acta Neurol Scand. 2004;109(5):303–17.
64. García-Borreguero D, Allen RP, Benes H, Earley C, Happe S, Högl B, et al. Augmentation as a treatment complication of restless legs syndrome: concept and management. Mov Disord. 2007;22(Suppl 18):S476–84.
65. Buchfuhrer MJ. Strategies for the treatment of restless legs syndrome. Neurotherapeutics. 2012;9(4):776–90.
66. Kurlan R, Richard IH, Deeley C. Medication tolerance and augmentation in restless legs syndrome: the need for drug class rotation. J Gen Intern Med. 2006;21(12):C1–4.
67. Ondo W, Romanyshyn J, Vuong KD, Lai D. Long-term treatment of restless legs syndrome with dopamine agonists. Arch Neurol. 2004;61(9):1393–7.
68. Chokroverty S. Long-term management issues in restless legs syndrome. Mov Disord. 2011;26(8):1378–85.
69. Trenkwalder C, Benes H, Grote L, Happe S, Hogl B, Mathis J, et al. Cabergoline compared to levodopa in the treatment of patients with severe restless legs syndrome: results from a multi-center, randomized, active controlled trial. Mov Disord. 2007;22:696–703.
70. Oertel W, Trenkwalder C, Beneš H, Ferini-Strambi L, Högl B, Poewe W, et al, SP710 Study Group. Long-term safety and efficacy of rotigotine transdermal patch for moderate-to-severe idiopathic restless legs syndrome: a 5-year open-label extension study. Lancet Neurol. 2011;10(8):710–20.
71. De Vecchis R, Esposito C, Ariano C. Cabergoline use and risk of fibrosis and insufficiency of cardiac valves: meta-analysis of observational studies. Herz. 2013 Jun 8 [Epub ahead of print].
72. Williams AM, Garcia-Borreguero D. Management of restless legs syndrome augmentation. Curr Treat Options Neurol. 2009;11(5):327–32.

Management of Augmentation

14

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Augmentation is a major clinical problem that emerges with the long-term treatment of RLS/WED. It can produce a severe exacerbation of RLS/WED symptoms and is thus something to be carefully assessed and managed. Some degree of augmentation has been reported with the use of all investigated dopaminergic drugs [1–5], tramadol being the only exception among the non-dopaminergic substances [6]. In the virtual absence of direct comparative studies between dopaminergic agents, the incidence rate seems to be highest during treatment with levodopa and higher for shorter acting (pramipexole, ropinirole) than longer acting (rotigotine, cabergoline) dopamine-receptor agonists. However, it is unclear whether this finding is related to masking of earlier symptom onset by the longer acting dopaminergic agents, or whether this reflects a truly reduced risk of augmentation.

The propensity of augmentation increases with longer duration of treatment and possibly with higher doses. [7, 8] It is unclear whether the apparent relationship between dose and augmentation rate is, in fact, secondary to patient characteristics such as disease duration or severity. Nevertheless, it is recommended that dose increases be carefully considered, particularly if they exceed usually accepted or approved dose levels. Increases should be limited to breakthrough of clinically important symptoms that cannot be managed behaviorally [9] and should be balanced against the option of adding an alternative type of medication.

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When to Treat Augmentation?

Augmentation can sometimes be mild and not interfere with the main activities of the patient. Thus, any decision on whether to treat augmentation is usually guided by the presence or absence of clinical relevance.

Among the criteria that might be helpful to define clinical relevant augmentation are [10]:

a. Change in daily activities and/or behavior (e.g., the patient stops riding in cars in the afternoon) due to augmentation;
b. Negative impact on the patient's quality of life (sleep, mood, etc.) due to augmentation;
c. Need to change the treatment dose or the patient needs to take the dose earlier in the day (e.g., dividing the dose);
d. Adjustments in concomitant medication are made to compensate for augmented RLS symptoms (e.g., an increased intake of analgesics or hypnotics to cover an increase in symptom intensity);
e. Any other aspect as judged by the evaluator.

Furthermore, in some cases, the only sign of augmentation might be a minimal reduction of the efficacy of the dopaminergic treatment. In this way, patients might notice only mild RLS/WED symptoms during the day that are not bothersome because usual daytime activities help to alleviate them. Although, in such cases no change of treatment might be necessary. Some preventive measures are always needed to avoid a progression of the condition: physicians and patients should be aware that dopaminergic medication might lead to an iatrogenic increase in symptom severity and should be encouraged to use lower dopaminergic doses. Moreover, a careful observation of the clinical course will be necessary in such cases to allow future changes in the severity of symptoms to be noticed.

Even in mild cases, before a change of treatment regimen is even considered, serum ferritin levels should be measured [7]. Thus, if serum ferritin is <75 μg/L, oral iron treatment should be considered [7]. Furthermore, any medication that might exacerbate RLS/WED symptom severity, such as antidepressants, antihistamines or dopamine blockers should be carefully reviewed and eventually interrupted.

When the sole sign of augmentation consists of symptoms starting earlier in the day, without an increase in the number of hours occupied by symptoms over the entire 24-hr period, the time of administration of the dopaminergic medication can be changed to an earlier time in the afternoon. However, if the earlier onset of symptoms in the day is accompanied by an increase in the number of hours with symptoms each day, dividing the tablet into two halves (with one half being administered earlier in the PM and a second one at bedtime) is a frequently used strategy. However, no empirical evidence exists on its efficacy to effectively alleviate symptoms or to prevent the on-going process of augmentation. A reasonable caution when doing this would be to ensure that the actual plasma levels obtained

by partition of the former dose are still therapeutic. An alternative, but still relatively unexplored strategy based on the same concept would be the use of an extended release form of the same medication that had been used before [11].

When augmentation is clinically meaningful a change of treatment regimen might be necessary. If augmentation occurs during the use of either L-DOPA or a dopamine agonist with a short/intermediate half-life such as ropinirole or pramipexole, three alternative strategies seem feasible:

- First, any of these treatments should be substituted by a longer acting dopamine agonist. By far, the most investigated and only approved long-acting dopamine agonist is rotigotine. The dose of rotigotine should not exceed 3 mg/day, as the risk of augmentation increases [12, 13]. However, as mentioned above, it is still not known whether such an approach will just cover symptoms that would otherwise occur during the day without really preventing an emerging process from occurring.
- Second, the dose of the long-acting dopamine agonist should be reduced and kept as low as possible (i.e., 2 mg/day rotigotine). If symptoms cannot be managed adequately under a low dose, then a combination treatment with a non-dopaminergic drug (and a low dose of a long-acting dopamine agonist) should be considered. Unfortunately, the therapeutic efficacy of combination strategies remains largely unexplored in the literature. Still, expert opinion recommends [7] that the combination be tried first with an alpha-2 delta compound, such as pregabalin (150–300 mg/day), gabapentin enacarbil (300–1200 mg/day), or gabapentin (600–1800 mg). Alternatively, a low potency opiate can be used, being the combination slow release oxycodone/naloxone by far the most investigated in RLS/WED [14].
- Finally, and especially in cases of severe augmentation, all dopaminergic treatments might need to be interrupted for several months. The hypothesis that switching to a different dopamine agonist (other than to switching to a long-acting one) will reduce the problem of augmentation has not been systematically evaluated. At this point, however, the prudent action to avoid reoccurrence of significant augmentation resulting from dopamine agonists is to interrupt treatment with any dopamine agonist for a period of at least six months to one year.
- During the washout period off any dopaminergic treatment, two possibilities arise [15] Some authors recommend withholding any specific treatment for RLS/WED [10]. However, in most cases it might be necessary to alleviate symptoms and start treatment during that period with non-dopaminergic agents. Such alternatives include alpha-2 delta ligands and, particularly for severe cases, opiates [16, 17].
- Following a six- to twelve-month period off any dopaminergic treatment, an attempt can be eventually tried again with a low-dosed, preferably long-acting dopamine agonist (rotigotine) alone or in combination with alpha-2 delta ligands. However, if a second episode of augmentation arises under the renewed therapeutic regimen, all dopaminergic treatment should be avoided in future for this specific patient [15].

References

1. Hogl B, Garcia-Borreguero D, Kohnen R, Ferini-Strambi L, Hadjigeorgiou G, Hornyak M, et al. Progressive development of augmentation during long-term treatment with levodopa in restless legs syndrome: results of a prospective multi-center study. J Neurol. 2010;257:230–7.
2. Silver N, Allen RP, Senerth J, Earley CJ. A 10-year, longitudinal assessment of dopamine agonists and methadone in the treatment of restless legs syndrome. Sleep Med. 2011;12:440–4.
3. Garcia-Borreguero D, Hogl B, Ferini-Strambi L, Winkelman J, Hill-Zabala C, Asgharian A, et al. Systematic evaluation of augmentation during treatment with ropinirole in restless legs syndrome (Willis-Ekbom disease): results from a prospective, multicenter study over 66 weeks. Mov Disord. 2012;27:277–83.
4. Oertel W, Trenkwalder C, Benes H, Ferini-Strambi L, Hogl B, Poewe W, et al. Long-term safety and efficacy of rotigotine transdermal patch for moderate-to-severe idiopathic restless legs syndrome: a 5-year open-label extension study. Lancet Neurol. 2011;10:710–20.
5. Trenkwalder C, Benes H, Grote L, Happe S, Hogl B, Mathis J, et al. Cabergoline compared to levodopa in the treatment of patients with severe restless legs syndrome: results from a multi-center, randomized, active controlled trial. Mov Disord. 2007;22:696–703.
6. Earley CJ, Allen RP. Restless legs syndrome augmentation associated with tramadol. Sleep Med. 2006;7:592–3.
7. 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.
8. Allen RP, Chen C, Garcia-Borreguero D, Polo O, DuBrava S, Miceli J, et al. Comparison of pregabalin with pramipexole for restless legs syndrome. N Engl J Med. 2014;370:621–31.
9. 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.
10. Earley CJ. Latest guidelines and advances for treatment of restless legs syndrome. J Clin Psychiatry. 2014;75:e08.
11. Maestri M, Fulda S, Ferini-Strambi L, Zucconi M, Marelli S, Staedler C, et al. Polysomnographic record and successful management of augmentation in restless legs syndrome/Willis-Ekbom disease. Sleep Med. 2014;15:570–5.
12. Oertel W, Trenkwalder C, Benes H, Ferini-Strambi L, Hogl B, Poewe W, et al. Long-term safety and efficacy of rotigotine transdermal patch for moderate-to-severe idiopathic restless legs syndrome: a 5-year open-label extension study. Lancet Neurol. 2011;10:710–20.
13. Dohin E, Hogl B, Ferini-Strambi L, Schollmayer E, Fichtner A, Bauer L, et al. Safety and efficacy of rotigotine transdermal patch in patients with restless legs syndrome: a post-hoc analysis of patients taking 1–3 mg/24 h for up to 5 years. Expert Opin Pharmacother. 2013;14:15–25.
14. Trenkwalder C, Benes H, Grote L, Garcia-Borreguero D, Hogl B, Hopp M, et al. Prolonged release oxycodone-naloxone for treatment of severe restless legs syndrome after failure of previous treatment: a double-blind, randomised, placebo-controlled trial with an open-label extension. Lancet Neurol. 2013;12:1141–50.
15. Garcia-Borreguero D, Allen RP, Benes H, Earley C, Happe S, Hogl B, et al. Augmentation as a treatment complication of restless legs syndrome: concept and management. Mov Disord. 2007;22:S476–84.
16. Walters AS. Opioids and restless legs syndrome. Lancet Neurol. 2013;12:1128–9.
17. Ondo WG. Methadone for refractory restless legs syndrome. Mov Disord. 2005;20:345–8.

Managing Concurrent Medications

15

Denise Sharon

One of the main strategies in the treatment of Restless Legs Syndrome/Willis Ekbom Disease (RLS/WED) is to avoid substances that may trigger or exacerbate its symptoms [1]. It implies the management of concurrent medications. Frequently, these patients have additional medical conditions that need occasional or continuous treatment. When treating concurrent disorders, it is important to consider drug interactions and the effect of these medications on RLS/WED symptoms.

Concurrent medications can be divided in two categories: medications prescribed for symptoms associated with RLS/WED and medications prescribed for other disorders that can trigger or worsen RLS/WED symptoms. Medications prescribed for symptoms associated with RLS/WED are described elsewhere in this book. This chapter will focus on concurrent medications that may trigger or worsen RLS/WED symptoms and on possible safer alternatives. Even though anecdotal reports abound, including in the social media, the availability of controlled data is too limited for evidence-based guidelines.

Several classes of over the counter and prescription medications have been noted to trigger or worsen RLS/WED symptoms. These include antihistamines, cold medications, antinausea preparations, analgesics, antidepressants, antipsychotics and other substances. A recent review of data from the end-stage renal disease registry showed that these medications were associated with increased odds of an RLS diagnosis [2]. The wide range of substances that can affect RLS/WED symptoms underscore the importance of alerting patients and their providers on the possible adverse effects of these compounds and of counseling on available alternatives.

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Antihistamines

Antihistamines reduce the neuronal excitation of histamine (H) receptors. In common language, antihistamines refer to pharmaceutical compounds that have an effect on the H1 receptor. Antihistamines can block H1 receptors (histamine antagonists, or compete with histamine by binding to the H1 receptor (histamine inverse agonists). All antihistamines are lipid soluble, thus potentially cross the blood–brain barrier and cause sedation and drowsiness. Second generation antihistamines are less soluble in lipid, consequently limiting their blood–brain barrier penetration and reducing sedative effects [3]. Among them, loratadine and fexofenadine were reported to be less sedating than acrivastine and cetirizine [4]. Used to treat allergic reactions, antihistamines are widely available as over the counter preparations.

The literature on the impact of antihistamines on RLS/WED is minimal, even though there is an abundance of anecdotal data. A small study [5] showed that when given diphenhydramine, an H1 inverse agonist, RLS patients experienced a three-fourfold worsening in their symptoms. The mechanism is not well understood. When the authors looked at autopsied brains from RLS patients, they found that the substantia nigra in five of the six brains examined, contained a higher number of histamine-3 receptors proteins. The H3 receptors act as autoreceptors that modulate and inhibit the synthesis and release of histamine and other neurotransmitters including dopamine. H2 receptor antagonists have also been reported to worsen RLS/WED symptoms [6], but no controlled data has been published so far. Even though there is no adequate evidence-based data, patients stories about symptom worsening following use of antihistamines seem to be common. Reports are found on different websites, some of which attempted to quantify the posts (Table 15.1). The advantage in using websites information is in the sheer number of reports. There are though, many limitations, such as the reports and posts are voluntary and require computer access and it is hard to determinate how many are self or lay people reports and how many are provider or pharmacist reports, making the accuracy of the diagnosis, or worsening of the RLS/WED questionable, just to name a few.

Frequently Mentioned Antihistamines (H1 Antagonists)

Diphenhydramine HCl (Benadryl®, Sominex®, Banophen®, Diphenhist®, Wal-Dryl®, Hydramine®, Dicopanol®, Silphe®) is one of the most commonly used over the counter products to self-medicate or treat allergic reactions and insomnia.

Combinations of an antihistamine and a decongestant, such as Actifed, Genac, Aprodine, Wal-Act, etc., of which the original combination included triprolidine hydrochloride 2.5 mg, and pseudoephedrine hydrochloride 60 mg. The current combination used in the US includes chlorpheniramine maleate 4 mg and

Table 15.1 Web reports of RLS with antihistamines and cold medications

Compound name	EHealthMe			Treato			DrugCite		MedsFacts			Drug informer		
	#SE	#RLS	%RLS	#Posts	#RLS	%RLS	#RLS/r-less	%RLS	#SE	#RLS	%RLS	#Posts	#RLS	%RLS
Diphenhydramine	24,543	73	0.3	269,440	2188	0.81	70	0.02					62 2:1f	24 50–69y
Chlorpheniramine	523	1	0.19											
Ephenedrine				110,245	18	0.02	11f 60+	0.15						
Pseudoephedrine HCL	519	10	1.93	50.528	16 crawl	0.31	11 60+	0.15						
Cheratussin				33,786	12	0.04								
Phenylephrine									577	1	0.17			
Fexofenadine	21,467	90	0.42										47	0.1
Loratadine	8773	28	0.32									81,286	47	0.57
Desloratadine	1838	1	0.05											
Cetirizine	25,806	80	0.31											

SE Side effects
RLS Restless legs syndrome

phenylephrine HCl 10 mg). Chlorpheniramine or chlorphenamine is a H1 receptor antagonist and a serotonin-norepinephrine reuptake inhibitor with weak sedative effects. It is used for the treatment of colds and allergy symptoms.

Second Generation H1 Antagonists

Second generation H1 antagonists typically have less blood–brain barrier permeability and therefore have less central nervous system (CNS) effects. In the absence of controlled data and based on the clinical experience it is generally assumed that as a group, second generation H1 antagonists have less effect on RLS/WED symptoms. The websites reports only partially corroborate this assumption.

Fexofenadine Hydrochloride 180 (Allegra, Fexidine, Telfast, Fastofen, Tilfur, Vifas, Telfexo, Allerfexo) is a second generation peripheral H1 antagonist, used for the treatment of allergies and urticaria.

Loratadine (Claritin/Alavert) used for the relief of allergies is a second generation peripheral inverse H1 agonist with a structure related to tricyclic antidepressants. Claritin-D or Clarinase combines loratadine with pseudoephedrine thus potentially worsening RLS/WED symptoms.

Desloratadine (NeoClarityn, Claramax, Clarinex, Larinex, Aerius, Dazit, Azomyr, Deselex, Delot) is the major active metabolite of loratadine and is used to treat allergies. It is a tricyclic antihistamine with selective and peripheral H1 antagonist action with limited blood–brain barrier permeability and no anticholinergic properties.

Cetirizine (Zyrtec, Reactine, CTZ, Benadryl Once a Day) is a selective H1 receptor inverse agonist with limited ability to cross the blood–brain barrier. It is used for the treatment of allergies, hay fever, angioedema and urticaria.

Over-the-Counter Cold Medications

Ephedrine is a sympathomimetic amine that stimulates the adrenergic receptor system, increasing the release of norepinephrine at the postsynaptic alpha and beta receptors. It crosses the blood–brain barrier and releases noradrenaline and dopamine in the substantia nigra, causing vasoconstriction. It is used as a decongestant, antiasthmatic, stimulant, and increases blood pressure.

Pseudoephedrine HCl (Sudafed), an isomer of ephedrine is a sympathomimetic amine that activates postsynaptic adrenergic receptors by the release of norepinephrine. It causes less vasoconstriction and has no significant effect on the blood pressure. It is used as a decongestant, cough suppressant, and stimulant.

Cheratussin DAC (Robitussin) contains 10 mg of codeine, 100 mg of guaifenesin, and 30 mg of pseudoephedrine per 5 ml.

Phenylephrine (Nostril, Carbinoxamine, Neo-Synephrine) is a selective alpha-1-adrenergic receptor agonist used as a decongestant or vasopressor, commonly used in anesthesia and critical care practices. It is likely to cause side effects, such as hypertension, CNS stimulation, insomnia, anxiety, irritability, and restlessness.

Compounds Used During Surgery: Antiemetics and Analgesics

Surgery, critical care, and acute hospitalizations can trigger or worsen symptoms of RLS/WED [7]. Contributing factors include: irregularity or discontinuation of home medications, including oral preparations, increased bed rest, blood loss, and use of antiemetic and anesthesia preparations. In a prospective study transient RLS occurred in 8.7% of patients undergoing spinal anesthesia [8]. Acute exacerbation of symptoms in RLS patients during perioperative procedures was noted [9, 10] and two cases of "anesthesia related periodic limb movements" were reported [11, 12].

Antinausea preparations that can block the dopamine receptors and can worsen RLS/WED symptoms include the following:

Promethazine (Phenergan, Promethegan, Romergan, Prothiazine, Sominex) is a phenothiazine derivative, a strong H1 antagonist and a moderate anticholinergic, serotonergic, and dopaminergic antagonist.

Dimenhydrinate (Dramamine) combines diphenhydramine and chlorotheophylline. It is used to prevent nausea and motion sickness and is available over the counter.

Meclozine or meclizine (Antivert, Bonine, Dramamine II) is a piperazine derivative, a H1 antagonist, mildly anticholinergic, and a CNS depressant. It is used to treat motion sickness and vertigo.

Metoclopramide (Reglan) is a dopamine D2 receptor antagonist and a 5-HT4-receptor antagonist. It is an antiemetic and a gastrokinetic. Metoclopramide is used frequently to treat gastrointestinal motility disturbances in patients with systemic sclerosis. In a study on 27 patients with systemic sclerosis, those treated with metoclopramide had a 3:1 RLS ratio [13]. However, RLS symptoms could not be provoked by an infusion of metoclopramide in eight drug-naïve RLS patients [14]. The ability of metoclopramide to reverse the effects of apomorphine was tested in nine patients with RLS. Compared to apomorphine alone, metoclopramide with apomorphine seem to increase symptoms of RLS on the visual analog scale (the results did not reach significance) and showed a trend for reappearance of periodic limb movements of wakefulness (PLMW) [15].

Prochlorperazine (Compazine, Stemzine, Buccastem, Stemetil, Phenotil) is a dopamine (D2) receptor antagonist phenothiazine. It is commonly used as an antiemetic and analgesic and is a potent antipsychotic. It was reported to cause akathisia [16] tardive dyskinesia and can cause neuroleptic malignant syndrome.

Domperidone (Motilium, Motillium, Motinorm Costi, Nomit, Escacid, Dompan, Domstal, Abdopen, Ridon, Dotitone) is a peripheral dopamine (D2 and D3) receptor antagonist that does not cross the blood–brain barrier. It is an antiemetic, a gastrokinetic and promotes lactation. It is not FDA approved in the US. It was used to oppose the prolactin reducing effects of pergolide [17], bromocriptine and cabergoline. Domperidone was used to support the role of dopaminergic neurons outside the blood–brain barrier to better understand RLS pathophysiology. The prevalence of RLS is more than doubled (48% vs. 21%) in Parkinson's disease (PD) patients treated with domperidone [18]. Chang et al. [19] reported one case of RLS-induced by mirtazapine when added to domperidone.

Antinausea preparations that block serotonin receptors are less probable to affect RLS/WED symptoms.

Odansetron (Zofran, Ondanzetron, Anset, Zuplenz, Ondisolv, Emeset, Emetron, Emodan, Ondemet, Setronax) is a serotonin 5-HT3 receptor antagonist used to treat nausea and vomiting with possible use in irritable bowel syndrome (IBS), substance use, and Parkinson's disease psychosis.

Analgesics reported to affect RLS symptoms include:

Tramadol (Ultram, Ralivia, Tramal) is a synthetic opioid analgesic, a weak mu-opioid receptor agonist, a serotonin agonist, and a norepinephrine reuptake inhibitor. It is used to treat pain. It is not clear how tramadol impacts RLS/WED. Several studies reported that it relieved RLS symptoms. By itself or as an adjuvant, it has been used in the treatment of RLS [20], RLS with chorea [21] and in RLS with persistent genital arousal coined restless genital syndrome (RGS) by the authors [22]. RLS was also noted to be part of Tramadol abstinence symptoms [23, 24]. Several studies, though suggested that tramadol can worsen symptoms of RLS/WED. One study reported on tramadol associated augmentation of RLS symptoms and return to pretreatment severity when tramadol was discontinued [25]. Tramadol associated RLS augmentation that subsided after switch to niaprazine was reported in an 86-year-old woman after long-term treatment [26]. Indeed, social media reports show that approximately half of the posts on RLS as side effects are 2–5 years after starting tramadol and mostly in females aged 60 and older. Another study noted that tramadol enhanced the risk of mirtazapine associated RLS [27].

A study that proposed non-opioid analgesics as a risk factor for RLS in patients on antidepressants [28] was deemed as flawed due to selection bias, misclassification of disease and drug exposures [29]. The study's attempt to assess the association between regular analgesic use and RLS is still worth evaluating.

Anticonvulsants and CNS Depressants

Anticonvulsants have been used in the treatment of RLS as described elsewhere in this book. Few case reports document *zonisamide, mesuximide, and phenytoin*-induced restless legs symptoms that subsided with decreasing the dose or a change in medication [30, 31].

Gamma hydroxybutyric acid (Sodium Oxybate, Xyrem) binds to excitatory GHB receptors and to inhibitory GABA-B receptor while reducing dopamine release and is used in the treatment of narcolepsy. A case report described a severe occurrence of de novo RLS symptoms that reversed after withdrawal [32].

Zolpidem (Ambien, Ambien CR, Intermezzo, Stillnox, Sublinox) is a short acting imidazopyridine gabaergic hypnotic used for the treatment of insomnia. Reported zolpidem induced parasomnias included sleep-walking and sleep eating. Nocturnal eating has been frequently reported in RLS patients [33] and noted in the case of an RLS patient treated with Zolpidem [34].

Antidepressants

Depressive symptoms are common in RLS/WED [35]. Frequently, the patients receive antidepressant treatment even before they receive treatment for RLS. Comorbidity between depressive disorders and RLS is common. However, the effect of antidepressants on RLS/WED symptoms is not clear. A prospective multi-center study involving different antidepressants resulted in 9% of the patients having RLS as a side effect [36]. Conversely, a chart review on 200 patients treated with a variety of antidepressants found no correlation between RLS and any of the antidepressant classes [37]. In another study 243 patients were interviewed before and after 6 months of treatment. The results indicated that antidepressant medications (tricyclic antidepressants and selective serotonin reuptake inhibitors) had no effect on the development of RLS symptoms [28]. However, when variables such as caffeine drinking and treatment with non-opioid analgesics were added, the patients who drank 5 or more cups of coffee a day and were on non-opioid analgesics did have an increase rate of RLS symptoms. A handful of studies suggest that antidepressants may affect RLS patients variably and the difference could be gender dependent [38, 39].

Even though the data on RLS is inconclusive at best, the data on periodic limb movements of sleep (PLMS) points toward a more definite effect. Several studies reported the occurrence of antidepressant dependent myoclonus [40–42].

Antidepressants can be divided into several groups that include tricyclic antidepressants, tetracyclic antidepressants, serotonin reuptake inhibitors, serotonin-norepinephrine reuptake inhibitors, monoamine oxydase inhibitors, and others.

Tricyclic Antidepressants (TCA) are compounds with a typical three rings of atoms structure that increase the availability of serotonin and norepinephrine by inhibiting their uptake and may have minimal dopamine affinity. RLS/WED patients are frequently cautioned against the use of TCA, but the evidence-backed data relates to PLMS. The development of clinically significant myoclonus was reported in almost 10% (9 of 98) of patients receiving different TCA's. Almost a third of the patients developed clinically insignificant myoclonus. The myoclonus persisted when the medications were not changed, but was reversed when TCA's were discontinued [42].

Amitriptyline (Elavil, Endep, Tryptomer, Tryptizol, Laroxyl, Saroten, Sarotex, Lentizol) is a tricyclic antidepressant (TCA) that acts as a serotonin-norepinephrine reuptake inhibitor (SNRI), but does not affect dopamine reuptake. Amitriptyline was associated with RLS in men, but not in women [38]. It also increased PLMS when given to healthy males [39] However, another study found no increase in RLS symptoms with amitriptyline [28].

Nortrityline HCl (Pamelor, Aventyl, Sensoval, Norpress, Allegron, Noritrn, Nortrilen) is a TCA, the active metabolite of amitriptyline with adrenergic, anticholinergic, and antihistamine properties. There is one case reported on myoclonus induced by nortriptyline [43].

Imipramine HCl (Tofranil, Melipramine) is a TCA, a strong serotonin and norepinephrine reuptake inhibitor with dopaminergic and anticholinergic properties and a H1 antagonist. At therapeutic doses, there was one report of severe imipramine-induced myoclonus [44].

Desipramine (Norpramine, Pertofane) is a TCA that inhibits the reuptake of norepinephrine and to a lesser degree, serotonin. There is one case reported on desipramine-induced jaw myoclonus [45].

Clomipramine (Anafranil) is a potent serotonin and norepinephrine reuptake inhibitor. It is used to treat depression and obsessive-compulsive disorder (OCD). Increased PLMS was noted in two out of 21 patients with narcolepsy who were treated with clomipramine [46]. In another study, myoclonic movements have been observed in depressed patients receiving therapeutic doses of clomipramine [47].

Trimipramine (Surmontil, Rhotrimine, Stangyl) is a TCA, a weak norepinephrine, serotonin, and dopamine reuptake inhibitor and a strong histamine H1, serotonin 5-HT2, acetylcholine, and alpha1-adrenergic receptor antagonist; also a weak to moderate serotonin 5-HT1, alpha2 adrenergic and dopamine2 receptor agonist. It is used for its antidepressant, anxiolytic, antipsychotic, sedative, and analgesic effects. Patients who had PLMS before being treated with either imipramine or trimipramine had increased periodic limb movements index (PLMI) [48].

Tetracyclic antidepressants (TeCA) are compounds with a typical four rings of atoms structure, otherwise closely related to TCA in their different affinity for the serotonin, norepinephrine and dopamine binding sites.

Maprotiline (Ludiomil, Deprilept, Psymion) is a TeCA, a strong norepinephrine reuptake inhibitor with weak serotonin and dopamine effects. It is used as antidepressant, anxiolytic, and sedative. Maprotiline was reported to induce myoclonus [49, 50].

Mianserin (Bolvidon, Depnon, Norval, Tolvon, Lerivon) is a TeCA, a norepinephrine reuptake inhibitor with serotonergic and antihistamine properties. It is used as an antidepressant, anxiolytic, hypnotic, antiemetic, antihistamine, and as an appetite stimulator. Mianserin-induced RLS was reported in two small case series [51, 52].

Mirtazapine (Remeron) is a TeCA with serotonergic and noradrenergic properties, is an antagonist or inverse agonist of the serotonin, adrenaline, dopamine, histamine, and acetylcholine receptors and is used as antidepressant, anxiolytic, hypnotic, antiemetic, and appetite stimulant. Mirtazapine has been consistently

reported to provoke or deteriorate RLS in peer-reviewed data and on social websites. In a study looking at the effects of antidepressant medications, mirtazapine was recorded as provoking or deteriorating RLS symptoms in 28% of the patients, while other antidepressants affected only 5–10% of the patients [36]. Several studies and case reports noted mirtazapine-induced RLS symptoms [53–57] and some noted a worsening in RLS symptoms following treatment with mirtazapine [58, 59]. The mirtazapine-related RLS effects were improved or completely resolved with the discontinuation of mirtazapine, with a switch to a different antidepressant, such as bupropion, which seems to be "RLS protective" and with the addition of a dopaminergic in one study. In a well-controlled study, de novo mirtazapine at 30 mg (double the regular starting dose) was shown to result in increased PLMS in eight out of 12 young, healthy men. The distribution of the PLMS was similar to the distribution in RLS patients, but only three of the eight subjects reported any RLS-related symptoms. The presence of PLMS was attenuated on the second night and thereafter, suggesting rapid tolerance [60].

Monoamine Oxydase Inhibitors

Monoamine oxydase inhibitors (MAOI) are preventing the breakdown of monoamine transmitters, increasing the availability of serotonin, melatonin, norepinephrine, and dopamine and are used for depression, panic disorder, posttraumatic stress disorder (PTSD), borderline personality disorder, and Parkinson's disease.

Phenelzine (Nardil, Nardelzine) is a nonselective, irreversible MAOI affecting the breakdown of serotonin, melatonin, norepinephrine, and dopamine, and used as an antidepressant and anxiolytic. Several case reports noted phenelzine induced, sleep-associated limb movements that improved or resolved with reduction or cessation of treatment [61–63]. In a report of two cases, the limb movements started 6 weeks after treatment initiation [64].

Selegeline (Anipryl, L-deprenyl, Eldepryl, Emsam, Zelapar) is a selective irreversible MAO-B inhibitor used for PD, depression, and senile dementia. Selegeline is reported to decrease periodic limb movements in sleep [65]. The authors reviewed pre and posttreatment polysomnograms on 31 patients receiving selegiline for PLMS and reported a significant decrease in PLMI with no evidence of alerting effect on sleep efficiency or sleep onset latency.

Selective Serotonin Reuptake Inhibitors

Selective Serotonin Reuptake Inhibitors (SSRI's) are compounds that inhibit the reuptake of serotonin, thus increasing the level of serotonin in the synaptic cleft, while having limited affinity for other receptors. SSRI's are used to treat depression, anxiety, and personality disorders. They have slow onset of action and some of the side effects can take weeks to manifest. The SSRI's have been associated with the

serotonin syndrome, a life threatening drug reaction characterized by changes in mental status, hypertension, restlessness, myoclonus, hyperreflexia, diaphoresis, shivering, and tremor [66]. In addition, tremors, akathisia, and paresthesia are common side effects and it is important to differentiate these from RLS symptoms with or without PLM's. One study reported that SSRI's might have different effects on RLS symptoms [67]. In that report on 66 patients treated with SSRI, 43 patients who had a prior RLS history, claimed their RLS symptoms resolved, improved, or not changed, while among the 23 patients with no prior RLS history, two developed RLS. On social websites, only 0.3–0.4% report RLS symptoms as part of the side effects while on various SSRI's. However, these symptoms tend to appear in the first 6 months and up to 10 years after treatment initiation, are more frequent in the 50 year and older group, tend to be within the severe range and tend to persist.

Fluoxetine (Depex, Prozac, Fontex, Seromex, Seronil, Sarfem, Ladose, Motivest, Flutop, Fluctin, Fluox, Depress, Lovan, Prodep) is one of the first SSRI's to be approved for the treatment of major depression and remains a popular option. It can also increase plasma levels and half-life of antipsychotics, such as perphenazine. One case report noted fluoxetine-related RLS that was relieved 6 weeks after the drug was discontinued [68]. In a case series clinically significant periodic limb movement disorder (PLMD) was noted in four out of nine patients treated with fluoxetine [69]. In one case report, severe myoclonus developed 1-year after the initiation of treatment with fluoxetine and resolved with drug discontinuation [70]. In another case, myoclonus secondary to the use of trazodone and fluoxetine resolved when both medications were discontinued [71].

Paroxetine (Paxil, Aropax, Pexeva, Seroxat, Sereupin, Brisdelle) is one of the most potent and most selective SSRI used to treat depression, panic attacks, anxiety disorders, PTSD, and OCD. In one case report, RLS symptoms worsened by paroxetine [72] and in another were induced by it [73].

Sertraline (Zoloft, Lustral) is a SSRI and a dopamine reuptake inhibitor used for depression, OCD, panic attacks, and social anxiety disorders. Severe sleep-related movement disorder induced by sertraline was reported [74]. PLM and arousal indices seem to increase with sertraline, an increase that is dose dependent, but not associated with clinical symptoms [75]. One case reported on RLS worsened by sertraline [76]. In another case myoclonus developed 6 years after treatment with sertraline and methylphenidate and did not resolve by discontinuing sertraline [77].

Citalopram (Celexa, Cipramil) is a SSRI with minimal effect on norepinephrine or dopamine uptake and used to treat depression. One case reported on RLS being severely worsened by citalopram and relieved by bupropion [78].

Escitalopram (Lexapro, Cipralex, Citalin, Esitalo, Esto, Lexamil, Selectra, Sipralexa) is a highly selective SSRI used for the treatment of depression and anxiety disorder. One case report noted severe escitalopram-induced RLS that was relieved with discontinuation of the drug [79].

Serotonin-norepinephrine reuptake inhibitors (SNRI) are compounds that inhibit both the uptake of serotonin and to a significantly lesser degree of norepinephrine in the synaptic cleft and therefore are used for the treatment of depressive disorders, anxiety disorders, OCD, attention deficit hyperactive disorder (ADHD),

fibromyalgia, and pain disorders. With the exception of venlafaxine and duloxetine, that are more frequently reported, 0.5 and 0.7%, respectively, the profile of SNRI's-related RLS posting on the social websites is similar to that of SSRI's.

Duloxetine (Cymbalta) is a serotonin-norepinephrine reuptake inhibitor (SNRI) used for the treatment of depression and anxiety disorder as well as pain-associated disorders, such as osteoarthritis, neuropathies, and fibromyalgia. A review of patients treated with duloxetine among other second generation antidepressants in four neurology clinics showed increased reports of RLS symptoms as side effects [33].

Venlafaxine (Effexor) is a serotonin-norepinephrine-dopamine reuptake inhibitor (SNDRI) that interacts with opioid receptors and with alpha2 adrenergic receptors and is used for the treatment of depressive and anxiety disorders, but it can induce mania and psychosis. It is also used for the treatment of cataplexy in narcolepsy patients.

Assessment of PLMS among 274 patients on antidepressants and 69 controls showed that patients on venlafaxine and on SSRI had significantly higher mean PLMI than control or bupropion groups [80]. De novo development of PLMS occurred in six out of eight volunteers on venflaxine [81]. In a case report, venaflaxine-induced RLS symptoms in a 44-year-old woman and the symptoms resolved after drug discontinuation [82].

Lithium (Eskalith, Lithobid, Cibralith, Lithane, Lithium Citrate) is a chemical element belonging to the alkali metal group. In a salt form it is used as a mood stabilizer by increasing serotonin, inhibition of inositol monophosphatase and interaction with nitric oxide and glutamate. Several case reports and a case series addressed the provocation or worsening of leg movements with or without RLS by lithium. In a case report of RLS induced by lithium, symptoms persisted even when lithium was discontinued [83]. However, in another case report, aggravated nocturnal myoclonus and RLS subsided when lithium was withdrawn [84]. A five case series and a case report noted the disappearance of lithium-induced nocturnal myoclonus with discontinuation of therapy [85] only to reoccur when lithium was reinstated [84].

Atypical Antidepressants

Bupropion (Welbutrin, Budeprion, Prexaton, Elontril, Aplenzin, Zyban, Voxra) is an atypical antidepressant, dopamine, and norepinephrine reuptake inhibitor used in the treatment of depression and smoke cessation with possible effect on neuropathic pain. A double-blinded randomized controlled trial examined the effect of bupropion on RLS symptoms in 60 patients [86]. The results showed a decrease in the International Restless Legs Syndrome Study Group severity scale (IRLS Rating Scale) with bupropion that was significant at 3 weeks after treatment, but not at 6 weeks. A small case series showed that bupropion improved RLS symptoms in three depressed patients [87] A case report noted quick (3 days) resolution of RLS symptoms in a 45-year-old female presenting with chronic insomnia [88]. In a case

series, bupropion SR treatment was associated with a reduction in measures of PLMD and an improvement in depression [89].

Trazodone (Desyrel, Oleptro, Beneficat, Deprax, Desirel, Molipaxin, Thombran, Trazorel, Trialodine, Trittico, Mesyrel) is an antidepressant, serotonin antagonist and reuptake inhibitor with anxiolytic and sedative effects. Trazodone was shown to improve polysomnographic parameters of sleep in patients with depression and increased PLMI [90].

Antipsychotics

Antipsychotics or neuroleptics are compounds that are mainly dopamine antagonists, and are used for the treatment of psychosis in schizophrenia and bipolar disorders. The psychotropic effect is directly correlated with the affinity for the D2 receptor raising the question of psychotropic-induced RLS [91–94] and PLMS [95–97]. One of the most common side effects, akathisia could mimic RLS with leg movements during sleep [98–100]. This makes it more difficult to differentiate the leg movements, as in a case report of neuroleptic-induced unilateral akathisia with contralateral PLM [101]. It is also possible that RLS patients might have an increased risk of developing akathisia, as in the case of severe headache patients treated with dopamine receptor blocking agents [102]. Other common side effects include extrapyramidal effects on motor control that, in addition to akathisia, manifest by tremor, restlessness, and tardive dyskinesia. The severity of the side effects can affect compliance with these medications.

Typical Antipsychotics

The first generation of compounds is referred as typical antipsychotics. These include butyrophenones, phenothiazines, and thioxantenes. The first generation affects mainly the dopamine system and therefore, can trigger and worsen RLS symptoms [103]. An interesting scenario is then posed when D2 dopamine agonists, such as pramipexole are used to counter the side effects of antipsychotics D2 antagonists. One case report of an acute manic episode developed after taking pramipexole in combination with olanzapine [104] reflects this conundrum. To complicate it even more, these RLS symptoms are not always relieved by dopaminergics, implying additional causative mechanisms.

Haloperidol (Haldol, Serenace, Aloperidin, Bioperidolo, Brotopon, Dozic, Duraperidol, Halostene, Halosten, Linton, etc.*)* is a butyrophenone derivative with dopamine inverse agonist properties used in the treatment of schizophrenia, acute psychotic states, and delirium. Depot and long acting forms are used as an injection given every two–four weeks to control schizophrenia. It has a very rapid onset of action, mainly as an intravenous injection making it one of the most commonly used drugs in conditions such as acute states of psychosis, delirium, aggressive

hyperactivity, severe agitation, alcohol, and opioid withdrawal and postoperatively. A case report notes haloperidol-related RLS and nocturnal eating and drinking in a schizophrenic patient [105].

Droperidol (Inapsine, Droleptan, Dridol, Xomolix, Innovar) is a butyrophenone derivative, a potent dopamine D2 antagonist with some histamine and serotonin antagonist activity, with antiemetic and antinausea properties. It is used as an antipsychotic and to prevent postoperative nausea. Droperidol was reported to cause severe restlessness in a RLS patient [106]. Others also noted severe restlessness similar to akathisia [107, 108] that was interpreted as a possible exacerbation of restless legs symptoms [109].

Chlorpromazine (Thorazine, Largactil, Megaphen) is the first phenothiazine developed to treat schizophrenia. It acts as a postsynaptic dopamine antagonist, thus initially increasing dopamine release before the drop in dopamine production. In one early report, it was recommended for the treatment of RLS before worsening was noted. [110].

Prometazine (Phenergan, Promethegan, Romergan, Fargan, Prothiazine, Avomine, Atosil, Receptozine, Lergigan, Sominex) is a phenothiazine with strong antihistamine effects, acting primarily on the H1 receptor, a moderate anticholinergic with weak to moderate affinity for serotonin, dopamine, and alpha1 adrenergic receptors. It is used as an antiallergic and in anaphylactoid conditions, as a sedative and peri-operatively for sedation and nausea, as a motion or morning sickness remedy, as a weak antipsychotic and for migraines. Promethazine was reported to trigger RLS [111].

Perphenazine (Trilafon, Decentan, Etrafon/Triavil) is a piperazinyl phenothiazine, medium potency antipsychotic with sedating properties used to treat psychosis and agitated depression and for the treatment of nausea and vertigo. In an attempt to assess the prevalence of RLS in patients taking neuroleptic drugs, among 100 patients interviewed, one (1%) patient showed symptoms 4 years after starting perphenazine and the symptoms decreased in severity and frequency after drug discontinuation [112].

Atypical Antipsychotics

Atypical antipsychotics or second generation antipsychotics were designed to provide greater efficacy with less side effects, but this challenge was not met according to the research data. Commonly, they restructure the neuronal networks and act on the dopamine system, but they differ in their binding profile.

Clozapine is an atypical antipsychotic that binds to serotonin and dopamine receptors and is used for treatment resistant schizophrenia. One case report described clozapine-associated RLS [113].

Olanzapine (*Zyprexa, or Symbyax*, which combines it with fluoxetine) has a higher affinity for serotonin receptors and for muscarinic receptors. Several case series and case reports note that olanzapine triggers RLS symptoms that resolve with drug discontinuation [114–119].

Risperidone (Risperdal) is an atypical antipsychotic, dopamine D2 antagonist, and serotonin 5HT2 antagonist with antiadrenergic and anti-histaminergic properties. A case report described RLS symptoms during treatment with risperidone, relieved with quetiapine [120].

Aripiprazole (Abilify, Aripiprex) is a partial dopamine agonist with serotonergic and adrenergic properties used in the treatment of schizophrenia, bipolar disorder, and autism.

In one case report it improved venlafaxine-related RLS symptoms when added to clonazepam [121]. Its sublingual form, asenapine was reported to precipitate RLS [122].

Quetiapine (Seroquel, Xeroquel, Ketipinor) is a short acting atypical antipsychotic, a dopamine, serotonin, and norepinephrine antagonist with potent antihistamine and weak anticholinergic properties. It s used to treat schizophrenia and bipolar and depressive disorders. In a case series of seven affective disorders patients quetiapine dose-dependent RLS was described [123]. Several case reports detailed the quetiapine-induced RLS [124–126].

Hormones

Levothyroxine (L-thyroxine, T4, Synthroid, Eutirox, Levoxyl,Tirosin, Thyrax, Letrox, Levaxin, Thyrin) is a synthetic form of the thyroid hormone thyroxine used to treat thyroid hormone deficiency. Based on charts review Brown et al. [37] found a positive correlation between RLS and treatment for hypothyroidism. In a case report levothyroxine-related RLS is described in a hypothyroid and low serum ferritin patient, improved after the hormone was discontinued [127].

Estrogen: the correlation between hormone replacement therapy and increased levels of estrogen with RLS symptoms is controversial. The correlation is corroborated by several studies [34, 128] and contradicted by others [129, 130].

Cardiovascular Preparations

Calcium Channel Blockers such as Diltiazem

These are chemicals that disrupt the movement of calcium through calcium channels and are used in the treatment of hypertension, angina pectoris and supraventricular tachycardias. There are two classes of calcium channel blockers: the dihydropyridines and the nondihydropyridines. Diltiazem is a calcium channel blocker in the nondihydropyridine group. A couple of case reports described diltiazem induced myoclonus [131] In one case report, the myoclonus was noted after 3 years of diltiazem treatment and improved but was not completely resolved with drug discontinuation [132].

Angiotensin-Converting Enzyme (ACE) Inhibitors such as Captopril and Enalapril

ACE inhibitors inhibit angiotensin-converting enzyme and lower blood pressure by decreasing the blood vessels tension. A case report noted ACE inhibitors-induced myoclonus [133].

Beta-Blockers affect the sympathetic nervous system by targeting the beta adrenergic receptors and are used in the treatment of cardiac arrhythmias, angina pectoris, high blood pressure, and in migraine prophylaxis. One author described beta-blockers precipitating RLS [134] but others reported them to be effective in the treatment of RLS [135–137]. However, beta-blockers might induce insomnia regardless of RLS.

Clonidine (Catapres, Kapvay, Nexiclon) is a sympatholytic alpha2 adrenergic agonist and imidazoline receptor agonist used to treat high blood pressure, neuropatic pain, opioid detoxification, sleep hyperhidrosis, insomnia, and menopausal symptoms. It carries an "option" level of recommendation from the American Academy of Sleep Medicine as treatment for RLS.

Aliskiren (Tekturma, Rasilez) is a direct renin inhibitor used in the treatment of hypertension. There are no reports on the effect of aliskiren on RLS. However due to parallel mechanism of action with calcium channel blockers it is possible that renin inhibitors will have a similar effect.

Summary

Summarizing clinical experience, limited peer-reviewed data [138, 139] and questionable social website information, several suggestions might be considered when managing the concurrent medications in the RLS patient including:

1. Consider the patient, the current medications, and their side effects profile:
    a. If symptoms are in control, monitor.
    b. If change is needed, review previous effects.
2. Choose a second generation antihistamine over a first generation antihistamine.
3. Avoid ephedrine and phenylephrine products.
4. Choose a serotonin antagonist antinausea medication, such as ondansetron over a dopamine antagonist such as metoclopramide.
5. Choose an anticonvulsant with an already documented ability to control RLS symptoms as described in the RLS treatment chapter.
6. For an antidepressant bupropion or trazodone are preferred to MAOI's, SSRI's, SNRI's, TCA's, and TeCA's. Consider also within the group different profiles.

7. As antipsychotic prescribe one of the second generation compounds rather than the first generation with specific consideration to different profiles within group.
8. As for cardiovascular preparations, the availability of different products even within the same class surpasses by far the limited data we have on their effect on WED. Once side effects are encountered old medications such as clonidine or new ones such as direct rennin inhibitors (aliskiren) might be considered in consultation with a cardiologist.

Notes: Please note that all the websites' analyses are based on the voluntary, self or provider reported data. The data might be uneven in the assessment of RLS. Also different websites present data in different ways.

EHealthMe is a medical analysis website that compiles data from FDA and social media reports and presents data on the total number of side effects reported on a specific compound, the number of RLS symptoms reported as a side effect and the percentage of RLS symptoms reported.

Treato is a medical analysis website that identifies, analyzes, and aggregates medical user generated content across the intrenet and presents data on the total number of posts on a specific compound, the number of posts of RLS symptoms as a side effect associated with the compound and the percentage of RLS side effect.

DrugCite is a medical informatics and drug safety company that compiles data from the Adverse Events Reporting System (AERS) also known as the Food and Drug Administration Adverse Events Reporting System (FAERS) used by healthcare providers and consumers to report to the FDA. It presents the number of RLS reported and the percentage while taking a specific compound. It can add data on gender and age such as in the ephedrine and pseudoephedrine case, where RLS was reported by 11 women over the age of 60. It is possible that the data on ephedrine and pseudoephedrine was based on the same reports.

Medfacts is an interactive website that promotes itself as a provider of "health information for everybody." It compiles information from FDA, social media and website users and presents data of medication users that developed RLS, why the medication was prescribed and the physician opinion on the causality of RLS as related to the medication.

Drug Informer is a website that informs about drugs and allows individuals to discuss personal experiences with drug reports. It compiles data from FDA reports and from social media reports and presents it separately. It also presents data on gender and age groups. For example: diphenydramine-related RLS was reported by 24 patients age 50–69 years, out of a total of 62 patients, of which 2/3 were females.

References

1. Silber MH, Ehrenberg BL, Allen RP, Buchfuhrer MJ, Earley CJ, Hening WA, Rye DB, Medical Advisory Board of the Restless Legs Syndrome Foundation. An algorithm for the management of restless legs syndrome. Mayo Clin Proc. 2004;79(7):916–22.
2. Bliwise DL, Zhang RH, Kutner NG. Medications aasociated with restless legs syndrome: a case-control study in the US renal data system (USRDS). Sleep Med. 2014;15(10):1241–5.
3. Yanai K, Ryu JH, Watanabe T, Iwata R, Ido T, Sawai Y, Ito K, Itoh M. Histamine H1 receptor occupancy in human brains after single oral doses of histamine H1 antagonists measured by positron emission tomography. Br J Pharmacol. 1995;116(1):1649–55.
4. Mann RD, Pearce GL, Dunn N, Shakir S. Sedation with "non-sedating" antihistamines: four prescription-event monitoring studies in general practice. BMJ. 2000;320(7243):1184–7.
5. Allen RP, Lesage S, Earley CJ. Anti-histamines and benzodiazepines exacerbate daytime restless legs syndrome symptoms [abstract]. Sleep. 2005;28:A279.
6. O'Sullivan RL, Greenberg DB. H2 antagonists, restless leg syndrome, and movement disorders. Psychosomatics. 1993;34(6):530–2.
7. Hogl B, Gschliesser V. Management of restless legs syndrome in the hospital and during surgery. In: Hening WA, Allen RP, Chokroverty S, Earley CJ, Saunders, editors Restless Legs Syndrome. 2009.
8. Högl B, Frauscher B, Seppi K, Ulmer H, Poewe W. Transient restless legs syndrome after spinal anesthesia: a prospective study. Neurology. 2002;59(11):1705–7.
9. Karroum EG, Raux M, Riou B, Arnulf I. Acute exacerbation of restless legs syndrome during perioperative procedures: case reports and suggested management. Ann Fr Anesth Reanim. 2010;29(12):920–4.
10. Shin YK. Restless leg syndrome: unusual cause of agitation under anesthesia. South Med J. 1987;80(2):278–9.
11. Watanabe S, Sakai K, Ono Y, Seino H, Naito H. Alternating periodic limb movement induced by spinal anesthesia in an elderly male. Anesth Analg. 1987;66(10):1031–2.
12. Watanabe S, Ono A, Naito H. Periodic leg movements during either epidural or spinal anesthesia in an elderly man without sleep-related (nocturnal) myoclonus. Sleep. 1990;13 (3):262–6.
13. Ostojic P, Jovic T, Stojic B. Restless legs syndrome in patients with systemic sclerosis: prevalence and possible causes. Z Rheumatol. 2013;72(6):590–3.
14. Winkelmann J, Schadrack J, Wetter TC, Zieglgänsberger W, Trenkwalder C. Opioid and dopamine antagonist drug challenges in untreated restless legs syndrome patients. Sleep Med. 2001;2(1):57–61.
15. Tribl GG, Sycha T, Kotzailias N, Zeitlhofer J, Auff E. Apomorphine in idiopathic restless legs syndrome: an exploratory study. J Neurol Neurosurg Psychiatry. 2005;76(2):181–5.
16. Drotts DL, Vinson DR. Prochlorperazine induces akathisia in emergency patients. Ann Emerg Med. 1999;34(4):469–75.
17. Winkelmann J, Wetter T, Stiasny K, Oertel W, Trenkwalder C. Treatment of restless legs syndrome with pergolide-an open clinical trial. Mov Disord. 1998;13(3):586–9.
18. Romenets S, Dauvilliers Y, Cochen De Cock V, Carlander B, Bayard S, Galatas C, Wolfson C. Restless legs syndrome outside the blood brain barrier; evidence from domperidone. Mov Disord Suppl. 2012;(27).
19. Chang CC, Shiah IS, Chang HA, Mao WC. Does domperidone potentiate mirtazapine-associated restless legs syndrome? Prog Neuropsychopharmacol Biol Psychiatry. 2006;30(2):316–8 (Epub 2005 Nov 23).
20. Lauerma H, Markkula J. Treatment of restless legs syndrome with tramadol: an open study. J Clin Psychiatry. 1999;60(4):241–4.
21. Shin YK, Hong SC, Ihn YK, Jeong JH, Han JH, Lee SP. A case of a patient with both chorea and restless legs syndrome. J Korean Med Sci. 2008;23(3):533–6.

22. Waldinger MD, Schweitzer DH. Persistent genital arousal disorder in 18 Dutch women: part II. A syndrome clustered with restless legs and overactive bladder. J Sex Med. 2009;6(2):482–97. doi:10.1111/j.1743-6109.2008.01114.x (Epub 2008 Dec 2).
23. Park YM, Park HK, Kim L, Lee HJ, Kang SG. Acute-withdrawal restless legs syndrome following abrupt cessation of short-term tramadol. Psychiatry Investig. 2014;11(2):204–6.
24. Freye E, Levy J. Acute abstinence syndrome following abrupt cessation of long-term use of tramadol (Ultram): a case study. Eur J Pain. 2000;4(3):307–11.
25. Earley CJ, Allen RP. Restless legs syndrome augmentation associated with tramadol. Sleep Med. 2006;7(7):592–3 (Epub 2006 Aug 22).
26. Vetrugno R, La Morgia C, D'Angelo R, Loi D, Provini F, Plazzi G, Montagna P. Augmentation of restless legs syndrome with long-term tramadol treatment. Mov Disord. 2007;22(3):424–7.
27. Kim SW, Shin IS, Kim JM, Park KH, Youn T, Yoon JS. Factors potentiating the risk of mirtazapine-associated restless legs syndrome. Hum Psychopharmacol 2008;23(7):615–20.
28. Leutgeb U, Martus P. Regular intake of non-opioid analgesics is associated with an increased risk of restless legs syndrome in patients maintained on antidepressants. Eur J Med Res. 2002;7(8):368–78.
29. Berger K. Non-opioid analgesics and the risk of restless leg syndrome-a spurious association? Sleep Med. 2003;4(4):351–2.
30. Chen JT, Garcia PA, Alldredge BK. Zonisamide-induced restless legs syndrome. Neurology. 2003;60(1):147.
31. Drake ME. Restless legs with antiepileptic drug therapy. Clin Neurol Neurosurg. 1988;90(2):151–4.
32. Abril B, Carlander B, Touchon J, Dauvilliers Y. Restless legs syndrome in narcolepsy: a side effect of sodium oxybate? Sleep Med. 2007;8(2):181–3 (Epub 2007 Feb 1).
33. Howell MJ, Schenck CH. Restless nocturnal eating: a common feature of Willis-Ekbom syndrome (RLS). J Clin Sleep Med. 2012;8(4):413–9.
34. Yun CH, Ji KH. Zolpidem-induced sleep-related eating disorder. J Neurol Sci. 2010;288(1–2):200–1.
35. Becker PM, Sharon D. Mood disorders in restless legs syndrome (Willis-Ekbom disease). J Clin Psychiatry. 2014;75(7):e679–94.
36. Rottach KG, Schaner BM, Kirch MH, Zivotofsky AZ, Teufel LM, Gallwitz T, Messer T. Restless legs syndrome as side effect of second generation antidepressants. J Psychiatr Res. 2008;43(1):70–5.
37. Brown LK, Dedrick DL, Doggett JW, Guido PS. Antidepressant medication use and restless legs syndrome in patients presenting with insomnia. Sleep Med. 2005;6(5):443–50.
38. Baughman KR, Bouguet CC, Ober SK. Gender differences in the association between antidepressant use and restless legs syndrome. Mov Disord. 2009;24(7):1054–9.
39. Goerke M, Rodenbeck A, Cohrs S, Kunz D. The influence of the tricyclic antidepressant amitriptyline on periodic limb movements during sleep. Pharmaco-psychiatry. 2013;46(3):108–13. doi:10.1055/s-0032-1331702 (Epub 2013 Jan 4).
40. Evidente VG, Caviness JN. Focal cortical transient preceding myoclonus during lithium and tricyclic antidepressant therapy. Neurology. 1999;52(1):211–3.
41. Husain MRG, Novak M, Jindal R, Shapiro CM. Periodic leg movements in patients on different antidepressant therapies. Sleep Res. 1997;26.
42. Garvey MJ, Tollefson GD. Occurrence of myoclonus in patients treated with cyclic antidepressants. Arch Gen Psychiatry. 1987;44(3):269–72.
43. Patterson JF. Myoclonus caused by a tricyclic antidepressant. South Med J. 1990;83(4):463–5.
44. Black KJ, Kilzieh N. Severe imipramine-induced myoclonus in a patient with psychotic bipolar depression, catatonia, and schizencephaly. Ann Clin Psychiatry. 1994;6(1):45–9.
45. Massand P. Desipramine-induced oral-pharyngeal disturbances: stuttering and jaw myoclonus. J Clin Psychopharmacol. 1992;12(6):444–5.

46. Guilleminault C, Raynal D, Takahashi S, Carskadon M, Dement W. Evaluation of short-term and long-term treatment of the narcolepsy syndrome with clomipramine hydrochloride. Acta Neurol Scand. 1976;54(1):71–87.
47. Casas M, Garcia-Ribera C, Alvarez E, Udina C, Queralto JM, Grau JM. Myoclonic movements as a side-effect of treatment with therapeutic doses of clomipramine. Int Clin Psychopharmacol. 1987;2(4):333–6.
48. Ware JC, Brown FW, Moorad J, Pittard JT, Murphy M, Franklin D. Nocturnal myoclonus and tricyclic antidepressants. Sleep Res. 1984;13:72.
49. Ketl P, DePaulo JR Jr. Maprotiline-induced myoclonus. J Clin Psychopharmacol. 1983;3 (4):264–5.
50. Cording-Tömmel C, von Zerssen D. Mianserin and maprotiline as compared to amitriptyline in severe endogenous depression. A new methodological approach to the clinical evaluation of the efficacy of antidepressants. Pharmacopsychiatria. 1982;15(6):197–204.
51. Paik IH, Lee C, Choi BM, Chae YL, Kim CE. Mianserin-induced restless legs syndrome. Br J Psychiatry. 1989;155:415–7.
52. Markkula J, Lauerma H. Mianserin and restless legs. Int Clin Psychopharmacol. 1997;12 (1):53–8.
53. Ağargün MY, Kara H, Ozbek H, Tombul T, Ozer OA. Restless legs syndrome induced by mirtazapine. J Clin Psychiatry. 2002;63(12):1179.
54. Bahk WM, Pae CU, Chae JH, Jun TY, Kim KS. Mirtazapine may have the propensity for developing a restless legs syndrome? A case report. Psychiatry Clin Neurosci. 2002;56 (2):209–10.
55. Bonin B, Vandel P, Kantelip JP. Mirtazapine and restless leg syndrome: a case report. Therapie. 2000;55(5):655–6.
56. Markkula J, Lauerma H. Mirtazapine-induced restless legs. Hum Psychopharm. 1997;12 (5):497–9.
57. Park YM, Lee HJ, Kang SG, Cho JH, Kim L. Resolution of pregabalin and mirtazapine associated restless legs syndrome by bupropion in a patient with major depressive disorder. Psychiatry Investig. 2009;6(4):313–5.
58. Chopra A, Pendergrass DS, Bostwick JM. Mirtazapine-induced worsening of restless legs syndrome (RLS) and ropinirole-induced psychosis: challenges in management of depression in RLS. Psychosomatics. 2011;52(1):92–4.
59. Teive HA, de Quadros A, Barros FC, Werneck LC. Worsening of autosomal dominant restless legs syndrome after use of mirtazapine: case report. Arq Neuropsiquiatr. 2002;60 (4):1025–9.
60. Fulda S, Kloiber S, Dose T, Lucae S, Holsboer F, Schaaf L, Hennings J. Mirtazapine provokes periodic leg movements during sleep in young healthy men. Sleep. 2013;36 (5):661–9.
61. Askenasy JJ, Yahr MD. Is monoamine oxidase inhibitor induced myoclonus serotoninergically mediated? J Neural Transm. 1988;72(1):67–76.
62. Levy AB, Bucher P, Votolato N. Myoclonus, hyperreflexia and diaphoresis in patients on phenelzine-tryptophan combination treatment. Can J Psychiatry. 1985;30(6):434–6.
63. White PD. Myoclonus and episodic delirium associated with phenelzine: a case report. J Clin Psychiatry. 1987;48(8):340–1.
64. Morgan JL, Brown TM, Wallace ER 4th. Monoamine oxidase inhibitors and sleep movements. Am J Psychiatry. 1994;151(5):782.
65. Grewal M, Hawa R, Shapiro C. Treatment of periodic limb movements in sleep with selegeline HCl. Mov Disord. 2002;17(2):398–401.
66. Skop BP, Finkelstein JA, Mareth TR, Magoon MR, Brown TM. The serotonin syndrome associated with paroxetine, an over-the-counter cold remedy, and vascular disease. Am J Emerg Med. 1994;12(6):642–4.
67. Dimmitt SB, Riley GJ. Selective serotonin receptor uptake inhibitors can reduce restless legs symptoms. Arch Intern Med. 2000;160(5):712.

68. Bakshi R. Fluoxetine and restless legs syndrome. J Neurol Sci. 1996;142(1–2):151–2.
69. Dorsey CM, Lukas SE, Cunningham SL. Fluoxetine-induced sleep disturbance in depressed patients. Neuropsychopharmacology. 1996;14(6):437–42.
70. Lauterbach EC. Reversible intermittent rhythmic myoclonus with fluoxetine in presumed Pick's disease. Mov Disord. 1994;9(3):343–6.
71. Darko W, Guharoy R, Rose F, Lehman D, Pappas V. Myoclonus secondary to the concurrent use of trazodone and fluoxetine. Vet Hum Toxicol. 2001;43(4):214–5.
72. Sanz-Fuentenebro FJ, Huidobro A, Tejadas-Rivas A. Restless legs syndrome and paroxetine. Acta Psychiatr Scand. 1996;94(6):482–4.
73. Oztürk O, Eraslan D, Kumral E. Oxcarbazepine treatment for paroxetine-induced restless leg syndrome. Gen Hosp Psychiatry. 2006;28(3):264–5.
74. Bušková J, Vorlová T, Piško J, Sonka K. Severe sleep-related movement disorder induced by sertraline. Sleep Med. 2012;13(6):769–70.
75. Zhang B, Hao Y, Jia F, Li X, Ren Y, Zhou P, Liu W, Wing YK. Sertraline and periodic limb movments during sleep: an 8-week open-label study in depressed patients with insomnia. Sleep Med. 2013;14(12):1405–12.
76. Hargrave R, Beckley DJ. Restless leg syndrome exacerbated by sertraline. Psychosomatics. 1998;39(2):177–8.
77. Ghaziuddin N, Iqbal A, Khetarpal S. Myoclonus during prolonged treatment with sertraline in an adolescent patient. J Child Adolesc Psychopharmacol. 2001;11(2):199–202.
78. Perroud N, Lazignac C, Baleydier B, Cicotti A, Maris S, Damsa C. Restless legs syndrome induced by citalopram: a psychiatric emergency? Gen Hosp Psychiatry. 2007;29(1):72–4.
79. Page RL 2nd, Ruscin JM, Bainbridge JL, Brieke AA. Restless legs syndrome induced by escitalopram: case report and review of the literature. Pharmacotherapy. 2008;28(2):271–80.
80. Yang C, White DP, Winkelman JW. Antidepressants and periodic leg movements of sleep. Biol Psychiatry. 2005;58(6):510–4 (Epub 2005 Jul 7).
81. Salín-Pascual RJ, Galicia-Polo L, Drucker-Colín R. Sleep changes after 4 consecutive days of venlafaxine administration in normal volunteers. J Clin Psychiatry. 1997;58(8):348–50.
82. Milanlioglu A. Venlafaxine-induced restless legs syndrome. J Psychiatry Neurol Sci. 2012;25(4):388–9.
83. Terao T, Terao M, Yoshimura R, Abe K. Restless legs syndrome induced by lithium. Biol Psychiatry. 1991;30(11):1167–70.
84. Heiman EM, Christie E. Lithium-aggravated nocturnal myoclonus and restless legs syndrome. AJ Psychiatry. 1986;143(9):1191–2.
85. Caviness JN, Evidente VG. Cortical myoclonus during lithium exposure. Arch Neurol. 2003;60(3):401–4.
86. Bayard M, Bailey B, Acharya D, Ambreen F, Duggal S, Kaur T, Rahman ZU, Roller K, Tudiver F. Bupropion and restless legs syndrome: a randomized controlled trial. J Am Board Fam Med. 2011;24(4):422–8.
87. Kim SW, Shin IS, Kim JM, Yang SJ, Shin HY, Yoon JS. Bupropion may improve restless legs syndrome: a report of three cases. Clin Neuropharmacol. 2005;28(6):298–301.
88. Lee JJ, Erdos J, Wilkosz MF, LaPlante R, Wagoner B. Bupropion as a possible treatment option for restless legs syndrome. Ann Pharmacother. 2009;43(2):370–4.
89. Nofzinger EA, Fasiczka A, Berman S, Thase ME. Bupropion SR reduces periodic limb movements associated with arousals from sleep in depressed patients with periodic limb movement disorder. J Clin Psychiatry. 2000;61(11):858–62.
90. Saletu-Zyhlarz GM, Abu-Bakr MH, Anderer P, Gruber G, Mandl M, Strobl R, Gollner D, Prause W, Saletu B. Insomnia in depression: differences in objective and subjective sleep and awakening quality to normal controls and acute effects of trazodone. Prog Neuropsychopharmacol Biol Psychiatry. 2002;26(2):249–60.
91. Chiodo LA. Dopamine-containing neurons in the mammalian central nervous system: electrophysiology and pharmacology. Neurosci Biobehav Rev. 1988;12(1):49–91.

92. Kang SG, Lee HJ, Jung SW, Cho SN, Han C, Kim YK, Kim SH, Lee MS, Joe SH, Jung IK, Kim L. Characteristics and clinical correlates of restless legs syndrome in schizophrenia. Prog Neuropsychopharmacol Biol Psychiatry. 2007;31(5):1078–83.
93. Kang SG, Lee HJ, Park YM, Yang HJ, Song HM, Lee YJ, Cho SJ, Cho SN, Kim L. The BTBD9 gene may be associated with antipsychotic-induced restless legs syndrome in schizophrenia. Hum Psychopharmacol. 2013;28(2):117–23.
94. Kim SW, Shin IS, Kim JM, Park KH, Youn T, Yoon JS. Factors potentiating the risk of mirtazapine associated restless legs syndrome. Hum Psychpharmacol. 2008;7:615–20.
95. Nishimatsu O, Horiguchi J, Inami Y, Innami T, Sasaki A, Kondo K. Nocturnal myoclonus observed in a patient with neuroleptic-induced akathisia. Jpn J Psychiatry Neurol. 1992;46 (1):121–6.
96. Nishimatsu O, Horiguchi J, Inami Y, Sukegawa T, Sasaki A. Periodic limb movement disorder in neuroleptic-induced akathisia. Kobe J Med Sci. 1997;43(5):169–77.
97. Staedt J, Dewes D, Danos P, Stoppe G. Can chronic neuroleptic treatment promote sleep disturbances in elderly schizophrenic patients? Int J Geriatr Psychiatry. 2000;15(2):170–6.
98. Walters AS, Hening W, Rubinstein M, Chokroverty S. A clinical and polysomnographic comparison of neuroleptic-induced akathisia and the idiopathic restless legs syndrome. Sleep. 1991;14(4):339–45.
99. Lipinski JF, Hudson JI, Cunningham SL, Aizley HG, Keck PE Jr, Mallya G, Aranow RB, Lukas SE. Polysomnographic characteristics of neuroleptic-induced akathisia. Clin Neuropharmacol. 1991;14(5):413–9.
100. Cotter PE. O'Keeffe ST Improvement in neuroleptic-induced akathisia with intravenous iron treatment in a patient with iron deficiency. J Neurol Neurosurg Psychiatry. 2007;78(5):548.
101. Yamashita H, Horiguchi J, Mizuno S, Kuramoto Y, Yamawaki S, Inami Y. A case of neuroleptic-induced unilateral akathisia with periodic limb movements in the opposite side during sleep. Psychiatry Clin Neurosci. 1999;53(2):291–3.
102. Young WB, Piovesan EJ, Biglan KM. Restless legs syndrome and drug-induced akathisia in headache patients. CNS Spectr. 2003;8(6):450–6.
103. Murray TJ. The restless leg syndrome. Can Med Assoc J. 1967;96(24):1571–4.
104. Bet PM, Franken LG, Klumpers UM. Could pramipexole induce acute mania? A case report. Bipolar Disord. 2013. doi:10.1111/bdi.12067 (Epub ahead of print).
105. Horiguchi J, Yamashita H, Mizuno S, Kuramoto Y, Kagaya A, Yamawaki S, Inami Y. Nocturnal eating/drinking syndrome and neuroleptic-induced restless legs syndrome. Int Clin Psychopharmacol. 1999;14(1):33–6.
106. Shin YK, Hong SC, Ihn YK, Jeong JH, Han JH, Lee SP. A case of a patient with both chorea and restless legs syndrome. J Korean Med Sci. 2008;23(3):533–6.
107. Silberstein SD, Young WB, Mendizabal JE, Rothrock JF, Alam AS. Acute migraine treatment with droperidol: a randomized, double-blind, placebo-controlled trial. Neurology. 2003;60(2):315–21.
108. Larner AJ. Migraine with aura and restless legs syndrome. J Headache Pain. 2007;2:141–2.
109. Ehrenberg B. Acute migraine treatment with droperidol: letter to the editor. Neurology. 2003;61:1826.
110. Sandyk R. The restless legs syndrome (Ekbom's syndrome). BMJ 1983;283:885.
111. Morgan LK. Restless limbs: a commonly overlooked symptom controlled by "valium". Med J Aust. 1967;2(13):589–94.
112. Jagota P, Asawavichienjinda T, Bhidayasiri R. Prevalence of neuroleptic-induced restless legs syndrome in patients taking neuroleptic drugs. J Neurol Sci. 2012;314(1–2):158–60.
113. Duggal H, Mendhekar D. Clozapine-associated restless legs syndrome. Lett J Clin Psychopharm. 2007;27(1):89–90.
114. Basu A, Kundu S, Khurana H. Olanzapine-induced restless leg syndrome: a case report and review of literature. Indian J Pharmacol. 2014;46(4):450–2.
115. Zhao M, Geng T, Qiao L, Zhang M, Shi J, Huang F, Lin X, Wang J, Zuo H. Olanzapine-induced restless legs syndrome. J Clin Neurosci. 2014;21(9):1622–5.

116. Aggarwal S, Dodd S, Berk M. Restless leg syndrome associated with olanzapine: a case series. Curr Drug Saf. 2010;5(2):129–31.
117. Kang SG, Lee HJ, Kim L. Restless legs syndrome and periodic limb movements during sleep probably associated with olanzapine. J Psychopharmacol. 2009;23(5):597–601.
118. Khalid I, Rana L, Khalid TJ, Roehrs T. Refractory restless legs syndrome likely caused by olanzapine. J Clin Sleep Med. 2009;5(1):68–9.
119. Kraus T, Schuld A, Pollmächer T. Periodic leg movements in sleep and restless legs syndrome probably caused by olanzapine. J Clin Psychopharmacol. 1999;19(5):478–9.
120. Wetter TC, Brunner J, Bronisch T. Restless legs syndrome probably induced by risperidone treatment. Pharmacopsychiatry. 2002;35(3):109–11.
121. Virit O, Selek S, Savas HA, Kokaçya H. Improvement of restless legs syndrome and trichotillomania with aripiprazole. J Clin Pharm Ther. 2009;34(6):723–5.
122. McCall WV, Riley MA, Hodges C, et al. Asenapine-induced restless legs syndrome: differentiation from akathisia. J Clin Sleep Med. 2014;10(12):1341–2.
123. Rittmannsberger H, Werl R. Restless legs syndrome induced by quetiapine: report of seven cases and review of the literature. Int J Neuropsychopharmacol. 2013;16(6):1427–31.
124. Pinninti NR, Mago R, Townsend J, Doghramji K. Periodic restless legs syndrome associated with quetiapine use: a case report. J Clin Psychopharmacol. 2005;25(6):617–8.
125. Urbano MR, Ware JC. Restless legs syndrome caused by quetiapine successfully treated with ropinirole in 2 patients with bipolar disorder. J Clin Psychopharmacol. 2008;28(6): 704–5.
126. Chou KJ, Chen PY, Huang MC. Restless legs syndrome following the combined use of quetiapine and paroxetine. Prog Neuropsychopharmacol Biol Psychiatry. 2010;4:444–5.
127. Tan EK, Ho SC, Koh L, Pavanni R. An urge to move with L-thyroxine: clinical, biochemical, and polysomnographic correlation. Mov Disord. 2004;19(11):1365–7.
128. Dzaja A, Wehrle R, Lancel M, Pollmächer T. Elevated estradiol plasma levels in women with restless legs during pregnancy. Sleep. 2009;32(2):169–74.
129. Wesstrom J, Nilsson S, Sundstrom-Poromaa I, Ulfberg J. Restless legs syndrome among women: prevalence, co-morbidity and possible relationship to menopause. Climacteric. 2008;11(5):422–8.
130. Sieminski M, Karwacka M, Nyka W. Restless legs syndrome and hormonal replacement therapy in women at menopausal age. Neurology. 2012. Meeting Abstracts P05.010.
131. Jeret JS. Diltiazem–induced myoclonus. Neurology. 2002;59(6):962.
132. Swanoski MT, Chen JS, Monson MH. Myoclonus associated with long-term use of diltiazem. Am J Health Syst Pharm. 2011;68(18):1707–10.
133. Gonzalez L, Feijoo M. Myoclonus and angiotensin converting enzyme inhibitors. Med Clin (Barc). 2005;125(10):398.
134. Morgan LK. Restless legs: precipitated by beta-blockers, relieved by orphenadrine. Letter. Med J Aust. 1975;2(19):753.
135. Strang RR. The symptom of restless legs. Med J Aust. 1967;1(24):1211–3.
136. Ginsberg HN. Propranolol in the treatment of restless legs syndrome induced by imipramine withdrawal. Am J Psychiatry. 1986;143(7):938.
137. O'Sullivan RL, Greenberg DB. H2 antagonists, restless leg syndrome, and movement disorders. Psychosomatics. 1993;34(6):530–2.
138. Hogue R, Chesson AL. Pharmacologically induced/exacerbated restless legs syndrome, peirodic limb movements of sleep, and REM behavior disorder/REM without atonia: literature review, qualitative scoring, and comparative analysis. J Clin Sleep Med. 2010;6 (1):79–83.
139. Pichietti D, Winkelman JW. Restless legs syndrome, periodic limb movements in sleep and depression. Sleep. 2005;28(7):891–8.

Impulsive Behaviors: Definition, Prevalence, Neurobiology, and Management

16

Gary P.H. Ho, Charlene E. Gamaldo, Seema Gulyani and Rachel E. Salas

Dopamine agents remain the most efficacious class of medications for the treatment of restless legs syndrome (RLS) [1], also known as Willis–Ekbom Disorder (WED). However, standard of care and first line therapy have been dictated by the balance between efficacy and adverse side effect profile. The best example is levodopa that has an efficacy as high as 90% but due to a relatively high augmentation [2, 3] rate it has fallen out of favor and is recommended only for limited intermittent use. Rebound symptoms in the middle of the night are also common due to the short half-life of the drug [2, 4]. Since RLS (WED) remains a lifelong and debilitating condition of unknown origin, providers and patients must constantly reevaluate not only the cost and benefit of treatment options, but also the potential consequences.

In this chapter, we focus on another adverse manifestation that also appears to be associated with central dopamine dysregulation in the context of long-term dopamine agonist exposure. Various impulsive and compulsive behaviors are increasingly being recognized as side effects of long-term treatment for RLS (WED). Such behaviors, whether primarily impulsive or compulsive in nature, share the common element of being habit-forming due to an inability to resist an impulse or drive. Pathological gambling, hypersexuality, and compulsive eating are representative examples of such behaviors. We refer to these collectively as impulse control disorders (ICDs) or behaviors (ICBs). This terminology highlights the variable severity in these phenomena, which may range from subtle, barely noticeable

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changes in patients' behavioral habits to truly destructive actions with significant functional consequences.

This chapter will provide a comprehensive review of the current understanding of the clinical presentation [including differentiation from clinical presentation seen in Parkinson's disease (PD) patients on the same drugs], diagnostic tools and assessment strategies, existing evidence regarding the neurobiological mechanisms involved in its manifestation, and management strategies. Finally, we will conclude with some comments on the implications for patient and family counseling using two case study examples.

Definition: Impulse Control Disorder

Impulse control disorders (ICD) encompass a wide range of behaviors, ranging from pathologic gambling to compulsive shopping. Fundamentally, they all share the same common element of an inability to resist a reoccurring impulse or drive. As a result, a habitual pattern of engaging in these acts develops over time. The wide range of manifestations of ICD in our clinical experience is summarized in Table 16.1.

ICDs may be due to dysregulation of either impulsivity or compulsivity. These tendencies may be conceptualized as existing on opposite sides of an "impulsive-compulsive" spectrum. With impulsivity, patients' behaviors are characterized as being largely unplanned and without regard for the possible consequences of those actions. In contrast, compulsivity describes a tendency to perform repetitive and stereotyped actions. While they may have distinct underlying drives, both aberrant behaviors of impulsivity and compulsivity share the root cause of dysregulated impulse control. Thus, ICDs may include pathologic gambling or hypersexuality, which are primarily defects of impulsivity, as well as compulsive shopping or punding (purposeless repetitive actions), which are primarily due to

Table 16.1 Range of ICD seen in our clinic

Pathologic gambling
Binge eating
Compulsive shopping • Increased garage sale and auction visits
Hypersexuality • Increase in sexual experimentation with partner • Excessive viewing of pornography
Overdressing for simple errands (i.e., full makeup and nicest clothes for getting groceries)
Medication hoarding
Refusal to wear seatbelt despite traffic citations
New participation in costume play (i.e., Cosplay)
Compulsive attendance at Broadway shows only in New York (despite the same shows playing in hometown)

compulsions. Consistent with the conceptualization of impulsivity and compulsivity as existing on a spectrum, there is significant interaction between these two tendencies in ICD. For example, as patients consistently engage in impulsive behaviors, they may acquire compulsive characteristics as the behaviors become more habitual in nature.

The complex interactions between impulsivity, compulsivity, and addiction are active areas of research and are beyond the scope of this chapter. Nevertheless, it is clear that dysregulation of impulse control may manifest as a number of behavioral disorders which may vary greatly in severity. We use the term ICD to describe actions that result in significant functional impairment, and ICB to describe those that do not. Yet it is important to recognize that these are distinctions on a continuous spectrum of behavior.

While some of the aforementioned ICDs are formally designated as such in the fifth edition of the *Diagnostic and Statistical Manual of Mental Disorders*, as a whole its precise classification in that system overlaps with addiction disorders and obsessive-compulsive disorder. For the purposes of this chapter, we use the definitions of particular ICDs used in epidemiological studies of PD and in more recent studies of RLS [5].

Frequency of ICD Behaviors

Accurate assessments of the exact frequency of ICD in RLS patients taking dopaminergic agents are complicated by the lack of standard criteria and validated assessment instruments used in earlier studies. Looking at specific ICDs, including gambling and excessive sexual activity, one group noted that 7% of patients reported a change in gambling habits and 5% an increase in sexual desire [6]. More recently, studies have drawn upon the experience from ICD in PD, utilizing common criteria to define specific conditions [5]. These not only provide a clearer picture of how often ICDs occur in RLS patients on treatment but also allow for comparisons with ICDs in PD patients. Using these criteria, the frequency for any ICD in RLS is approximately 7–17% depending on the study [7, 8]. It is important to keep in mind however that ICD in RLS has only recently become appreciated whereas ICD has been reported within the PD population since at least the late 1990s [9] on dopaminergic medications. In the largest cross-sectional study involving 3090 patients with PD, ICD frequency was 13.6% [10]. Based on these data, the frequency of ICD in both PD and RLS patients treated with dopaminergic agents are similar. Due to its relatively recent recognition within the RLS population, larger and more longitudinal studies are needed.

Interestingly, there may be differences in the types of patients who develop ICD when comparing RLS and PD. In the latter, most patients are younger at onset of ICD symptoms, have earlier PD onset, and are taking relatively higher doses of dopaminergic medications [6]. In contrast, RLS patients who develop ICD tend to be older and are generally on lower doses of dopaminergic medications [6, 7].

Table 16.2 Factors associated with ICD in RLS and PD

ICD in RLS	ICD in PD
Female sex	No gender predisposition (gender differences may exist for individual ICDs)
Older age	Younger age
Lower dose dopaminergics	Higher dose dopaminergics
History of experimental drug use	History of experimental drug use
Family history of gambling disorder	Family history of gambling disorder

As an illustrative example, in two separate studies the mean dopamine dose for RLS patients with ICDs was 63.7 mg/d levodopa dose equivalents, compared to between 780–1100 for PD patients with similar behaviors [7, 11]. While the contrasting prevalence of impulsive behaviors in these individual studies (7.1% for RLS *vs.* 13.7% for PD) precludes a direct comparison, it highlights the significant difference in dopaminergic doses seen in patients with RLS or PD who develop ICD. Further, there appear to be no gender differences for ICDs overall in PD [10], whereas female gender is associated with a higher risk of ICD in RLS [7]. It should also be noted that although RLS is roughly twice as common in women, while PD is more likely to affect men, female gender is still associated with a higher rate of ICD in RLS after controlling for this difference [7]. Other factors which may predispose RLS patients to impulse control disorders include a history of experimental drug use and a family history of gambling disorder [7] (Table 16.2). Along with the aforementioned demographic differences between the RLS and PD populations with ICD, these factors suggest that while the underlying mechanism for these behaviors likely involves dopaminergic pathways, there may be additional differences in the underlying pathophysiology of the two disease states which result in the observed epidemiology. In the following section, we discuss the current models describing these phenomena, including recent functional imaging evidence supporting the role of aberrant dopaminergic signaling.

Pathophysiology

Epidemiological evidence and clinical experience implicate medication-induced aberrant dopaminergic signaling at the center of impulse control disorders in both PD and RLS. In the largest cross-sectional study of ICD in PD to date, 17.1% of patients treated with a dopamine agonist had an ICD of some type in contrast to 6.9% in those not taking a dopamine agonist, with an odds ratio of 2.72 [10]. While there are fewer epidemiological data for RLS, use of dopaminergic medications is similarly associated with ICD. This idea is further supported by case reports which have described resolution of these behaviors upon discontinuation of the dopamine agonist, findings which concur with our clinical experience [12–14].

Another theory is that ICD in both RLS and PD relates to the primary disease process, not to drug treatment [15]. However, the increased risk of developing these behaviors in patients taking dopamine agonists, and their resolution upon discontinuation of these medications, argues against this hypothesis. Furthermore, RLS and PD likely represent distinct neuropathophysiologic processes. Thus, similar impulsive and/or compulsive behaviors seen during treatment are more likely related to medications than the underlying disease.

The idea that dopamine agonist treatment influences these behaviors is consistent with our current understanding of dopaminergic reward pathways. While ICDs encompass a range of different behaviors, they are all reward driven and become repetitive and reinforced over time. Thus, the dopaminergic pathways which govern reward systems are the likely neuro-anatomic substrates for these medication effects. The precise pathways and anatomy have been extensively characterized and are beyond the scope of this chapter. However, the critical ones involve the ventral tegmental area, which contains dopaminergic mesolimbic neurons that project to the nucleus accumbens and prefrontal cortex. The D3 subtype of the dopamine receptor is particularly enriched in the mesolimbic system and thus may be intimately involved in addiction and control of impulsive behaviors [16, 17].

Dopamine agonists may interfere with these pathways in a number of ways resulting in aberrant behavior (Fig. 16.1). One prominent hypothesis relates to the disruption of normal phasic, or periodic, release of dopamine through the mesolimbic projections to the nucleus accumbens [5]. Under physiologic conditions, these events occur when an individual anticipates a reward and when an unexpected reward is received, a phenomenon known as reward prediction error manifests. When a reward is unexpectedly not given, phasic suppression of dopamine release occurs instead. Thus, mesolimbic dopaminergic pathways regulate reward and serve as a feedback teaching signal, modulating habit formation and other learned behaviors.

Interestingly, behaviors which do not consistently result in reward may be reinforced by the same system. This applies to many of the behaviors discussed in this chapter, most notably pathologic gambling. We may understand its physiology in terms of tonic, or sustained, release of dopamine. This occurs when individuals anticipate a reward in the setting of uncertainty, in other words, when the probability of actually obtaining or not obtaining a reward is similar. Thus tonic dopamine release may explain the repetitive nature of these behaviors, where simply anticipating a reward in the context of uncertainty is inherently rewarding.

Disruption of these physiologic pathways, which may occur with exogenous dopamine treatment, can explain the impulse control behaviors seen in RLS (Fig. 16.1c, d). For example, the teaching of feedback signaling may be absent, increasing the susceptibility for repetitive behaviors. In this setting, dopamine agonists or exogenous dopamine may further exacerbate the situation by enhancing the habit-forming properties of reward while having no effect on the feedback teaching that normally occurs with “losses” [18]. By influencing behavior through only positive reward reinforcement, impulsive and repetitive behaviors may be increased.

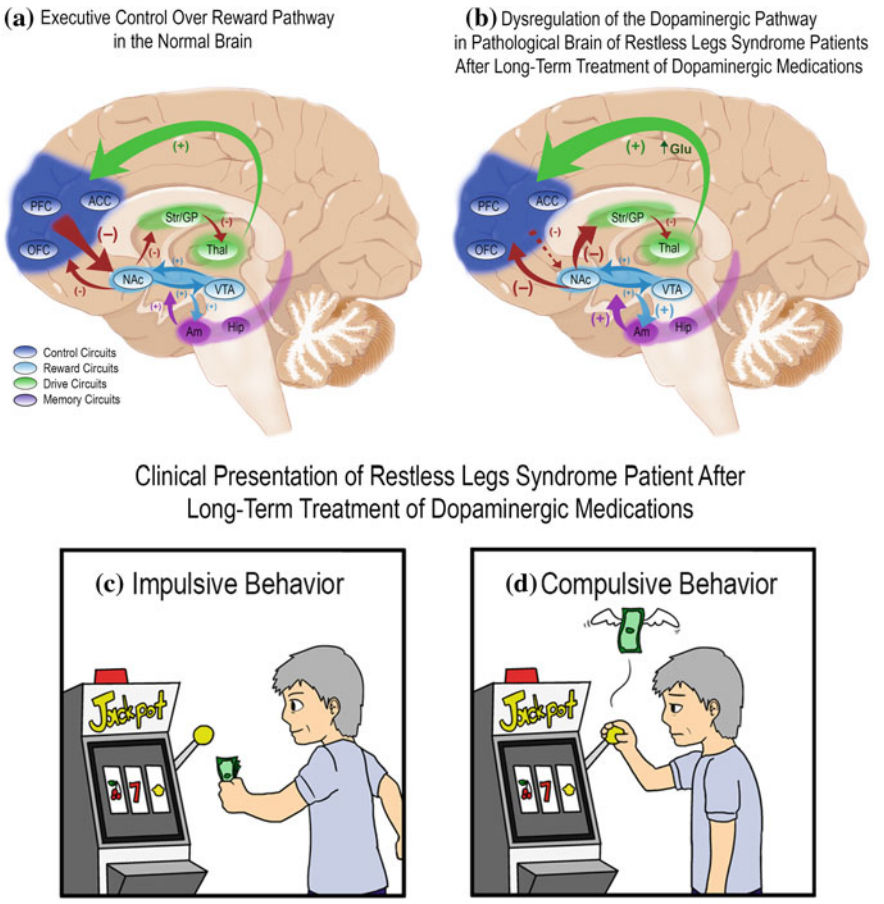

Fig. 16.1 **a**-**d**. Model proposing the network of interacting pathways influencing impulsive-compulsive behaviors: Projection of dopaminergic cells of the ventral tegmental area (VTA) into the nucleus accumbens (NAc) is critical for impulsive-compulsive behaviors. A reciprocal excitatory pathway subsequently occurs between these two regions and the amygdala (Am) and hippocampus (Hip), resulting in conditioning/memory response of these rewarding behaviors (i.e., impulsive behaviors). The reciprocal excitatory pathway generated with VTA and NAc with the motor cortex, thalamus (Thal), striatum and globus pallidus (Str/GP) results in conditioning/memory response to maintain the motivation to repeat these rewarding behaviors (i.e., compulsions). The executive control centers (prefrontal cortex (PFC), anterior cingulate cortex (ACC), and orbital frontal cortex (OFC)) balance these pathways to inhibit compulsive behavior. In a normal brain (**a**), executive centers regulate the reward pathway and thus inhibit impulsive-compulsive behaviors. Weaker inputs from the control center result in compulsive-impulsive behaviors (**b**). Long-term treatment of dopaminergic medications in patients with restless leg syndrome may lead to impulsive behavior for rewarding behavior (**c**), but this impulsivity is under the control of the executive center. Weakening of the executive control centers may result in compulsivity (**d**). Proposed model of impulsive-compulsive behavior in patients with restless legs syndrome was adapted by Anthony Kwan from current models of drug addiction [see Volkow et al., The addicted human brain: insights from imaging studies. J Clin Invest 2003;111:1444–51; and Volkow et al., Addiction: beyond dopamine reward circuitry. Proc Natl Acad Sci U S A 2011;108:15037–42.]

Alternatively, dopamine agonists may overstimulate mesolimbic pathways resulting in ICD, in particular in the case of pathologic gambling. Indeed, one study measuring brain perfusion with single-photon emission computed tomography has demonstrated overactivity in these pathways in PD patients on dopaminergic medication [19]. Specific subpopulations of dopamine receptors may be affected, which may contribute to habit formation instead of goal-directed actions. Behavior sensitization from chronic stimulation of dopaminergic neurons may be an additional contributing factor. Interestingly, elevated levels of glutamate have recently been found in the thalami of RLS patients, supporting the idea that glutamate dysregulation may be a contributing factor in RLS [20]. Glutamatergic systems have also been implicated in the regulation of impulse control, with some studies finding reduced impulse control with glutamate receptor antagonist treatment [21, 22] and others suggesting a positive correlation between glutamate and impulsivity [19]. Thus, while the data do not clearly implicate either glutamate receptor hypo- or hyperfunction in ICD, further studies are needed to clarify any potential linkage between glutamatergic systems and RLS pathophysiology.

Specific ICD Behaviors and Assessment Tools and Strategies

Pathologic Gambling

Pathologic gambling is one of the most recognized ICDs in both RLS and PD patients on dopamine agonists. The majority of studies thus far have utilized DSM-IV criteria to diagnose this condition in the setting of both PD and RLS (Table 16.2). While patients may be asked directly during their clinic visit about any of the phenomenology listed in the DMS-IV, there are other assessment methods which have been used extensively in epidemiological studies of pathologic gambling in both RLS and PD. These include the South Oaks Gambling Screen, a sensitive 20-item questionnaire which may be either self- or provider-administered, and the Massachusetts Gambling Screen, which may be more specific [23]. In our experience and in several case reports, discontinuation of the dopamine agonist and replacement with gabapentin results in resolution of symptoms [12, 13].

Compulsive Eating

Compulsive eating or binge eating are among the commonest manifestations of ICD in RLS, possibly more so than in PD when measured as a percentage of patients experiencing ICB. In one study, the prevalence of binge eating in RLS patients on dopaminergic agents was 11%, compared to 5.6% in PD patients in a separate study [8, 10]. In the RLS study, compulsive eating had the highest prevalence among the ICDs found. Interestingly, compulsive eating was also the commonest ICD found in

a study examining ICD in a German RLS population, where binge eating disorder is less common generally than in the North American population [7]. Since binge-eating disorder is described extensively in the DSM-V, that definition is used in most studies. There are a number of questionnaires designed to assess patients based on the DSM-IV. One of these is the research criteria for binge-eating disorder in the DSM-IV, considered positive if the patient responds affirmatively to both gateway questions and greater than three secondary questions. Other clinicians have designed questionnaires to assess binge-eating which are based on studies investigating ICD in the PD population [8]. Cornelius et al. did an excellent review that evaluated specific ICD behaviors resulting in the development of their own questionnaire [8, 24].

Compulsive Shopping

Compulsive eating may often coexist with compulsive shopping. The range of severity may vary, from noticeable only in hindsight to resulting in hundreds of thousands of dollars in credit card debt. Here, patients may exhibit such extreme compulsivity that it results in hoarding behaviors. In other more mild occurrences shopping desire may appear to rise to the level of a "passionate hobby" such as antique collecting. In one instance, a 47-year-old woman spent more than five thousand dollars on buying "ugly clothes and jewelry I didn't even need" on television shopping networks and arose particularly early in the morning because she could not "miss a sale" [8]. Interestingly, her behavioral changes ceased the following discontinuation of pramipexole treatment.

These behaviors may be seen in both RLS and PD with similar frequency. The criteria most often used are the McElroy criteria [21]. These may be assessed using a variety of instruments, most commonly the Minnesota Impulsive Disorders interview (which may also be used to assess hypersexuality) [25]. However, any survey designed to address the McElroy criteria may be used. We will discuss compulsive buying in one of our case studies later in the chapter.

Hypersexuality

The Minnesota Impulsive Disorders interview also addresses hypersexuality. This ICD is found between 1.5–3% of patients with RLS on dopamine agonists [7, 8], and approximately 3.5% in PD patients on similar treatment [10]. In PD, male gender confers increased risk of compulsive sexual behavior [10, 26], which is consistent with its prevalence in the general population. The limited number of relevant studies precludes any definitive assessment regarding any potential gender predilection for hypersexuality in the setting of RLS. Hypersexuality may often coexist with multiple other ICDs. One case report in particular has described a 71-year-old man with RLS who exhibited pathologic gambling and hypersexuality [27]. In our clinical experience, we have also seen patients with not only increased

sexual desire but also participation in sexual experimentation atypical of their habits prior to dopamine agonist treatment. Viewing of pornography may be seen as another manifestation of hypersexuality. Important legal and social ramifications should be considered. In one particular case in our practice, a physician who was being treated with dopaminergic agents had lost his job due to his viewing of pornography while at work. Thus, patients should be counseled to report as early as possible any noticeable changes in their behavior.

Punding

Punding involves stereotyped, repetitive movements which may or may not be related to the patient's individual occupation or previous habits. Usually, punding behaviors are complex in nature but purposeless. Examples include manipulation of nearby objects in a repetitive manner, continuous grooming or cleaning oneself, sorting, and hoarding. The majority of punding assessments performed in studies of RLS are drawn from previous experience in PD and most often use some variation of the punding questionnaire from Evans et al. [28].

Compulsive Medication Use

While compulsive medication use is a recognized consequence of PD treatment, it has not been extensively described in the RLS population. When seen in the setting of PD, it is sometimes referred to as dopamine dysregulation syndrome or hedonistic homeostatic dysregulation. The prevalence in the PD population is between 3.4–4% [9]. While there are case reports of this occurring in RLS [14], epidemiological studies have not measured its prevalence in that population.

Other Behaviors

The spectrum of behaviors resulting from dysregulated impulse control encompasses an extremely wide range which cannot be easily summarized into specific categories. Thus, clinicians should always be vigilant for any changes in their patients' behavior—some of which may be unusual and not commonly thought of in the context of ICBs. Our clinical experience is consistent with these, at times, purportedly "subtle" or "not so subtle" behavioral patterns (Table 16.1). For example, one patient's manifestation of "risky" behavior was continuing to refuse to wear his seatbelt in his car in the face of accumulating police citations. Another is a lady who would compulsively go to Broadway shows—but only in New York, despite the same shows being performed closer to home. One father, while being treated with dopaminergics, began to display an inclination for costume play, engaging in full dress-up for conventions with his kids. In this case, his family thought that perhaps he had always had a propensity for cosplay (i.e., costume

dress) but simply had not been exposed to it. Another illustrative example is one patient who began to dress up extensively to go anywhere, even for simple errands that did not demand it. After her medication was discontinued, she noted that her habits returned to their normal baseline. Smoking [29], itself associated with RLS, has also been seen as a behavioral change with RLS treatment in clinical experience.

Global Assessment of Suspected ICD: A Systematic Approach

Given the wide range of behavioral manifestations of ICD and their variable severity, it may be difficult to elicit evidence of symptoms during a routine follow-up visit in the absence of significant functional deficit. As recent epidemiological evidence suggests, ICD is not an uncommon effect of treatment of RLS. Thus, clinicians should be aware of this possibility when treating patients with dopaminergic medication. Furthermore, family members and patients should be counseled on this possibility and should be advised to be observant of any changes in behavior while being treated.

If the clinician suspects the presence of an ICD, the use of questionnaires to address specific types of behaviors may be helpful for diagnosis and management. Patients and family members should be made aware of the factors that increase the risk for ICD prior to treatment so they are educated, informed, and have insight should a pattern start to develop. While there are no universally accepted standard assessment instruments for each ICD, based on recent epidemiological studies a consensus is emerging with regard to definitions of each ICD. A number of questionnaires, as described in the previous section, are used to screen for these behaviors. A recent study used simple yes/no assessment instruments to rapidly screen for common ICDs based on the emerging consensus criteria for diagnosis. The questionnaires are a simple, rapid, and systematic method for eliciting symptoms suggestive of impulse dysfunction. They may even be self-administered by the patient and may be easily done while in the waiting room.

Management

There have not been large-scale studies that have rigorously assessed the question of ICD management. However, given the likely pathophysiology, the epidemiological evidence attributing increased risk to those on dopaminergic medication, and various case reports suggesting cessation of symptoms upon medication discontinuation, the universal strategy for treatment of ICD is discontinuing the dopaminergic agent or lowering its dose. This has been shown to be effective in a number of case reports [12–14]. Switching from the dopamine agonist to

alpha-2-delta ligands such as gabapentin may be a viable alternative if RLS treatment is necessary. It is important to weigh the relative benefits of better control of RLS symptoms, which may require dopaminergic agents, *versus* any deleterious consequences of impulse dysfunction. Furthermore, patients may not readily volunteer information about symptoms related to impulsivity or compulsivity, seeing them as unrelated to their primary neurological condition. Instead they and even family and friends may see the behaviors as hobbies, annoyances, or even be encouraging of it (as the case of the husband of the patient who became interested in sexual experimentation) (Salas personal communication). We have highlighted some of these concepts in management in real-life clinical context with two case studies both of which were published in medical journals [13, 14].

Conclusion

In this chapter, we have discussed the various forms of impulsive and compulsive behaviors that may occur as a consequence of RLS treatment. These behaviors share certain clinical and pathophysiological features with PD patients on similar medications, but also exhibit key demographic differences. Several tools exist to rapidly and effectively identify behaviors consistent with ICD and in most cases symptoms resolve after removal of the dopamine agent. The manifestations of ICD however can range from behaviors that seem mild or benign on the surface to those that can result in significant financial and criminal ramifications. Thus aside from early identification, it is critical that patients are made aware of this potential adverse effect and the factors that potentially increase the risk for development. With many patients wanting to be more engaged in their treatment plan decisions, health providers should see this as an important disclosure at start and maintenance of therapy for this class of medication.

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References

1. Scholz H, Trenkwalder C, Kohnen R. Dopamine agonists for the treatment of restless legs syndrome. … Database Syst Rev. 2011.
2. Allen RP, Earley CJ. Augmentation of the restless legs syndrome with carbidopa/levodopa. Sleep. 1996;19(3):205–13.
3. 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(10):801–10.
4. Leschziner G, Gringras P. Restless legs syndrome. BMJ. 2012;344(2):e3056.
5. Voon V, Fox SH. Medication-related impulse control and repetitive behaviors in Parkinson disease. Arch Neurol. 2007;64(8):1089–96.

6. Driver-Dunckley ED, Noble BN, Hentz JG, et al. Gambling and Increased sexual desire with dopaminergic medications in restless legs syndrome. Clin Neuropharmacol. 2007;30(5): 249–55.
7. Voon V, Schoerling A, Wenzel S, et al. Frequency of impulse control behaviours associated with dopaminergic therapy in restless legs syndrome. BMC Neurol. 2011;11(1):117.
8. Cornelius JR, Tippmann-Peikert M, Slocumb NL, Frerichs CF, Silber MH. Impulse control disorders with the use of dopaminergic agents in restless legs syndrome: a case-control study. Sleep. 2010;33(1):81–7.
9. Giovannoni G, O'Sullivan JD, Turner K, Manson AJ, Lees AJL. Hedonistic homeostatic dysregulation in patients with Parkinson's disease on dopamine replacement therapies. J Neurol. 2000.
10. Weintraub D, Koester J, Potenza MN, et al. Impulse control disorders in Parkinson disease: a cross-sectional study of 3090 patients. Arch Neurol. 2010;67(5):589 (American Medical Association).
11. Voon V, Hassan K, Zurowski M, et al. Prevalence of repetitive and reward-seeking behaviors in Parkinson disease. Neurology. 2006;67(7):1254–7.
12. Tippmann-Peikert M, Park JG, Boeve BF, Shepard JW, Silber MH. Pathologic gambling in patients with restless legs syndrome treated with dopaminergic agonists. Neurology. 2007;68 (4):301–3.
13. Salas RE, Allen RP, Earley CJ, Gamaldo CE. A case of compulsive behaviors observed in a restless legs syndrome patient treated with a dopamine agonist. Sleep. 2009;32(5):587 (American Academy of Sleep Medicine).
14. Salas RE, Allen RP, Earley CJ, Gamaldo CE. Drug hoarding: a case of atypical dopamine dysregulation syndrome in a RLS patient. Mov Disord. 2009;24(4):627–8.
15. Bayard S, Langenier MC, Dauvilliers Y. Decision-making, reward-seeking behaviors and dopamine agonist therapy in restless legs syndrome. Sleep. 2013;36(10):1501–7.
16. Suzuki M, Hurd YL, Sokoloff P, Schwartz JC, Sedvall G. D3 dopamine receptor mRNA is widely expressed in the human brain. Brain Res. 1998;779(1–2):58–74.
17. Dang D, Cunnington D, Swieca J. The emergence of devastating impulse control disorders during dopamine agonist therapy of the restless legs syndrome. Clin Neuropharmacol. 2011;1.
18. Pessiglione M, Seymour B, Flandin G, Dolan RJ, Frith CD. Dopamine-dependent prediction errors underpin reward-seeking behaviour in humans. Nature. 2006;442(7106):1042–5 (Nature Publishing Group).
19. Cilia R, Siri C, Marotta G, et al. Functional abnormalities underlying pathological gambling in parkinson disease. Arch Neurol. 2008;65(12):1604–11.
20. Allen RP, Barker PB, Horská A, Earley CJ. Thalamic glutamate/glutamine in restless legs syndrome: Increased and related to disturbed sleep. Neurology. 2013;80(22):2028–34.
21. Murphy ER, Fernando ABP, Urcelay GP, et al. Impulsive behaviour induced by both NMDA receptor antagonism and GABAA receptor activation in rat ventromedial prefrontal cortex. Psychopharmacology. 2011;219(2):401–10.
22. Pattij T, Vanderschuren L. The neuropharmacology of impulsive behaviour. Trends Pharmacol Sci. 2008;29(4):192–9.
23. Weinstock J, Whelan JP, Meyers AW, McCausland C. The performance of two pathological gambling screens in college students. Assessment. 2007;14(4):399–407.
24. Provini F, Antelmi E, Vignatelli L, et al. Association of restless legs syndrome with nocturnal eating: a case-control study. Mov Disord. 2009;24(6):871–7.
25. Christenson GA, Faber RJ, de Zwaan M, et al. Compulsive buying: descriptive characteristics and psychiatric comorbidity. J Clin Psychiatry. 1994;55(1):5–11.
26. Antonini A, Cilia R. Behavioural adverse effects of dopaminergic treatments in Parkinson's disease: incidence, neurobiological basis, management and prevention. Drug Saf. 2009;32 (6):475–88.
27. d'Orsi G, Demaio V, Specchio LM. Pathological gambling plus hypersexuality in restless legs syndrome: a new case. Neurol Sci. 2011;32(4):707–9.

28. Evans AH, Katzenschlager R, Paviour D, et al. Punding in Parkinson's disease: its relation to the dopamine dysregulation syndrome. Mov Disord. 2004;19(4):397–405.
29. Bayard M, Avonda T, Wadzinski J. Restless legs syndrome. Am Fam Physician. 2008;78 (2):235–40.

Impulse Control Behavior in Movement Disorders: Focus on Restless Leg Syndrome

17

Salvatore Galati

Movement disorders are frequently associated with abnormal impulse behaviors that can be generally related to deficits in the ability to suppress reacting behaviors leading to impulsive actions or, the suppression of decision-making with impulsive choices. Both categories of impulsive behavior are reported in restless legs syndrome (RLS) and represent behaviors that are encompassed by the term impulse control behaviors (ICBs).

In movement disorders, the most frequent ICBs observed are pathological gambling, compulsive shopping, hypersexuality, and binge or compulsive eating [1]. While the relationship between Parkinson's disease (PD) and dopamine (DA) agonists is well established, prevalence in rates of ICBs in DA-treated patients with RLS is matter of debate with inconsistent findings. Unlike other monoamine systems, the mesencephalic DA system is heterogeneous with respect to differential projection target, receptor expression, and functional effects [2, 3].

In PD, a variable spatiotemporal involvement in the different stages of neurodegeneration is responsible for the extremely variable phenotype and response to DA replacement therapy (DRT). For instance, the early stages of dopaminergic cell degeneration in PD primarily involves the nigrostriatal interplay [4–6] and then, as the disease progresses, the mesolimbic systems with effects on cognitive-associative processes and reward-mediated behaviors [7]. Working across the entire dopaminergic system, the effects of DRT might be beneficial for the impaired DA system, but at the same time, detrimental to the spared one [8].

As opposed to PD, a dopaminergic deficit has not been clearly demonstrated in RLS. However, an imbalanced dopaminergic system at diencephalon-spinal level seems to be crucial in the pathophysiology of the disease [9]. The extremely positive response to RLS symptoms achieved with DRT strongly suggests the

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involvement of dopaminergic pathways which share a mechanism with iron metabolism [10]. In this context, the emergence of ICBs symptoms in RLS patients could be related to an unfavorable effect of DAs on the intact mesolimbic system that is particularly rich in D2/D3 receptors. At this level, dopaminergic transmission follows two distinct patterns of firing discharge [11, 12]. In the ventral striatum (VS), dopaminergic fibers from the ventral tegmental area (VTA) release DA in a tonic fashion for a sustained "background" release acting as "volume" transmission. VTA spontaneously active neurons are responsible for tonic stimulation being transiently suppressed in response to the omission of expected rewards [13] or aversive stimuli [14, 15]. In contrast, phasic activity is associated with a transient increase in the dopaminergic cleft [16]. Behaviorally relevant stimuli underlie short-term phasic activation of dopaminergic VTA neurons. Despite this pattern of discharge or the nature of the disease, DRT acts widely, influencing dopaminergic basal tone and phasic reward-related DA release. The balance of the two DA cell firing patterns has crucial consequences in the limbic, associative, and sensorimotor striatum, and some functional imaging studies in PD patients with ICBs seem to confirm this hypothesis [17, 18].

While the DA overdose hypothesis is supported by substantial evidence in PD patients with ICBs, other extra-striatal mechanisms seem to be involved in RLS. Of note, recent evidence has shown that an intrinsic preference toward risky choices in a decision-making test irrespective of DRT is crucial in patients with RLS [19]. This evidence suggests that RLS patients have an intrinsic propensity to develop impulsive behavior regardless of the treatment, due to the disease pathophysiology itself or, indirectly, to sleep-related consequences of it.

Impulse Control Disorders

Definition and Classification

ICB encompasses repetitive behaviors characterized by the failure to control an impulse, drive, or temptation to perform an act despite the negative consequences, as reported in the fourth edition text revised revision of the diagnostic and statistical manual of mental disorders [20]. This psychiatric manual also classifies pyromania, trichotillomania, kleptomania, intermittent explosive disorder, pathological gambling, and "not otherwise specified" as ICBs. The latter category includes other conditions that can be frequently observed in patients suffering from movement's disorders such as PD or RLS. Among these behaviors, pathological gambling, compulsive eating, hypersexuality disorder, compulsive shopping, punding, and DA dysregulation syndrome appear as the most frequently observed disorders [21, 22]. Other ICBs, such as hoarding and compulsive smoking have been codified in the same category.

In the fifth edition of the DSM [23], some of these behaviors are included in a distinct chapter related to "disruptive, impulse-control, and conduct disorders"

together with emotional and behavioral self-control. In the new DSM edition, pathological gambling was redefined as gambling disorder in the chapter regarding substance-related disorders. Indeed, ICBs, such as gambling disorder, are closely linked to substance abuse in terms of their neurobiological basis and genetics, [24] justifying such reclassification. Along with repetitive engagement in a specific task, patients with ICBs manifest features quite similar to addictions represented by a sense of tension or urge state before performing the compulsive behavior, as well as tolerance and withdrawal [25].

Neuropathological Basis of Impulse Control Disorders

Impulsivity is a "predisposition towards rapid, unplanned reactions to internal or external stimuli without regards to the negative consequences of these reactions to themselves or others" [26]. Impulsivity is part of the impulsive-compulsive spectrum [27]. Despite impulsion and compulsion generally being characterized by repetitive behaviors, they exhibit some substantial differences. Insensitivity to reward, for instance, is a distinct feature of compulsive disorders. These patients are engaged in egodystonic behavior and tend to overestimate consequences, obtaining high scores on measures of harm avoidance. Compulsivity represents a tendency to perform unpleasantly repetitive behaviors in order to prevent apparent negative consequences. In contrast, patients with ICBs typically manifest insensitivity to punishment and tend to seek pleasurable or egosyntonic behaviors [28]. Impulsion and compulsion may be viewed as diametrically opposed but strictly related, in that each implies a dysfunction of motivational control networks. ICBs patients may show an excessive engagement in habitual perseverative behavior despite negative outcomes. On the other hand, compulsive patients are driven by a desire to avoid harm [29].

Impulse-compulsive networks are intimately linked underlying processes involved in the transition of reward-related learning to habitual behaviors. In general terms, prefrontal cortex (PFC) can be considered the region deputed to associative learning (mainly its subregion, the orbitofrontal cortex, OFC) and discriminative and cognitive control (mainly the other subregion, the anterior cingulate cortex, ACC) [29]. The PFC exerts a "top down" control of the "bottom up" subcortical structures involved in reward behaviors [30]. Subcortical regions including basolateral amygdala, are involved in the assignment of emotional content in relevant stimuli and the subsequent associative learning through its connection with orbitofrontal cortex and with VTA (Fig. 17.1).

Additional structures are the hippocampus, which provides memory-related information and the hypothalamic nucleus, which provides contextual information to primitive internal motivation. Among subcortical structures, the nucleus accumbens (NAcc) represents a key station engaged in the initiation and maintenance of motivational behavior. Anatomically placed in the ventral region of striatum, the NAcc is considered the functional interface between motivation and movement [31]. NAcc is comprised of a shell and a core [32]. The former plays a

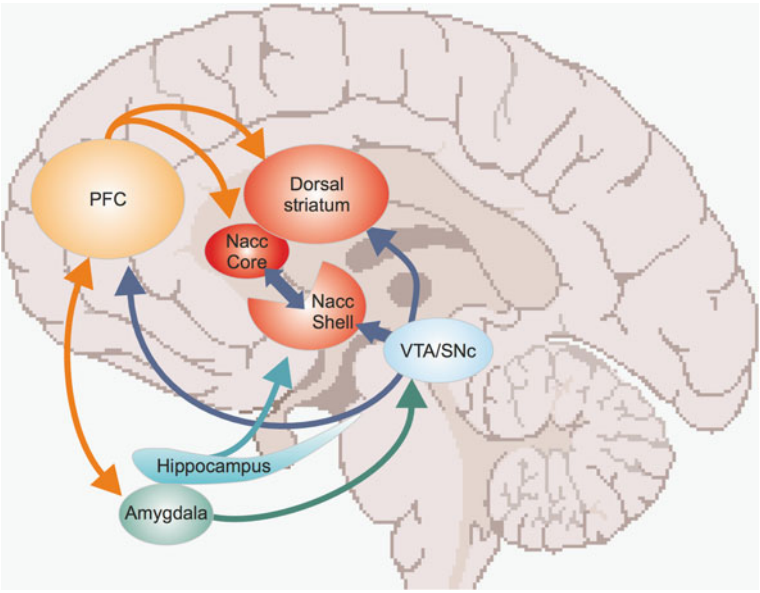

Fig. 17.1 Schematic illustrations of putative neural circuits of impulse-compulsive control. For detailed explanations, see text. *PFC* prefrontal cortices; *NAcc* nucleus accumbens; *SNc* substantia nigra pars compacta; *VTA* ventral tegmental area

crucial role in governing unconditioned reactions in association with unconditional stimuli as suggested by experimental studies with local DA infusions [32–34]. In contrast, neurons in the core appear to be engaged in motor responses to conditional stimuli [35]. Briefly, the NAcc shell seems to be mainly implicated in the primary reinforcing learning of unconditioned stimuli, whereas, the core is preferentially involved in the reinforcement of conditioned events. Through the subsequent involvement of the shell (involved in unconditioned stimuli), the core (involved in conditioned stimuli), the caudate (involved in associative relations) and the putamen (in sensorimotor response), a particular behavior, if given a favorable context, will pass through reward- learning, reward expectancy, associative consolidation, and finally arrive at habit formation.

The VTA DA neurons project to amygdala, NAcc ad PFC (both the OFC and the ACC) facilitating the associative learning in the context of motivational salient events (Fig. 17.1). One of the most compelling pieces of evidence for the role of DA in reinforcement learning comes from the VTA firing patterns during the presentation of conditioned and unconditioned stimuli [36]. In response to the delivery of unpredicted rewards, VTA neurons show phasic transient discharge chasing soon after that stimulus predicts reward [36, 37]. In contrast, the omission of expected rewards, silences the tonic spontaneously activity of VTA dopaminergic neurons [11–13]. Thus, an unexpected reward following a neutral cue is a

positive error and favors learning, on the contrary, the omission of an expected reward after a predictive cue is a negative error and favors extinction.

There are several neuroimaging studies in agreement with the dysregulation of "bottom up" and "top down" systems in patients affected with PD with ICBs. They are difficult to summarize but there is substantial convergence in highlighting dysfunction of the 'compulsive' and 'impulsive' cortico—striatal circuits. PD patients with ICBs show an enhanced VS DA release measured by (^{11}C)raclopride during a conditioned cue or a gambling task [18]. Consistently, greater VS activity was observed in PD patients with hypersexuality [38]. Cilia and colleagues [39] demonstrated in a single photon emission tomography (SPECT), that PD with gambling disorder had a decreased activity of PFC and a functional ACC—striatal disconnection in comparison with PD patient without ICBs. Other structures seem to be involved in the pathophysiology of ICDs, such as pedunculopontine nucleus that have several connections to the basal ganglia [40].

Regarding RLS, in a within-subjects design, using functional magnetic resonance imaging (fMRI), 12 RLS patients without a history of ICDs were scanned during their regular DA therapy and again after a period of drug washout. The patients were submitted to fMRI while performing a gambling game task. Under DA therapy and during expected rewards, patients with RLS, and without manifested ICBs, show a clear VS activation. This finding suggests an intrinsic inclination to motivational silence reward learning in patients with RLS, despite clinically evident ICBs.

On the other hand, these patients had a normal activation of OFC that was consistent with the absence of clinically manifested ICBs [41].

Epidemiology of Impulse Control Disorders and Dopamine Agonist Medication Effect

The largest epidemiological study related to the prevalence of ICBs in patients with movement disorders is the multicenter cross-sectional, North American DOMINION study [1]. Prevalence rate of ICBs in PD treated with DRT was 13.6% [1] compared to 0.5–1% in the general population [42]. However, a recent study with 115 PD, did not show a significant difference in the rate of tobacco or alcohol addiction and pathological gambling compared with the general population, suggesting that PD patients do not have specific profiles for ICBs. In the DOMINION study (Fig. 17.2a), the most common ICDs was compulsive shopping (5.7%) followed by pathological gambling (5.0%), binge eating disorder (4.3%), and compulsive sexual behavior (3.5%). The study showed also that most frequently a single ICB is observed in PD patients rather than multiple ICBs. Regarding DAs, their use is clearly associated with a higher risk of developing ICBs. In the DOMINION study [1], ICBs were more common in users than in patients not taking DAs (17.1% vs. 6.9%, Fig. 17.2b) confirming a previous study in which DAs significantly increased the frequency of pathological gambling, hypersexuality, and compulsive shopping in PD patients [43]. Consistently, a

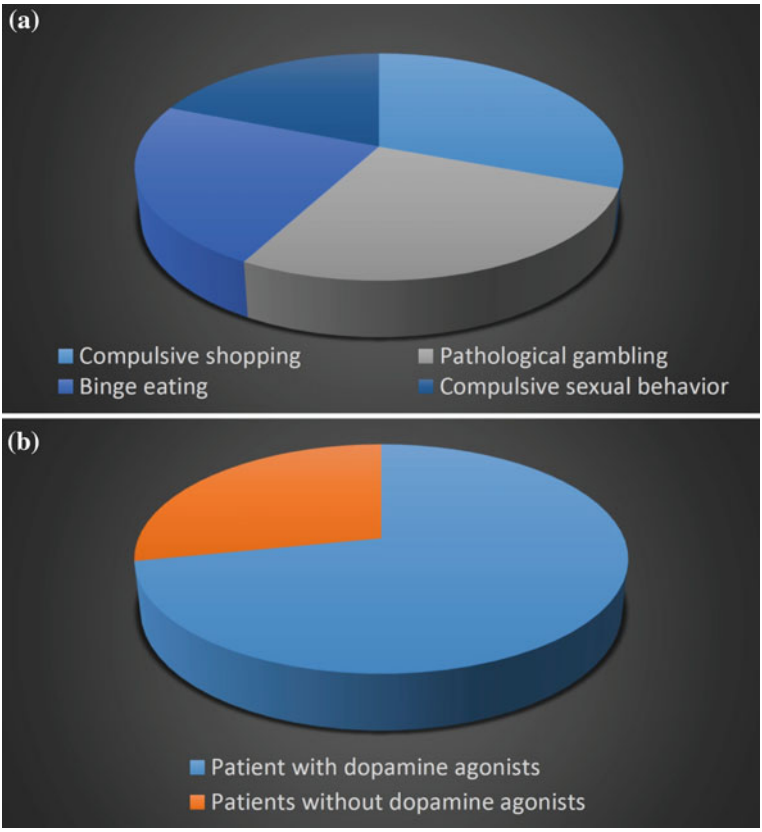

Fig. 17.2 **a** Prevalence of ICBs in a large cohort of PD patients of the DOMINION study. **b** Percentage of PD patients with and without DA therapy in the same study. Data from Weintraub et al. [1]

similar relationship between ICDs and dopaminergic agents was documented in a retrospective study documenting the development of new-onset gambling or hypersexuality in 7 out of 267 patients [44]. Notably, all of these patients were in the DA-treated arm (7/66 patients; 10.6%).

As far as RLS is concerned, DAs treatment seems to have a similar effect on impulsive behaviors. In a case–control study based on a questionnaire followed by a phone interview, the ICBs frequency in RLS patients treated with dopaminergic agents was 17% [45]. The same study showed a latency of 9.5 months between initiation of the DA treatment and the onset of impulsive behaviors. ICBs were represented by compulsive eating with a frequency of 11% followed by compulsive shopping (9%), punding (7%), pathological gambling (5%), and hypersexuality (3%); [45].

In a cross-sectional study, Voon and colleagues [46] revealed a lower prevalence of any ICBs in RLS patients (11%) with a higher risk in patients with higher Das

dosage, younger age of onset of RLS, history of experimental drug use, female sex, and a family history of gambling disorders. However, in this study the patients were screened using self-administered patient questionnaires followed by a confirmatory psychiatric interview. Among the ICBs, the same authors reported that the most frequent was compulsive eating (4.3%), followed by compulsive shopping with a rate of 3.6%. Pathological gambling had a frequency of 2.1%, punding of 2.1%, and hypersexuality of 1.4% [46]. Higher ICBs frequency was observed in a recent retrospective case series of 28 RLS patients treated with the transdermal DA rotigotine. In this study, the overall prevalence of ICBs, including binge eating, hypersexuality, compulsive shopping, pathological gambling, and punding equals a rate of 21%. History taking and scoring with the Zurich Screening Questionnaire Symptoms were used for the ICBs assessing prior to and after initiation of rotigotne treatment. Of note, both patients with and without ICBs and irrespective of the therapy totalized higher scores on the Zurich Screening Questionnaire [47]. Similarly, regardless of the pharmacological treatment, RLS seem to be associated with impaired executive performances [48], reduced decision-making abilities under ambiguity but not risk [49] and deficits in short-term attention and verbal fluency [50]. These results could be an expression of intrinsic cognitive and behavioral traits of RLS patients consequently predisposing them to ICBs. Contrary to this hypothesis, patients suffering from multiple sclerosis with secondary RLS seem to be exposed to the same risk of DA-induced ICBs as patients with primary RLS [51]. Thus, rather than being a specific feature of RLS patients, the propensity to ICDs could be related to the sleep disturbance caused by RLS symptoms. Interestingly, ICBs can also be observed in a wide gamut of disorders with the same risk of DA use, such as progressive supranuclear palsy [52], multiple system atrophy [53], and pituitary adenomas [54] in addition to PD and RLS.

Another issue of undeniable importance in the risk of developing ICBs is the multiple co-medication regime. This is a crucial issue for PD patients that usually undergo a complex therapeutic scheme, but much less of an issue for RLS patients for which monotherapy is the rule. Thus, the DOMINION study showed that the combination of DA agonist and levodopa treatment induces a greater risk of ICDs [1]. The same study observed a higher risk in those patients with a higher levodopa dose, too. As far as the use of amantadine concerned, the DOMINION study demonstrated an association with ICDs [1] consistent with another study on pathological gambling in 1167 PD patients [55]. In this regard, these observations are contrary to those seen in a double-blind crossover study in which amantadine was actively administered to 17 PD patients with pathological gambling with beneficial effects [56].

There are no studies so far concerning the nature of DA agonist formulation and its association with ICBs, although some reports have hypothesized that long-acting drugs are associated with a lower risk of ICBs. However, in the above-mentioned study, transdermal rotigotine with putative long-lasting action is associated with the development of ICBs [47] similar to that observed for the other DA agonists. To date, no clear evidence is available for understanding the effect of dopaminergic drugs' half-life on ICDs.

Risk Factors

In the general population as well as in PD, younger age, poor socioeconomic status, maniac and depressive disorders, or alcohol or substance use have been recognized to be factors associated with the development of pathological gambling [57, 58]. Whereas on one side, DAs use is the stronger predictor of ICBs development (see the paragraph above), on the other hand, limited data are available about the other likely risk factors. In the last decade, great efforts have been made to identify intrinsic and environmental features of patients with impulsive disorders. Their recognition and prevention represent key advances in PD and RLS care limiting its subsequent socioeconomic consequences.

As stated above, both in the general population and in a large cohort of PD patient's, ICBs were independently associated with younger age [1, 59]. ICBs were also independently correlated with family history of gambling disorders, concurrent cigarette smoking, and single marital status [1]. Despite some evidence that males are more prone to gambling disorders in the general population; in the DOMINION study, there was no significant difference in gender amongst PD patients with ICBs. In this regard, the same study showed that females are more likely to express compulsive eating and shopping while men hypersexuality [1].

Recently, in a prospective cohort study, one hundred and sixty four PD patients with no previous impulsive deficiency treated with a DAs were followed longitudinally for 4-years in order to observe new-onset ICBs. 39.1% developed new-onset ICBs with a median onset time 23 months after DRT initiation. Even though baseline demographic characteristics were similar in patients with and without ICBs, subjects with ICBs had surprisingly a greater baseline prevalence of caffeine use and higher lifetime prevalence of cigarette smoking [60]. This finding appears remarkable in the light of the putative protective role of these habits in the development of PD [61].

Psychiatric symptoms such as depression, anxiety, obsessive-compulsive symptoms, disinhibition, and appetite disturbance are also associated with ICBs [62, 63]. For instance, pathological gambling correlates with two personality traits represented by high novelty seeking and high impulsivity [59]. These results point to the role of individual genetic background of DA system in the susceptibility to ICBs (see the next paragraph). Similarly, regardless of the pharmacological treatment, patients with RLS show preferences toward risk choices, as recently demonstrated in a case-control prospective study with 89 RLS patients [19]. The propensity to make greater impulsive choices under ambiguity, assessed by the Iowa Gambling task (IGT) [64], was comparable in drug-free and treated patients but it was significantly different compared to control voluntaries.

Genetics of Impulse Control Disorders

Theoretically, genes provide the first contribution to an individual's predisposition to impulsivity and the development of ICBs. Family and twin epidemiological

studies corroborate this general concept [65, 66]. Since DA system plays a crucial role in impulsivity and in addiction, greater attention has been paid to the exploration of the genetic background involved in dopaminergic neurotransmission. The association between DA and impulsivity is remarkable for some disorders, such as attention deficit hyperactivity disorder (ADHD). This disorder is characterized clinically by impulsivity, and amphetamine, a molecule able to increase the DA cleft release, is considered the gold standard for its treatment [67].

DA receptor (DR) polymorphisms have been studied in the general population and DRD2 Taq1A for instance, has been associated with ICBs [68]. However, recent functional imaging studies have not found clear differences in D2/D3 levels between healthy subjects and pathological gamblers as have been observed in substance abuse disorders [69]. Other DRs have been linked to ICBs. Among these, DRD1 polymorphisms have been associated with pathological gambling [70] while DRD4 polymorphism has been controversially reported in impulsive personality trait and ICBs subjects [71, 72]. Of interest, a recent study explored the allelic variants of DRD2, catechol-*O*-methyltransferase (COMT), and DA transporter (DAT) in 48 idiopathic PD patients without ICDs and 41 with ICDs. Surprisingly, no differences were observed in the frequency of variant of DRD2, COMT, and DAT1 between the two groups suggesting that polymorphisms of dopaminergic genes do not play a relevant role in the development of ICB at least in PD [73].

Other neurotransmitters seem to play a role in deficient impulse control and impulsive personality. Serotonin (5-HT), for instance, has been extensively studied [74–76]. Functional variants in the 5-HT transporter promoter gene (5-HTTLPR) have an effect on the neural mechanisms of disorders relating to impulse control [77] or in other neuropsychiatric disorders, such as anxiety or depression [78, 79]. Serotoninergic system is largely involved in aggressiveness [74, 76] or in impulsive behaviors as demonstrated in a Hungarian population cohort of healthy volunteers showing significant association with impulsiveness scales and genotype analysis for the receptor gene HTR1A [80]. Similarly, pathological gambling and risky-choice behaviors were considered in relation to alterations in serotonergic system functioning [81]. Consistent evidence has suggested that changes in brain-derived neurotrophic factor (BDNF) brain expression and release are involved in mood, anxiety, and eating disorders [82]. Genetic studies on the functional polymorphism Val66Met in the BDNF gene in patients and control subjects are in agreement with this hypothesis [83, 84]. The BDNF Val66Met may affect emotional decision-making performance assessed by using IGT in one hundred sixty-eight healthy subjects [85]. Indeed, BDNF largely determines the development and integrity of several systems, such as the noradrenergic, dopaminergic serotonergic, glutamatergic, and cholinergic neurotransmitter systems [86]. Additionally, BDNF has been found to exert important influences upon feeding behavior and compulsive hoarding [87].

Treatment

Since the best treatment for ICDs is prevention, patients with movement disorders and their caregivers should be warned about the risk of developing behavioral disorders. During follow-up visits, signs of ICBs should be actively searched for and some clinical tools have been recently developed for this purpose. The Questionnaire for Impulsive–Compulsive Disorders in Parkinson's Disease (QUIP), for instance, is a brief, self-report screening measure able to screen ICB positive patients which can be used as an additional evaluation tool [88].

Before starting a dopaminergic treatment, and above all one which involves a DA agonist, a premorbid history of substance abuse or impulsive-compulsive behaviors should be taken from patients and family members. A sustained monitoring of ICBs is mandatory in the long term, since the range latency onset encompasses a period of 1–84 months with a mean of 23 months as observed in PD [60, 89]. In a large cohort of RLS patients, a mean treatment duration of 9.5 months was observed before the development of ICBs [45] with a comparable timing in a small case series [90]. Physicians should discuss ICDs with their patients as early as possible before starting any DRT. Factors that have been associated with ICDs should be assessed in order to screen for individuals with a higher risk. In these patients, levodopa might be the first choice rather than a DA agonist since the probability of developing ICDs is lower [1]. Of note, patients with ICBs tend to hide their problem from the family most likely due to a lack of insight regarding the consequence of these behaviors, or for guilt.

Depending on the social impact of ICBs, non-pharmacological or DRT adjustment should be considered. One approach may be crucial and consist in limiting the economic consequences of the ICBs, mainly with regard to pathological gambling or compulsive shopping. Thus, by blocking access to a bank account or to a credit card, there is a good chance of controlling these kinds of ICBs. Consequently, a daily budget for patients, if she/he agrees, may be helpful and the spouse or the family could provide and manage it. Changes in pharmacotherapy should be considered primarily. Several studies suggest that a decrease or, if necessary, withdrawal of the DA agonists is efficacious [53, 89, 91]. Parkinsonian patients showing ICBs; however, seem to have a tendency to develop the so-called DA agonist withdrawal syndrome (DAWS). This is a disabling complication of DA agonist use [92], strongly linked to impulsive disorders, characterized by symptoms resembling those of other drug withdrawal syndromes, such as anxiety, panic attacks, agoraphobia, depression, dysphoria, diaphoresis, fatigue, pain, orthostatic hypotension, and drug cravings. Of note, this syndrome responds only to DA repletion and not to levodopa or other antiparkinsonian medications [93]. Of interest, a case of DAWS has been recently described in a patient with RLS [94]. With respect to DA agonists, several studies have not found any significant differences amongst these (e.g., ropinirole, pramipexole, or rotigone) and their association with ICBs [43, 89, 95].

Nowadays, no obviously effective drugs are available once ICBs have developed. Further, the role of amantadine has not yet been established since contrasting results were obtained by two different studies [1, 56]. Naltrexone, an antagonist at

mu and kappa opioid receptors, has been shown to be efficacious in treating substance addictions including alcohol and opioid dependence in general population [28]. Its efficacy was tested also in a case series of three PD patients with pathological gambling with positive outcomes [96].

Behavioral therapies, such as cognitive-behavioral, aversive, and motivational therapies have all shown efficacy in ICBs as evidenced in several trials in general population [97, 98]. In PD, a randomized controlled trial comparing up to 12 sessions of a cognitive-behavioral therapy to a waiting list control condition with standard medical care showed that behavioral therapy is effective in reducing the severity of ICBs [99].

Conclusions

The development of ICBs may have a serious impact on daily living and quality of life of patients and their families. Knowledge of predisposing factors, such as higher DA dosage, young age of PD or RLS onset, history of drug addiction, and a family history of gambling disorders is crucial for management of ICBs. Patients should be warned of potential behavioral side effects when starting with dopaminergic agents.

Further studies are essential to understand the pathophysiology of ICBs in movement disorder patients. Moreover, more effort is needed to identify risk factors for ICBs. Research in this field could be of vital importance for additional treatment options that are nowadays unfortunately limited.

In the future, genetic assessment of the DA or 5-HT system background of single individuals could represent a valid opportunity to identify patients with a strong possibility of developing ICBs, thereby excluding them from DA therapy or recommending that they undergo other non-pharmacological therapies. Indeed, DA agonist suspension could further complicate patient care through the development of DAWS. This side effect represents a considerable challenge for clinicians treating RLS or PD patients.

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References

1. Weintraub D, Koester J, Polenza MN, Siderowf AD, Stacy M, Voon V, Whetteckey J, Wunderlich GR, Lang AE. Impulse control disorders in Parkinson disease: a cross-sectional study of 3090 patients. Arch Neurol. 2010;67(5):589–95.
2. Schultz W. Responses of midbrain dopamine neurons to behavioral trigger stimuli in the monkey. J Neurophysiol. 1986;56:1439–61.
3. Björklund A, Dunnett SB. Dopamine neuron systems in the brain: an update. Trends Neurosci. 2007;30(5):194–202.

4. Galati S, Stanzione P, D'Angelo V, Fedele E, Marzetti F, Sancesario G, Procopio T, Stefani A. The pharmacological blockade of medial forebrain bundle induces an acute pathological synchronization of the cortico-subthalamic nucleus-globus pallidus pathway. J Physiol. 2009;587(Pt 18):4405–23.
5. Galati S, D'Angelo V, Olivola E, Marzetti F, Di Giovanni G, Stanzione P, Stefani A. Acute inactivation of the medial forebrain bundle imposes oscillations in the SNr: a challenge for the 6-OHDA model? Exp Neurol. 2010;225(2):294–301.
6. Prosperetti C, Di Giovanni G, Stefani A, Möller JC, Galati S. Acute nigro-striatal blockade alters cortico-striatal encoding: an in vivo electrophysiological study. Exp Neurol. 2013;247:730–6.
7. Galati S, Di Giovanni G. Neuroprotection in Parkinson's disease: a realistic goal? CNS Neurosci Ther. 2010;16(6):327–9.
8. Cools R. Dopaminergic modulation of cognitive function-implications for L-DOPA treatment in Parkinson's disease. Neurosci Biobehav Rev. 2006;30:1–23.
9. Paulus W, Schomburg ED. Dopamine and the spinal cord in restless legs syndrome: does spinal cord physiology reveal a basis for augmentation? Sleep Med Rev. 2006;10:185–96.
10. Allen RP, Earley CJ. The role of iron in restless legs syndrome. Mov Disord. 2007;22(Suppl 18):S440–8.
11. Grace AA, Bunney BS. The control of firing pattern in nigral dopamine neurons: burst firing. J Neurosci. 1984;4(11):2877–90.
12. Grace AA, Bunney BS. The control of firing pattern in nigral dopamine neurons: single spike firing. J Neurosci. 1984;4(11):2866–76.
13. Tobler PN, Dickinson A, Schultz W. Coding of predicted reward omission by dopamine neurons in a conditioned inhibition paradigm. J Neurosci. 2003;23(32):10402–10.
14. Grace AA, Bunney BS. Paradoxical GABA excitation of nigral dopaminergic cells: indirect mediation through reticulata inhibitory neurons. Eur J Pharmacol. 1979;59(3–4):211–8.
15. Ungless MA, Magill PJ, Bolam JP. Uniform inhibition of dopamine neurons in the ventral tegmental area by aversive stimuli. Science. 2004;303(5666):2040–2.
16. Schultz W, Apicella P, Ljungberg T, Romo R, Scarnati E. Reward-related activity in the monkey striatum and substantia nigra. Prog Brain Res. 1993;99:227–35.
17. Voon V, Pessiglione M, et al. Mechanisms underlying dopamine-mediated reward bias in compulsive behaviours. Neuron. 2010;65(1):135–42.
18. O'Sullivan SS, Wu K, Politis M, Lawrence AD, Evans AH, Bose SK, Djamshidian A, Lees AJ, Piccini P. Cue-induced striatal dopamine release in Parkinson's disease-associated impulsive-compulsive behaviours. Brain. 2011;134(Pt 4):969–78.
19. Bayard S, Langenier MC, Dauvilliers Y. Decision-making, reward-seeking behaviors and dopamine agonist therapy in restless legs syndrome. Sleep. 2013;36(10):1501–7.
20. American Psychiatric Association. Diagnostic and statistical manual of mental disorders: DSM-IV-TR. Washington, DC: American Psychiatric Association; 2000.
21. Evans AH, Strafella AP, Weintraub D, Stacy M. Impulsive and compulsive behaviors in Parkinson's disease. Mov Disord. 2009;24(11):1561–70.
22. Leeman RF, Billingsley BE, Potenza MN. Impulse control disorders in Parkinson's disease: background and update on prevention and management. Neurodegener Dis Manage. 2012;2 (4):389–400.
23. American Psychiatric Association. Diagnostic and statistical manual of mental disorders. 5th ed. Arlington, VA: American Psychiatric Association; 2013.
24. Grant JE, Brewer JA, Potenza MN. The neurobiology of substance and behavioral addictions. CNS Spectr. 2006;11(12):924–30.
25. Grant and Potenza. Impulse control disorders: clinical characteristics and pharmacological management. Ann Clin Psychiatry. 2004;16(1):27–34.
26. Moeller FG, Barratt ES, Dougherty DM, Schmitz JM, Swann AC. Psychiatric aspects of impulsivity. Am J Psychiatry. 2001;158(11):1783–93.

27. Hollander E, Wong CM. Obsessive-compulsive spectrum disorders. J Clin Psychiatry. 1995;56 Suppl 4:3–6; discussion 53–5.
28. Kim SW, Grant JE, Adson DE, Shin YC. Double-blind naltrexone and placebo comparison study in the treatment of pathological gambling. Biol Psychiatry. 2001;49(11):914–21.
29. Everitt BJ, Robbins TW. Neural systems of reinforcement for drug addiction: from actions to habits to compulsion. Nat Neurosci. 2005;8(11):1481–9.
30. Compton RJ. The interface between emotion and attention: a review of evidence from psychology and neuroscience. Behav Cogn Neurosci Rev. 2003;2(2):115–29.
31. Mogenson GJ, Yang CR. The contribution of basal forebrain to limbic-motor integration and the mediation of motivation to action. Adv Exp Med Biol. 1991;295:267–90.
32. Swanson CJ, Heath S, Stratford TR, Kelley AE. Differential behavioral responses to dopaminergic stimulation of nucleus accumbens subregions in the rat. Pharmacol Biochem Behav. 1997;58(4):933–45.
33. Baldo BA, Sadeghian K, Basso AM, Kelley AE. Effects of selective dopamine D1 or D2 receptor blockade within nucleus accumbens subregions on ingestive behavior and associated motor activity. Behav Brain Res. 2002;137(1–2):165–77.
34. Hernandez PJ, Andrzejewski ME, Sadeghian K, Panksepp JB, Kelley AE. AMPA/kainate, NMDA, and dopamine D1 receptor function in the nucleus accumbens core: a context-limited role in the encoding and consolidation of instrumental memory. Learn Mem. 2005;12(3): 285–95.
35. Cardinal RN, Parkinson JA, Lachenal G, Halkerston KM, Rudarakanchana N, Hall J, Morrison CH, Howes SR, Robbins TW, Everitt BJ. Effects of selective excitotoxic lesions of the nucleus accumbens core, anterior cingulate cortex, and central nucleus of the amygdala on autoshaping performance in rats. Behav Neurosci. 2002;116(4):553–67.
36. Schultz W, Dayan P, Montague PR. A neural substrate of prediction and reward. Science. 1997;275(5306):1593–9.
37. Waelti P, Dickinson A, Schultz W. Dopamine responses comply with basic assumptions of formal learning theory. Nature. 2001;412(6842):43–8.
38. Frosini D, Pesaresi I, Cosottini M, Belmonte G, Rossi C, Dell'Osso L, Murri L, Bonuccelli U, Ceravolo R. Parkinson's disease and pathological gambling: results from a functional MRI study. Mov Disord. 2010;25(14):2449–53.
39. Cilia R, Cho SS, van Eimeren T, Marotta G, Siri C, Ko JH, Pellecchia G, Pezzoli G, Antonini A, Strafella AP. Pathological gambling in patients with Parkinson disease is associated with fronto striatal disconnection: a path modeling analysis. Mov Disord. 2011;26:225–33.
40. Stefani A, Galati S, Brusa L, Pierantozzi M, Peppe A, Stanzione P. Pathological gambling from dopamine agonist and deep brain stimulation of the nucleus tegmenti pedunculopontine. BMJ Case Rep. 2010;18:2010.
41. Abler B, Hahlbrock R, Unrath A, Grön G, Kassubek J. At-risk for pathological gambling: imaging neural reward processing under chronic dopamine agonists. Brain. 2009;132(Pt 9):2396–402.
42. Petry NM, Stinson FS, Grant BF. Comorbidity of DSM-IV pathological gambling and other psychiatric disorders: results from the national epidemiologic survey on alcohol and related conditions. J Clin Psychiatry. 2005;66(5):564–74.
43. Voon V, Hassan K, Zurowski M, de Souza M, Thomsen T, Fox S, Lang AE, Miyasaki J. Prevalence of repetitive and reward-seeking behaviors in Parkinson disease. Neurology. 2006;67(7):1254–7.
44. Bostwick JM, Hecksel KA, Stevens SR, Bower JH, Ahlskog JE. Frequency of new-onset pathologic compulsive gambling or hypersexuality after drug treatment of idiopathic Parkinson disease. Mayo Clin Proc. 2009;84(4):310–6.
45. Cornelius JR, Tippmann-Peikert M, Slocumb NL, Frerichs CF, Silber MH. Impulse control disorders with the use of dopaminergic agents in restless legs syndrome: a case-control study. Sleep. 2010;33(1):81–7.

46. Voon V, Schoerling A, Wenzel S, Ekanayake V, Reiff J, Trenkwalder C, Sixel-Döring F. Frequency of impulse control behaviours associated with dopaminergic therapy in restless legs syndrome. BMC Neurol. 2011;28(11):117.
47. Schreglmann SR, Gantenbein AR, Eisele G, Baumann CR. Transdermal rotigotine causes impulse control disorders in patients with restless legs syndrome. Parkinsonism Relat Disord. 2012;18(2):207–9.
48. Fulda S, Szesny N, Ising M, Heck A, Grübl A, Lieb R, Reppermund S. Further evidence for executive dysfunction in subjects with RLS from a non-clinical sample. Sleep Med. 2011;12 (10):1003–7.
49. Bayard S, Yu H, Langenier MC, Carlander B, Dauvilliers Y. Decision making in restless legs syndrome. Mov Disord. 2010;25(15):2634–40.
50. Fulda S, Beitinger ME, Reppermund S, Winkelmann J, Wetter TC. Short term attention and verbal fluency is decreased in restless legs syndrome patients. Mov Disord. 2010;25:2641–8.
51. Evans AH, Butzkueven H. Dopamine agonist-induced pathological gambling in restless legs syndrome due to multiple sclerosis. Mov Disord. 2007;22(4):590–1.
52. O'Sullivan SS, Djamshidian A, Ahmed Z, Evans AH, Lawrence AD, Holton JL, Revesz T, Lees AJ. Impulsive-compulsive spectrum behaviors in pathologically confirmed progressive supranuclear palsy. Mov Disord. 2010;25(5):638–42.
53. Klos KJ, Bower JH, Josephs KA, Matsumoto JY, Ahlskog JE. Pathological hypersexuality predominantly linked to adjuvant dopamine agonist therapy in Parkinson's disease and multiple system atrophy. Parkinsonism Relat Disord. 2005;11(6):381–6.
54. Martinkova J, Trejbalova L, Sasikova M, Benetin J, Valkovic P. Impulse control disorders associated with dopaminergic medication in patients with pituitary adenomas. Clin Neuropharmacol. 2011;34(5):179–81.
55. Lee JY, Kim JM, Kim JW, Cho J, Lee WY, Kim HJ, Jeon BS. Association between the dose of dopaminergic medication and the behavioral disturbances in Parkinson disease. Parkinsonism Relat Disord. 2010;16(3):202–7.
56. Thomas A, Bonanni L, Gambi F, Di Iorio A, Onofrj M. Pathological gambling in Parkinson disease is reduced by amantadine. Ann Neurol. 2010;68(3):400–4.
57. Lim SY, Evans AH, Miyasaki JM. Impulse control and related disorders in Parkinson's disease: review. Ann N Y Acad Sci. 2008;1142:85–107.
58. Shaffer HJ, Martin R. Disordered gambling: etiology, trajectory, and clinical considerations. Annu Rev Clin Psychol. 2011;7:483–510.
59. Johansson A, Grant JE, Kim SW, Odlaug BL, Götestam KG. Risk factors for problematic gambling: a critical literature review. J Gambl Stud. 2009;25(1):67–92.
60. Bastiaens J, Dorfman BJ, Christos PJ, Nirenberg MJ. Prospective cohort study of impulse control disorders in Parkinson's disease. Mov Disord. 2013;28(3):327–33.
61. Tanner CM. Advances in environmental epidemiology. Mov Disord. 2010;25(Suppl 1): S58–62.
62. Voon V, Sohr M, Lang AE, Potenza MN, Siderowf AD, Whetteckey J, Weintraub D, Wunderlich GR, Stacy M. Impulse control disorders in Parkinson disease: a multicenter case-control study. Ann Neurol. 2011;69(6):986–96.
63. Pontone G, Williams JR, Bassett SS, Marsh L. Clinical features associated with impulse control disorders in Parkinson disease. Neurology. 2006;67:1258–61.
64. Brand M, Labudda K, Markowitsch HJ. Neuropsychological correlates of decision-making in ambiguous and risky situations. Neural Netw. 2006;19(8):1266–76.
65. Kreek MJ, Nielsen DA, Butelman ER, LaForge KS. Genetic influences on impulsivity, risk taking, stress responsivity and vulnerability to drug abuse and addiction. Nat Neurosci. 2005;8(11):1450–7.
66. Lobo DS, Kennedy JL. Genetic aspects of pathological gambling: a complex disorder with shared genetic vulnerabilities. Addiction. 2009;104(9):1454–65.
67. Sagvolden T, Sergeant JA. Attention deficit/hyperactivity disorder—from brain dysfunctions to behaviour. Behav Brain Res. 1998;94(1):1–10.

68. Comings DE, Rosenthal RJ, Lesieur HR, Rugle LJ, Muhleman D, Chiu C, Dietz G, Gade R. A study of the dopamine D2 receptor gene in pathological gambling. Pharmacogenetics. 1996;6(3):223–34.
69. Boileau I, Payer D, Chugani B, Lobo D, Behzadi A, Rusjan PM, Houle S, Wilson AA, Warsh J, Kish SJ, Zack M. The D2/3 dopamine receptor in pathological gambling: a positron emission tomography study with [11C]-(+)-propyl-hexahydro-naphtho-oxazin and [11C] raclopride. Addiction. 2013;108(5):953–63.
70. da Silva Lobo DS, Vallada HP, Knight J, Martins SS, Tavares H, Gentil V, Kennedy JL. Dopamine genes and pathological gambling in discordant sib-pairs. J Gambl Stud. 2007;23 (4):421–33.
71. Benjamin J, Li L, Patterson C, Greenberg BD, Murphy DL, Hamer DH. Population and familial association between the D4 dopamine receptor gene and measures of novelty seeking. Nat Genet. 1996;12(1):81–4.
72. Pogue-Geile M, Ferrell R, Deka R, Debski T, Manuck S. Human novelty-seeking personality traits and dopamine D4 receptor polymorphisms: a twin and genetic association study. Am J Med Genet. 1998;81(1):44–8.
73. Vallelunga A, Flaibani R, Formento-Dojot P, Biundo R, Facchini S, Antonini A. Role of genetic polymorphisms of the dopaminergic system in Parkinson's disease patients with impulse control disorders. Parkinsonism Relat Disord. 2012;18(4):397–9.
74. Lee R, Coccaro E. Neurobiology of impulsive aggression: focus on serotonin and the orbitofrontal cortex. New York, NY: Cambridge University Press; 2007.
75. Boulougouris V, Malogiannis I, Lockwood G, Zervas I, Di Giovanni G. Serotonergic modulation of suicidal behaviour: integrating preclinical data with clinical practice and psychotherapy. Exp Brain Res. 2013;230(4):605–24.
76. Bortolato M, Pivac N, Muck Seler D, Nikolac Perkovic M, Pessia M, Di Giovanni G. The role of the serotonergic system at the interface of aggression and suicide. Neuroscience. 2013;236:160–85.
77. Silva H, Iturra P, Solari A, Villarroel J, Jerez S, Jiménez M, Galleguillos F, Bustamante ML. Fluoxetine response in impulsive-aggressive behavior and serotonin transporter polymorphism in personality disorder. Psychiatr Genet. 2010;20(1):25–30.
78. Lowry CA, Hale MW, Evans AK, Heerkens J, Staub DR, Gasser PJ, Shekhar A. Serotonergic systems, anxiety, and affective disorder: focus on the dorsomedial part of the dorsal raphe nucleus. Ann N Y Acad Sci. 2008;1148:86–94.
79. Philibert RA, Sandhu H, Hollenbeck N, Gunter T, Adams W, Madan A. The relationship of 5HTT (SLC6A4) methylation and genotype on mRNA expression and liability to major depression and alcohol dependence in subjects from the Iowa adoption studies. Am J Med Genet B Neuropsychiatr Genet. 2008;147B(5):543–9.
80. Benko A, Lazary J, Molnar E, Gonda X, Tothfalusi L, Pap D, Mirnics Z, Kurimay T, Chase D, Juhasz G, Anderson IM, Deakin JF, Bagdy G. Significant association between the C (-1019)G functional polymorphism of the HTR1A gene and impulsivity. Am J Med Genet B Neuropsychiatr Genet. 2010;153B(2):592–9.
81. Juhasz G, Downey D, Hinvest N, Thomas E, Chase D, Toth ZG, Lloyd-Williams K, Mekli K, Platt H, Payton A, Bagdy G, Elliott R, Deakin JF, Anderson IM. Risk-taking behavior in a gambling task associated with variations in the tryptophan hydroxylase 2 gene: relevance to psychiatric disorders. Neuropsychopharmacology. 2010;35(5):1109–19.
82. Gratacòs M, González JR, Mercader JM, de Cid R, Urretavizcaya M, Estivill X. Brain-derived neurotrophic factor Val66Met and psychiatric disorders: meta-analysis of case-control studies confirm association to substance-related disorders, eating disorders, and schizophrenia. Biol Psychiatry. 2007;61(7):911–22.
83. Minelli A, Zanardini R, Bonvicini C, Sartori R, Pedrini L, Gennarelli M, Bocchio-Chiavetto L. BDNF serum levels, but not BDNF Val66Met genotype, are correlated with personality traits in healthy subjects. Eur Arch Psychiatry Clin Neurosci. 2011;261(5):323–9.

84. Frustaci A, Pozzi G, Gianfagna F, Manzoli L, Boccia S. Meta-analysis of the brain-derived neurotrophic factor gene (BDNF) Val66Met polymorphism in anxiety disorders and anxiety-related personality traits. Neuropsychobiology. 2008;58(3–4):163–70.
85. Kang JI, Namkoong K, Ha RY, Jhung K, Kim YT, Kim SJ. Influence of BDNF and COMT polymorphisms on emotional decision making. Neuropharmacology. 2010;58(7):1109–13.
86. Spenger C, Hyman C, Studer L, Egli M, Evtouchenko L, Jackson C, Dahl-Jørgensen A, Lindsay RM, Seiler RW. Effects of BDNF on dopaminergic, serotonergic, and GABAergic neurons in cultures of human fetal ventral mesencephalon. Exp Neurol. 1995;133(1):50–63.
87. Timpano KR, Schmidt NB, Wheaton MG, Wendland JR, Murphy DL. Consideration of the BDNF gene in relation to two phenotypes: hoarding and obesity. J Abnorm Psychol. 2011;120(3):700–7.
88. Weintraub D, Hoops S, Shea JA, Lyons KE, Pahwa R, Driver-Dunckley ED, Adler CH, Potenza MN, Miyasaki J, Siderowf AD, Duda JE, Hurtig HI, Colcher A, Horn SS, Stern MB, Voon V. Validation of the questionnaire for impulsive-compulsive disorders in Parkinson's disease. Mov Disord. 2009;24(10):1461–7.
89. Gallagher DA, O'Sullivan SS, Evans AH, Lees AJ, Schrag A. Pathological gambling in Parkinson's disease: risk factors and differences from dopamine dysregulation. An analysis of published case series. Mov Disord. 2007;22(12):1757–63.
90. Tippmann-Peikert M, Park JG, Boeve BF, Shepard JW, Silber MH. Pathologic gambling in patients with restless legs syndrome treated with dopaminergic agonists. Neurology. 2007;68(4):301–3.
91. Nirenberg MJ, Waters C. Compulsive eating and weight gain related to dopamine agonist use. Mov Disord. 2006;21(4):524–9.
92. Rabinak CA, Nirenberg MJ. Dopamine agonist withdrawal syndrome in Parkinson disease. Arch Neurol. 2010;67(1):58–63.
93. Pondal M, Marras C, Miyasaki J, Moro E, Armstrong MJ, Strafella AP, Shah BB, Fox S, Prashanth LK, Phielipp N, Lang AE. Clinical features of dopamine agonist withdrawal syndrome in a movement disorders clinic. J Neurol Neurosurg Psychiatry. 2013;84(2):130–5.
94. Dorfman BJ, Nirenberg MJ. Dopamine agonist withdrawal syndrome in a patient with restless legs syndrome. Parkinsonism Relat Disord. 2013;19(2):269–70.
95. Weintraub D, Siderowf AD, Potenza MN, Goveas J, Morales KH, Duda JE, Moberg PJ, Stern MB. Association of dopamine agonist use with impulse control disorders in Parkinson disease. Arch Neurol. 2006;63(7):969–73.
96. Bosco D, Plastino M, Colica C, Bosco F, Arianna S, Vecchio A, Galati F, Cristiano D, Consoli A, Consoli D. Opioid antagonist naltrexone for the treatment of pathological gambling in Parkinson disease. Clin Neuropharmacol. 2012;35(3):118–20.
97. McConaghy N, Armstrong MS, Blaszczynski A, Allcock C. Controlled comparison of aversive therapy and imaginal desensitization in compulsive gambling. Br J Psychiatry. 1983;142:366–72.
98. Grant JE, Donahue CB, Odlaug BL, Kim SW. A 6-month follow-up of imaginal desensitization plus motivational interviewing in the treatment of pathological gambling. Ann Clin Psychiatry. 2011;23(1):3–10.
99. Okai D, Askey-Jones S, Samuel M, O'Sullivan SS, Chaudhuri KR, Martin A, Mack J, Brown RG, David AS. Trial of CBT for impulse control behaviors affecting Parkinson patients and their caregivers. Neurology. 2013;80(9):792–9.

Management of RLS During Pregnancy

18

Mauro Manconi

Historical Background

Few years before that the term "restless legs syndrome" (RLS) was coined by the Swedish neurologist Ekbom in 1945 [1], two German physicians named Mussio-Fournier and Rawak [2] recognized a strange set of symptoms characterized by "pruritus, urtikaria and parästhetischer" of the lower limbs in three members of the same family. A women belonging to the family presented a typical exacerbation of symptoms during pregnancy. This was probably the first description of a temporal transient association between RLS and pregnancy. Few years later, Karl Axel Ekbom himself confirmed that RLS was particularly frequent during pregnancy, founding a prevalence of 11.3% in a sample of 486 pregnant women [1]. Afterward, Jolivet in 1953 addressed this topic in his medical dissertation; investigating 100 pregnant women he relived the syndrome in 27 of them [3]. The son of Ekbom replicated his father's study on 202 pregnant women (1960), diagnosing RLS in 12% of them [4]. The first structured survey was published in the British Medical journal in 1988 by Goodman et al. [5], herein in 19% of 500 pregnant women was ascertained an RLS phenotype. We have to wait until 2004 for the first epidemiological study performed by using the standard diagnostic criteria for RLS (1995), herein Manconi et al. [6] interviewed 606 women at the time of delivery, 26% of them reported to have suffered of RLS in some periods in their pregnancy.

Nowadays, it is well established that pregnancy is a strong risk factor for a transient form of RLS, and this raises three important clinical issues: the differential diagnosis with other pregnancy-related sensitive symptoms of lower limbs such as

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nocturnal cramps, sleep positional discomfort, ankle edema, radiculopathy, and venous stasis; the effect of the symptoms and of the possible sleep deprivation on the pregnancy outcome, and overall the therapeutic management of RLS during pregnancy and lactation with the clear safety limitation in using a pharmacological approach.

Epidemiology

More than 20 epidemiological investigations with the clear aim to assess the prevalence of RLS during pregnancy have been carried out so far (Table 18.1). Most of the studies were conducted in Europe and few in Asia and America. The prevalence rate resulted from these surveys ranges between 3 and 34% [7, 8]. Although the wide variability of these rates, all the studies agree on the fact that during pregnancy RLS is much more frequent than in age-matched non-pregnant women. Indeed, none of the studies included a control group of non-pregnant women; however, the prevalence obtained during pregnancy is clearly higher than the prevalence of RLS known by the available epidemiological literature in similar population. Moreover, prospective studies clearly relieved the transient nature of the symptoms, strictly associated with the pregnancy period in most of the women. This strongly suggests a pathogenetic role of pregnancy in this peculiar form of RLS. The large variability of the prevalence rates coming from the above-mentioned studies is well explained by the different methodological approaches used. The size of the population analyzed ranges broadly between 100 and more than 19,000 women [3, 7]. Around half of the studies assessed the RLS prevalence by using a self-administered questionnaire, while the remaining half of them by a face to face interview, with the result of a more accurate discrimination between real RLS and possible mimics in the second case. The oldest studies and few of the modern ones did not used the standard criteria to diagnose RLS. Even when precise and commonly accepted diagnostic criteria were used, the threshold of the frequency of occurrence of symptoms to classify a woman as RLS affected was often not mentioned or different among the studies. The latter issued raised the question if a woman who experienced RLS one or very few times during pregnancy should be considered or not as affected. Cross-sectional investigations conducted during pregnancy could underestimate the cumulative prevalence compare to prospective studies; this is due to the fact that the prevalence rate is asymmetrical distributed across pregnancy [6]. Lastly, several studies did not discriminate between women already affected by RLS before the considered pregnancy and women who experienced RLS symptoms for the first time during pregnancy, with the result that part of the final prevalence rate indeed includes also a percentage of women affected by a regular idiopathic RLS, which reemerges or maintains during pregnancy. Despite all these potential bias, it is reasonable to estimates the cumulative prevalence of

Table 18.1 Epidemiological studies on restless legs and pregnancy

Authors	Year	Country	Sample size	IRLSSG criteria + Face to face interview	Prevalence (%)
Ekbom [1]	1945	Sweden	486		11.3
Jolivet [3]	1953	France	100		27
Ekbom [4]	1960	Sweden	202		12.4
Goodman et al. [5]	1988	England	500		19
Suzuki et al. [22]	2003	Japan	16528		19.9
Manconi et al. [6]	2004	Italy	606	•	26
Tunc et al. [9]	2007	Turkey	146	•	26
Harano et al. [7]	2008	Japan	19441		2.9
Sikandar et al. [19]	2009	Pakistan	271	•	30
Facco et al. [47]	2010	US	189		17.5
Alves et al. [23]	2010	Brazil	524	•	13.5
Neau et al. [84]	2010	France	1022		23.7
Neau et al. [85]	2010	France	186		32.3
Ismailogullari et al. [86]	2010	Turkey	983	•	10.5
Uglane et al. [8]	2011	Norway	251		34
Balendran et al. [20]	2011	Australia	211		22.5
Sarberg et al. [13]	2012	Sweden	500	•	32
Chen et al. [87]	2012	Taiwan	461	•	10.4
Ko et al. [88]	2012	Korea	689		19.4
Vahdat et al. [89]	2013	Iran	443	•	17.8
Ramirez et al. [33]	2013	Peru	218	•	18.4
Minar et al. [90]	2013	Slovak	300		31.3
Hubner et al. [10]	2013	Switzerland	501	•	12
Wesstrom et al. [37]	2014	Sweden	1428		18.5
Shang et al. [91]	2014	China	1585	•	11.2
Terzi et al. [45]	2015	Turkey	600	•	13.8
Mindell et al. [92]	2015	US	2427		24
Ma et al. [35]	2015	China	3781	•	11.9

IRLSSSG International Restless Legs Study Group

RLS during pregnancy around 20–25%, which is also the percentage obtained by the studies that used the standard diagnostic criteria ascertained by a face to face interview on a population larger than 500 women and belonging to western countries [6, 9, 10]. This means that RLS is at least threefold more prevalent in pregnant vs non-pregnant women [11].

Course and Prognosis

Among women with pregnancy-related RLS, around one third are already affected by RLS before pregnancy or already experienced the symptoms some time in their life [6]. Around 70–80% of these women report a worsening of RLS symptoms during pregnancy [6]. Considering the new onset cases, the incidence of RLS increases across pregnancy, with the highest rate reached in the third trimester, with an abrupt resolution of the symptoms occurring around the delivery, with very few cases continuing to be affected even in the puerperium [6, 10]. While the short-term prognosis of RLS is benign, the long-term one seems to be less favorable. After a follow up of approximately 7 years, Cesnik et al. [12] demonstrated that women who suffered of RLS during pregnancy have a 4 fold higher risk to develop an "idiopathic" RLS form compared to women who did not experience a pregnancy-related RLS. Besides, more than 60% of women who experienced RLS during pregnancy suffered of a relapse of RLS during a second pregnancy, while this percentage resulted of only around 3% for women who did not refer symptoms in a previous pregnancy [12]. Later on, Sarberg et al. [13], although after a shorter follow up of 3 years, substantially confirmed these results. The results obtained by these two long-term prospective studies evidently suggest a genetic predisposition behind the pregnancy RLS form [14].

Pathogenetic Hypotheses

The mechanism behind the pregnancy-related form is unknown. Few pathogenetic hypotheses have been postulated and concern the possible role of sexual hormones and iron deficiency during pregnancy [15, 16]. Particularly during the third trimester of pregnancy, when RLS symptoms are worst, estradiol, prolactin, and progesterone reach the highest blood level, and ferritin decreases at its minimum level [11]. Although with a pulsatile trend, prolactin keeps to stay at high levels also during puerperium, while estrogens and progesterone fall down quite dramatically around delivery, together with RLS symptoms [17]. Iron storage restore much gradually after delivery following a trend less comparable with RLS symptoms [18]. No solid experimental data are available in sustaining any role of the above-mentioned factors. The general idea consists in a genetic predisposition to the disease, while pregnancy may act as a precipitating factor for the symptoms appearance [11]. The genetic theory is supported by three findings: first, almost all pregnant women with a preexisting form of RLS get worst during pregnancy [6]; second, women with new pregnancy-related RLS have a high chance to develop an idiopathic not pregnancy-related RLS in the future [12, 13]; lastly, the chances to have a close familiar member affected by RLS is much higher in pregnant women with RLS than in pregnant women not affected [6, 19, 20]. The genetic hypothesis could be tested, and a study on the frequency of the already known allelic variants associated with idiopathic RLS is warrant [14, 21].

Other factors found to be associated with RLS during pregnancy are: leg cramps [6, 9], snoring [6] and daytime somnolence [6, 9, 22]. More uncertain is the role of age, smoking, body max index, and iron deficiency; herein, some studies found a significant differences in the above-listed parameters between pregnant with and without RLS [6, 19, 20, 22, 23]. Interesting is the influence of previous pregnancies on the chance to develop a pregnancy-related RLS form. Women who experienced RLS during a previous pregnancy have a higher risk for relapse in a following pregnancy [12]. The role of multiparity per sè is less clear. In more than few studies, the number of previous pregnancies was not a significant risk factor for RLS during the investigated pregnancy. However, a large epidemiological investigation found that multiparity per sè is a risk factor for the idiopathic, not pregnancy related, RLS form [24].

Consequences

It is well known that idiopathic RLS has a significant impact on quality of life [25]. The impact of RLS is mainly mediated by the evening/night restlessness which limits all activities that require rest and reduces duration and quality of sleep. In a long-term prospective, RLS has a clear impact also on mood [26] and cognitive functions [27], while its role as a cardiovascular risk is likely but still under investigation [28–30]. Of course, the impact of RLS depends on the severity of symptoms, including its frequency and duration. Only few studies assessed the severity of RLS during pregnancy, finding unexpected results showing that in around 50% of women the standard RLS severity scale scored their symptoms as severe or very severe [10]. Prevalence of insomnia among pregnant women with RLS is higher than in women free of RLS [6]. In turn, a pour sleep quality during pregnancy is associated with a lower level of quality of life and possible consequences on pregnancy outcome. Preterm birth is more prevalent in women with pour quality of sleep during pregnancy compared to women without sleep complaint [31, 32]. Ramirez et al. [33] firstly found a significant association between RLS during pregnancy and pre-eclampsia. The other relevant pregnancy-related complications such as gestation diabetes, gestational hypertension, and eclampsia need still to be investigated in their relationship with RLS [34–36].

Recent data suggest that RLS during pregnancy significantly increases the risk of perinatal depression, which are common and important complications affecting around 10–15% of pregnant women in different level of severity [37]. When untreated, perinatal depression increases the risk of preterm delivery, smoking and substance use, shortening of breast feed, abusive behavior toward children, and can have significant negative effects on partner's relationship and emotional and cognitive development of infants [38].

Management of RLS During Pregnancy

The problem of RLS management during pregnancy has been underestimated for a long time, this was due to three important aspects: the pour knowledge of the syndrome, especially among gynecologists, which led to under diagnose the disease; the frequent transiency of symptoms which usually disappear around delivery, that led to consider RLS as a "normal" pregnancy-related phenomenon not well distinguishable from others such as ankle edema, fatigue, or insomnia, and therefore to be endured with patience by women until the end of pregnancy; the false belief of the low severity of symptoms. Indeed, symptoms can be severe with significant impact on women and potentially on the outcome of pregnancy, and, more importantly, even when RLS is mild and does not need to be treated, it should be recognize and well explained to women, who often are simply worried about their symptoms. Concerning this latter issue, the first and crucial step for a physician is to perform an accurate diagnosis of RLS. The recommendation is to use always the standard diagnostic criteria currently valid for idiopathic RLS [39]. There are no reasons to consider these criteria inadequate for pregnancy-related RLS. In both, idiopathic and pregnancy-related forms, the anatomical distribution and the other main features of symptoms are similar and a possible genetic vulnerability for RLS is suggested also for the pregnancy-related form, which is often associated with a positive family history and represents a risk for the onset of an idiopathic RLS in the future [12, 40]. The last version of the diagnostic criteria included a new fifth criterion specifically established to limit the misdiagnosis of the disease, reminding to always rule out possible mimics [41]. This is particularly necessary during pregnancy, in order to discriminate between true RLS and other frequent complications such as positional discomfort, leg cramps, venous stasis, ankle edema, and compression neuropathies [42]. However, should be taken into account that all the above-mentioned conditions may also co-occur with a real RLS.

The second step, after the recognition of RLS, is to quantify the severity of symptoms and their impact on the quality of life of women. Using the current definition of RLS, symptoms should be considered as clinically relevant when "significant distress or impairment in social, occupational, educational, or other important areas of functioning by its impact on sleep, mood, cognition, health, daily activities, behavior, or energy/vitality" [41]. Also during pregnancy, the severity of symptoms can be measured using the standard RLS rating scale validated by the international RLS study group [43]. This instrument consists in a 10 questions, self-administered questionnaire, which produces a final score ranging from 0 to 40, where a score between 10 and 20 corresponds to "moderate," from 20 to 30 to "severe" and over 30 to "very severe." The frequency of occurrence of symptoms is another relevant feature to be considered in the management of RLS during pregnancy; a suggested threshold for a clinical significance is twice per week.

Non-pharmacological Management During Pregnancy

After an accurate diagnosis and an appropriate quantification of symptoms, before considering a potential unsafe pharmacological approach, few possible non-pharmacological strategies should be contemplated [44]. In infrequent and mild cases, a simple reassurance by the physician on the nature and prognosis of symptoms can be sufficient.

The presence of factors already known to induce or aggravate RLS should be carefully checked and when is possible removed. Among these, a particular attention should be given to the comorbidity with other sleep disorders, especially sleep apnea, and primary insomnia [45–47]. Alcohol and tobacco, even if not directly linked to RLS, should be limited or better avoided for their impact on sleep quality. A careful pharmacological history must be collected, this to identify possible drugs known to induce or exacerbate RLS [48]. Among these, antidepressants, neuroleptics, antiemetics, and sedative antihistamines are the most important to be recognized [49, 50].

Moderate and safe physical exercise, preferably not too close to the bedtime, should be encouraged based on their beneficial effects on idiopathic RLS [51, 52]. Non-traumatic activity, such as yoga, water aerobics, or walking, is warrant prior consent of the gynecologist [44]. Massages of legs might be beneficial in primary RLS and are potential helpful during pregnancy.

Despite their discrete safety during pregnancy, no adequate evidence for the efficacy of vitamins (folate, C, D, E) or magnesium are available for non-pregnant RLS. Folate is commonly supplemented in pregnant women, overall for their protective property on neuronal tube defects. Except in one single small study, no solid evidences support the effectiveness of folate in RLS [16, 53].

Iron Supplementation

A special consideration has to be dedicated to iron deficiency. A pathogenetic linkage between iron and idiopathic RLS is supported by several studies [54–56] and pregnancy per se is the second cause of iron deficiency after abundant menstruation, especially in late pregnancy, when RLS symptoms are more prevalent or more severe. This is due to the expansion of the maternal red cells and the growth of fetus and placenta. Regardless to RLS, an oral iron supplementation is suggested for all pregnancies when ferritin value is lower than 30 mcg/L [57]. A threshold value of ferritin for pregnant women with RLS is not established. However, clinical guideline for management of RLS during pregnancy advise to supplement by a single of double daily dose of 65 mg of oral ferrous sulfate when ferritin levels drop below 75 mcg/L [44]. Despite oral iron adsorption is facilitate by concomitant intake of vitamin C, the safety of vitamin C during pregnancy is still debated [58]. An overload of iron is dangerous for women and their toddlers, and ferritin values should be rechecked regularly after starting with iron supplementation.

Consensus guideline suggested to consider intravenous (I.V.) iron administration when ferritin values are lower than 30 mcg/L or when oral iron administration was ineffective in correcting ferritin levels because of a pour intestinal adsorption [44].

Different types of I.V. iron are available on the market (dextran, sucrose, gluconate, and carboxy-maltose). The therapeutic dosage ranges between 500 and 1000 mg in single or multiple boluses. Physicians should be aware that recent febrile states or chronic inflammation might increase ferritin levels, and that in these cases a better indicator of iron storage is the iron percentage saturation. If women receive I.V. iron for the first time, than a particular attention has to be given to rare but severe anaphylactic reactions, and the administration needs to be performed at facilities where expert staff can promptly manage this complication. Except of this latter rare eventuality, iron supplementation during pregnancy is generally considered fairly safe. On the other hand, although some positive results mainly concerning I.V. iron, the effectiveness of iron in non-pregnant RLS need to be further consolidated. Few open label studies have been performed on the efficacy of I.V. iron in RLS during pregnancy, reporting encouraging results and no serious adverse events [59]. Large randomized controlled studies with I.V. and oral iron, in both idiopathic and pregnancy-related forms are needed.

Pharmacological Management During Pregnancy and Lactation

No structured investigations have been conducted so far on the pharmacological treatment of RLS during pregnancy. The information collected in the present paragraph come from the literature on idiopathic RLS to whom it concerns the efficacy, while from the literature of other diseases such as epilepsy, Parkinson disease or psychiatric conditions to whom it concerns the issue of safety. Based on the absence of specific literature, but motivated by an urgency to treat severe cases of RLS during pregnancy, the International Study Group endorsed a task force composed by nine experts in the field in order to suggest clinical practice guideline on the RLS management during pregnancy and lactation [44]. This paragraph is mostly based on the published results of this consensus. Figure 18.1 shows the final algorithm elaborated by the consensus which might help in RLS treatment during pregnancy and lactation.

Irrespective to the drug category, few general recommendations regarding the pharmacological approach of RLS during pregnancy should be considered. Currently, only three compounds have been approved for the treatment of idiopathic RLS: ropinirole, pramipexole, and rotigotine, all others are considered "off-label." These medications and most of the drugs used in idiopathic RLS belong to the category C, which includes drugs not recommended to be used during pregnancy because of pour knowledge about their effects on fetus or because of already recognized potential damages on fetus. Based on this, a pharmacological treatment should be indicated only for women with a real clinical significant RLS, which generally occurs more than twice per week, with a RLS rating score higher than 20 (severe or very severe), and without a previous response to a non-pharmacological intervention, included the iron one if needed [44]. Moreover, a drug treatment should be administered at lowest effective dose, for the shortest period as possible,

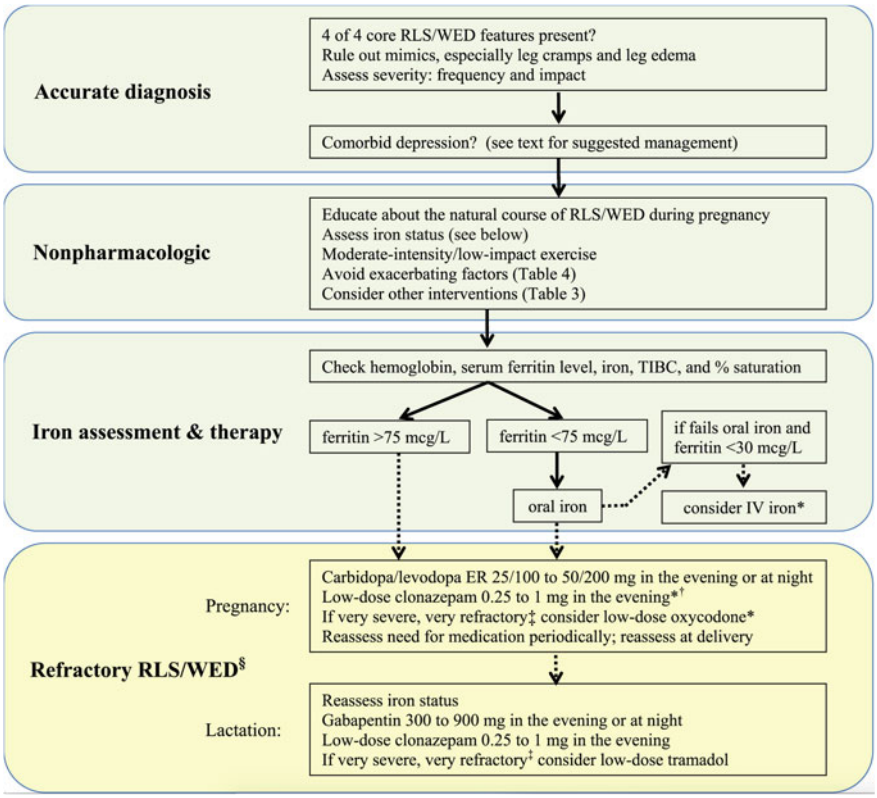

Fig. 18.1 Algorithm for the diagnosis and management of RLS/WED during pregnancy and lactation. *Dotted arrows*: proceed only after assessment of severity, risks, and benefits by provider and patient. *After 1st trimester. †Avoid concurrent use with diphenhydramine or anticonvulsants. §Refractory: an inadequate response to at least one nonpharmacologic intervention and iron (if ferritin <75 mcg/L), tried over an adequate period of time. ‡Very severe, very refractory: a score of >30 on the International RLS Study Group rating scale and failure to respond to at least one nonpharmacologic treatment, iron (if ferritin <75 mcg/L), and one non-opioid pharmacologic treatment. Abbreviations: ER, extended release; IV, intravenous; % saturation, percent iron saturation; RLS, restless legs syndrome; TIBC, total iron binding capacity; WED, Willis–Ekbom disease (From [44], with permission.)

and not during the first trimester of pregnancy when the risk of embryonal malformation is the highest. In case of infrequent RLS an on-demand treatment can be considered. Once a drug therapy is started, physicians must follow up women regularly at short intervals.

Dopamine-Agonists

Based on the published evidences, dopaminergic drugs are considered the first line medication in idiopathic RLS [60]. Except for the long-term risk of augmentation, dopamine-agonists (DA) are also well tolerated in non-pregnant RLS. What limit

their use in pregnancy-related RLS is the scarcity of safety data when used during pregnancy. Very few information are available for the use of DA in juvenile Parkinson Disease [61–63] and in Segawa syndrome [64, 65]. One single retrospective study is available on the use of DA during pregnancy to treat RLS [66]. In none of the mentioned cases major malformations or other adverse outcomes are reported. More literature is available for L-Dopa, which appears to be safe during pregnancy in its combination with carbidopa, while its combination with benserazide might induce alteration in skeletal development and should be avoided [44]. The use of the two DA bromocriptine and cabergoline during the first trimester of pregnancy is largely documented by the literature on hyperprolactinemia; however, both of the drugs are ergoline-derivatives and can induce severe fibrotic reactions [67, 68]. Pergolide is almost in disuse for the same reason. Lastly, should be highlighted that DA are inhibitors of prolactin secretion and may interfere with lactation, therefore, are not indicated for the puerperium of women who breastfeed. Based on this, low doses (25/100–50/200 mg) carbidopa/levodopa, even better in its extended release, can be considered for the treatment of severe RLS during late pregnancy, while for the other non-ergot DA more data on safety are needed [44].

Alpha-2-Delta Ligands

Although not available in certain countries, gabapentin, and gabapentin enacarbil, due for their efficacy and tolerance, have also been considered a first line medication in idiopathic RLS [60, 69]. However, like for DA, the real limitation for their use pertain the scarcity of safety data during pregnancy, which has been judged "insufficient to reach a consensus" [44]. Although the presence of some reassuring data on safety of alpha-2-delta drugs used during pregnancy in epileptic women, other evidences coming from animal research reported possible impaired synaptogenesis in mice receiving very high dose of gabapentin [70]. However, because gabapentin is estimated to pass scarcely into the maternal milk, it might be suitable for severe RLS in the puerperium at an evening daily dose ranging between 300 and 900 mg [71].

Benzodiazepines

Benzodiazepines (BDZ), especially clonazepam, are commonly used in idiopathic RLS even if they are not officially approved and considered as third line treatment after DA, alpha-2-delta ligands, or even opioids [60]. Despite the absence of large randomized controlled studies on clonazepam in RLS, empiric evidences and small studies suggest that it is effective in controlling sensory RLS symptoms and in facilitating and stabilizing sleep [72, 73]. Except for two single anecdotal RLS cases of pregnant women successfully and safely treated with clonazepam, the few remaining information are derived by the field of epilepsy or anxiety [11]. Although initial data reported an increased risk of fetal malformation and of newborn sedation with periodic breathing sing BDZ in the first trimester, larger and more recent reports did not confirm these negative effects caveat their use at low dosages [74]. An increased fetal mortality was reported by the combination between temazepam and diphenhydramine [75]. Due to limited available data on safety during

pregnancy and on the efficacy in idiopathic RLS, the so-called "Z drugs" such as zopiclone and zolpidem are to discourage in pregnant women. Finally, based on the practice guideline for RLS treatment during pregnancy, low doses of clonazepam (0.5–1 mg/day) may be considered for severe and refractory RLS during pregnancy and lactation [44]. Concerning lactation, especially night breastfeeding, the sedative effect should be carefully evaluated in order to avoid possible risky behavior of the mother on the newborn.

Opioids

Opioids are considered as second/third choice medication in idiopathic RLS and no doubts exist on their efficacy [76, 77]; however, their use as a first choice therapy is limited because of possible difficulty in managing side effects and addiction. However, a recent large clinical trial with oxycodone, besides a solid effectiveness, also showed a good tolerability without significant risk of addiction [77]. During pregnancy opioids are regularly used for pain and for heroin addiction, however, no studies tested opioids during pregnancy for RLS. When administered during the first trimester, opioids have been shown to increase the risk of birth defects in one study, while resulted safe in a second study [78]. Sedative effects, or withdraw/abstinence effects in newborns are two additional serious issues to consider, especially in women who regularly take heroin or methadone during pregnancy. The risk of over dosage is significantly increased in ultra-fast metabolizers carrying the genetic variant of CYP2D6 [79]. Still debated is the relationship between opioid treatment during pregnancy and lactation and the sudden infant death syndrome [80].

The atypical weak mu-receptor agonist tramadol might also have some efficacy in idiopathic RLS [81]. Although it has never been used for RLS during pregnancy, recent literature found it to be quite safe when used for pain in pregnant women [82]. Moreover tramadol cross very poorly the blood–placenta barrier, therefore might be considered during lactation [83]. Following the consensus guideline for RLS treatment during pregnancy, low-dose oxycodone (5–10 mg/day) should be reserved only to very severe and refractory cases and only during the second or third trimester; while during lactation low doses of tramadol are to prefer versus classical opioids [44].

References

1. Ekbom KA. Restles legs syndrome. Acta Med Scand. 1945;158:4–122.
2. Mussio-Fournier JC, Rawak F. Familiares auftreten von pruritus, urtikaria und parasthetischer hyperkinese der unteren extremitaten. Conf Neurol. 1940;3:110–4.
3. Jolivet B. Paresthesies agitantes nocturnes des membres inferieurs, impatiences. Paris; 1953.
4. Ekbom KA. Restless legs syndrome. Neurology. 1960;10:868–73.
5. Goodman JD, Brodie C, Ayida GA. Restless leg syndrome in pregnancy. BMJ. 1988;297:1101–2.
6. Manconi M, Govoni V, De Vito A, et al. Restless legs syndrome and pregnancy. Neurology. 2004;63:1065–9.

7. Harano S, Ohida T, Kaneita Y, Yokoyama E, Tamaki T, Takemura S. Prevalence of restless legs syndrome with pregnancy and the relationship with sleep disorders in the Japanese large population [abstract]. Sleep Biol Rhythms. 2008;102–9.
8. Uglane MT, Westad S, Backe B. Restless legs syndrome in pregnancy is a frequent disorder with a good prognosis. Acta Obstet Gynecol Scand. 2011;90:1046–8.
9. Tunc T, Karadag YS, Dogulu F, Inan LE. Predisposing factors of restless legs syndrome in pregnancy. Mov Disord. 2007;22:627–31.
10. Hubner A, Krafft A, Gadient S, Werth E, Zimmermann R, Bassetti CL. Characteristics and determinants of restless legs syndrome in pregnancy: a prospective study. Neurology. 2013;80:738–42.
11. Manconi M, Govoni V, De Vito A, et al. Pregnancy as a risk factor for restless legs syndrome. Sleep Med. 2004;5:305–8.
12. Cesnik E, Casetta I, Turri M, et al. Transient RLS during pregnancy is a risk factor for the chronic idiopathic form. Neurology. 2010;75:2117–20.
13. Sarberg M, Josefsson A, Wirehn AB, Svanborg E. Restless legs syndrome during and after pregnancy and its relation to snoring. Acta Obstet Gynecol Scand. 2012;91:850–5.
14. Hensley JG. On "heredity of restless legs syndrome in a pregnant population". J Obstet Gynecol Neonatal Nurs. 2014;43:270–1.
15. Dzaja A, Wehrle R, Lancel M, Pollmacher T. Elevated estradiol plasma levels in women with restless legs during pregnancy. Sleep. 2009;32:169–74.
16. Lee KA, Zaffke ME, Baratte-Beebe K. Restless legs syndrome and sleep disturbance during pregnancy: the role of folate and iron. J Womens Health Gend Based Med. 2001;10:335–41.
17. Abbassi-Ghanavati M, Greer LG, Cunningham FG. Pregnancy and laboratory studies: a reference table for clinicians. Obstet Gynecol. 2009;114:1326–31.
18. Fenton V, Cavill I, Fisher J. Iron stores in pregnancy. Br J Haematol. 1977;37:145–9.
19. Sikandar R, Khealani BA, Wasay M. Predictors of restless legs syndrome in pregnancy: a hospital based cross sectional survey from Pakistan. Sleep Med. 2009;10:676–8.
20. Balendran J, Champion D, Jaaniste T, Welsh A. A common sleep disorder in pregnancy: restless legs syndrome and its predictors. Aust NZ J Obstet Gynaecol. 2011;51:262–4.
21. Winkelmann J, Czamara D, Schormair B, et al. Genome-wide association study identifies novel restless legs syndrome susceptibility loci on 2p14 and 16q12.1. PLoS Genet. 2011;7: e1002171.
22. Suzuki K, Ohida T, Sone T, et al. The prevalence of restless legs syndrome among pregnant women in Japan and the relationship between restless legs syndrome and sleep problems. Sleep. 2003;26:673–7.
23. Alves DA, Carvalho LB, Morais JF, Prado GF. Restless legs syndrome during pregnancy in Brazilian women. Sleep Med. 2010;11:1049–54.
24. 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.
25. Walters AS, Frauscher B, Allen R, et al. Review of quality of life instruments for the restless legs syndrome/Willis-Ekbom disease (RLS/WED): critique and recommendations. J Clin Sleep Med. 2014;10:1351–7.
26. Castillo PR, Mera RM, Fredrickson PA, Zambrano M, Del Brutto VJ, Del Brutto OH. Psychological distress in patients with restless legs syndrome (Willis-Ekbom disease): a population-based door-to-door survey in rural Ecuador. BMC Res Notes. 2014;7:911.
27. Galbiati A, Marelli S, Giora E, Zucconi M, Oldani A, Ferini-Strambi L. Neurocognitive function in patients with idiopathic restless legs syndrome before and after treatment with dopamine-agonist. Int J Psychophysiol. 2015;95:304–9.
28. Van Den Eeden SK, Albers KB, Davidson JE, et al. Risk of cardiovascular disease associated with a restless legs syndrome diagnosis in a retrospective cohort study from Kaiser Permanente Northern California. Sleep. 2015;38:1009–15.
29. Katsi V, Katsimichas T, Kallistratos MS, et al. The association of restless legs syndrome with hypertension and cardiovascular disease. Med Sci Monit. 2014;20:654–9.

30. Ferini-Strambi L, Walters AS, Sica D. The relationship among restless legs syndrome (Willis-Ekbom disease), hypertension, cardiovascular disease, and cerebrovascular disease. J Neurol. 2014;261:1051–68.
31. Okun ML, Schetter CD, Glynn LM. Poor sleep quality is associated with preterm birth. Sleep. 2011;34:1493–8.
32. Okun ML, Luther J, Prather AA, Perel JM, Wisniewski S, Wisner KL. Changes in sleep quality, but not hormones predict time to postpartum depression recurrence. J Affect Disord. 2011;130:378–84.
33. Ramirez JO, Cabrera SA, Hidalgo H, et al. Is preeclampsia associated with restless legs syndrome? Sleep Med. 2013;14:894–6.
34. Innes KE, Kandati S, Flack KL, Agarwal P, Selfe TK. The association of restless legs syndrome to history of gestational diabetes in an appalachian primary care population. J Clin Sleep Med. 15 Oct 2015;11(10):1121–30.
35. Ma S, Shang X, Guo Y, Liu G, Yang J, Xue R. Restless legs syndrome and hypertension in Chinese pregnant women. Neurol Sci. 2015;36:877–81.
36. Sharma SK, Nehra A, Sinha S, et al. Sleep disorders in pregnancy and their association with pregnancy outcomes: a prospective observational study. Sleep Breath. 2015.
37. Wesstrom J, Skalkidou A, Manconi M, Fulda S, Sundstrom-Poromaa I. Pre-pregnancy restless legs syndrome (Willis-Ekbom disease) is associated with perinatal depression. J Clin Sleep Med. 2014;10:527–33.
38. Bei B, Coo S, Trinder J. Sleep and mood during pregnancy and the postpartum period. Sleep Med Clin. 2015;10:25–33.
39. 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.
40. Miri S, Rohani M, Vahdat M, et al. Presenting features of idiopathic versus secondary restless legs syndrome in pregnancy. Iran J Neurol. 2014;13:241–4.
41. Allen RP, Picchietti DL, Garcia-Borreguero D, et al. Restless legs syndrome/Willis-Ekbom disease diagnostic criteria: updated International Restless Legs Syndrome Study Group (IRLSSG) consensus criteria–history, rationale, description, and significance. Sleep Med. 2014;15:860–73.
42. Benes H, Walters AS, Allen RP, Hening WA, Kohnen R. Definition of restless legs syndrome, how to diagnose it, and how to differentiate it from RLS mimics. Mov Disord. 2007;22 Suppl 18:S401–8.
43. Walters AS, LeBrocq C, Dhar A, et al. Validation of the International Restless Legs Syndrome Study Group rating scale for restless legs syndrome. Sleep Med. 2003;4:121–32.
44. Picchietti DL, Hensley JG, Bainbridge JL, et al. Consensus clinical practice guidelines for the diagnosis and treatment of restless legs syndrome/Willis-Ekbom disease during pregnancy and lactation. Sleep Med Rev. 2015;22:64–77.
45. Terzi H, Terzi R, Zeybek B, et al. Restless legs syndrome is related to obstructive sleep apnea symptoms during pregnancy. Sleep Breath. 2015;19:73–8.
46. Oyiengo D, Louis M, Hott B, Bourjeily G. Sleep disorders in pregnancy. Clin Chest Med. 2014;35:571–87.
47. Facco FL, Kramer J, Ho KH, Zee PC, Grobman WA. Sleep disturbances in pregnancy. Obstet Gynecol. 2010;115:77–83.
48. Wilson S, Argyropoulos S. Antidepressants and sleep: a qualitative review of the literature. Drugs. 2005;65:927–47.
49. Tsuji Y, Miyama S, Uemura Y et al. Three cases of drug-induced akathisia due to antiemetics during cancer palliative care. Gan To Kagaku Ryoho. 2006;33:267–9.
50. Inami Y, Horiguchi J, Nishimatsu O, et al. A polysomnographic study on periodic limb movements in patients with restless legs syndrome and neuroleptic-induced akathisia. Hiroshima J Med Sci. 1997;46:133–41.

51. Lakasing E. Exercise beneficial for restless legs syndrome. Practitioner. 2008;252:43–5.
52. Aukerman MM, Aukerman D, Bayard M, Tudiver F, Thorp L, Bailey B. Exercise and restless legs syndrome: a randomized controlled trial. J Am Board Fam Med. 2006;19:487–93.
53. Botez MI, Lambert B. Folate deficiency and restless-legs syndrome in pregnancy. N Engl J Med. 1977;297:670.
54. Moon HJ, Chang Y, Lee YS, et al. A comparison of MRI tissue relaxometry and ROI methods used to determine regional brain iron concentrations in restless legs syndrome. Med Devices (Auckl). 2015;8:341–50.
55. Earley CJ, Ponnuru P, Wang X, et al. Altered iron metabolism in lymphocytes from subjects with restless legs syndrome. Sleep. 2008;31:847–52.
56. Allen RP, Earley CJ. The role of iron in restless legs syndrome. Mov Disord. 2007;22 Suppl 18:S440–8.
57. Pavord S, Myers B, Robinson S, Allard S, Strong J, Oppenheimer C. UK guidelines on the management of iron deficiency in pregnancy. Br J Haematol. 2012;156:588–600.
58. Swaney P, Thorp J, Allen I. Vitamin C supplementation in pregnancy–does it decrease rates of preterm birth? A systematic review. Am J Perinatol. 2014;31:91–8.
59. Schneider J, Krafft A, Manconi M, Hübner A, Baumann C, Werth E, Gyr T, Bassetti C. Open-label study of the efficacy and safety of intravenous ferriccarboxymaltose in pregnant women with restless legs syndrome. Sleep Med. Nov 2015;16(11):1342–7.
60. Garcia-Borreguero D, Kohnen R, Silber MH, 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.
61. Kranick SM, Mowry EM, Colcher A, Horn S, Golbe LI. Movement disorders and pregnancy: a review of the literature. Mov Disord. 2010;25:665–71.
62. Mucchiut M, Belgrado E, Cutuli D, Antonini A, Bergonzi P. Pramipexole-treated Parkinson's disease during pregnancy. Mov Disord. 2004;19:1114–5.
63. Hagell P, Odin P, Vinge E. Pregnancy in Parkinson's disease: a review of the literature and a case report. Mov Disord. 1998;13:34–8.
64. Watanabe T, Matsubara S. Good obstetric outcome in a patient with Segawa disease. Arq Neuropsiquiatr. 2012;70:559–60.
65. Watanabe T, Matsubara S, Baba Y, Tanaka H, Suzuki T, Suzuki M. Successful management of pregnancy in a patient with Segawa disease: case report and literature review. J Obstet Gynaecol Res. 2009;35:562–4.
66. Dostal M, Weber-Schoendorfer C, Sobesky J, Schaefer C. Pregnancy outcome following use of levodopa, pramipexole, ropinirole, and rotigotine for restless legs syndrome during pregnancy: a case series. Eur J Neurol. 2013;20:1241–6.
67. Horvath J, Fross RD, Kleiner-Fisman G, et al. Severe multivalvular heart disease: a new complication of the ergot derivative dopamine agonists. Mov Disord. 2004;19:656–62.
68. Danoff SK, Grasso ME, Terry PB, Flynn JA. Pleuropulmonary disease due to pergolide use for restless legs syndrome. Chest. 2001;120:313–6.
69. Allen RP. Pregabalin versus pramipexole for restless legs syndrome. N Engl J Med. 2014;370:2050–1.
70. Eroglu C, Allen NJ, Susman MW, et al. Gabapentin receptor alpha2delta-1 is a neuronal thrombospondin receptor responsible for excitatory CNS synaptogenesis. Cell. 2009;139:380–92.
71. Ohman I, Vitols S, Tomson T. Pharmacokinetics of gabapentin during delivery, in the neonatal period, and lactation: does a fetal accumulation occur during pregnancy? Epilepsia. 2005;46:1621–4.
72. Horiguchi J, Inami Y, Sasaki A, Nishimatsu O, Sukegawa T. Periodic leg movements in sleep with restless legs syndrome: effect of clonazepam treatment. Jpn J Psychiatry Neurol. 1992;46:727–32.

73. Montagna P, Sassoli dB, Zucconi M, Cirignotta F, Lugaresi E. Clonazepam and vibration in restless legs syndrome. Acta Neurol Scand. 1984;69:428–30.
74. Eros E, Czeizel AE, Rockenbauer M, Sorensen HT, Olsen J. A population-based case-control teratologic study of nitrazepam, medazepam, tofisopam, alprazolam and clonazepam treatment during pregnancy. Eur J Obstet Gynecol Reprod Biol. 2002;101:147–54.
75. Kargas GA, Kargas SA, Bruyere HJ Jr, Gilbert EF, Opitz JM. Perinatal mortality due to interaction of diphenhydramine and temazepam. N Engl J Med. 1985;313:1417–8.
76. Frampton JE. Oxycodone/Naloxone PR: a review in severe refractory restless legs syndrome. CNS Drugs. 2015;29:511–8.
77. Trenkwalder C, Benes H, Grote L, et al. Prolonged release oxycodone-naloxone for treatment of severe restless legs syndrome after failure of previous treatment: a double-blind, randomised, placebo-controlled trial with an open-label extension. Lancet Neurol. 2013;12:1141–50.
78. Broussard CS, Rasmussen SA, Reefhuis J, et al. Maternal treatment with opioid analgesics and risk for birth defects. Am J Obstet Gynecol. 2011;204:314.e1–11.
79. Smith HS. Opioid metabolism. Mayo Clin Proc. 2009;84:613–24.
80. Burns L, Conroy E, Mattick RP. Infant mortality among women on a methadone program during pregnancy. Drug Alcohol Rev. 2010;29:551–6.
81. Lauerma H, Markkula J. Treatment of restless legs syndrome with tramadol: an open study. J Clin Psychiatry. 1999;60:241–4.
82. Bloor M, Paech MJ, Kaye R. Tramadol in pregnancy and lactation. Int J Obstet Anesth. 2012;21:163–7.
83. Timm NL. Maternal use of oxycodone resulting in opioid intoxication in her breastfed neonate. J Pediatr. 2013;162:421–2.
84. Neau JP, Marion P, Mathis S, et al. Restless legs syndrome and pregnancy: follow-up of pregnant women before and after delivery. Eur Neurol. 2010;64:361–6.
85. Neau JP, Porcheron A, Mathis S, et al. Restless legs syndrome and pregnancy: a questionnaire study in the Poitiers district, France. Eur Neurol. 2010;64:268–74.
86. Ismailogullari S, Ozturk A, Mazicioglu MM, Serin S, Gultekin M, Aksu M. Restless legs syndrome and pregnancy in Kayseri, Turkey: a hospital based survey [abstract] Ismailogullari S, Ozturk A, Mazicioglu MM, Serin S, Gultekin M, Aksu M. Sleep Biol Rhythms. 2010;137–46.
87. Chen PH, Liou KC, Chen CP, Cheng SJ. Risk factors and prevalence rate of restless legs syndrome among pregnant women in Taiwan. Sleep Med. 2012;13:1153–7.
88. Ko H, Shin J, Kim MY, et al. Sleep disturbances in Korean pregnant and postpartum women. J Psychosom Obstet Gynaecol. 2012;33:85–90.
89. Vahdat M, Sariri E, Miri S, et al. Prevalence and associated features of restless legs syndrome in a population of Iranian women during pregnancy. Int J Gynaecol Obstet. 2013;123:46–9.
90. Minar M, Habanova H, Rusnak I, Planck K, Valkovic P. Prevalence and impact of restless legs syndrome in pregnancy. Neuro Endocrinol Lett. 2013;34:366–71.
91. Shang X, Yang J, Guo Y, Ma S, Jia Z, Xue R. Restless legs syndrome among pregnant women in China: prevalence and risk factors. Sleep Breath. 2014.
92. Mindell JA, Cook RA, Nikolovski J. Sleep patterns and sleep disturbances across pregnancy. Sleep Med. 2015;16:483–8.

Management of RLS in Children (Unique Features)

19

Oliviero Bruni and Marco Angriman

Restless legs syndrome (RLS) is a relatively common pediatric disease with an estimated prevalence of 2–4% in school-aged children and adolescents [1–4]. Often it is misdiagnosed and ignored by most pediatricians and general practitioners. The classical clinical presentation of a compelling urge to move the legs, often accompanied by uncomfortable dysesthesias, is the RLS presentation also in children. To make a diagnosis of RLS, this core of sensory-motor symptoms must be present at rest, at least temporarily relieved by movement, and most pronounced at night [5].

The exact prevalence of RLS in children is unknown, although one-third of adults with RLS are affected in childhood. Studies have reported that, in adults with RLS, 25% of them had onset of their symptoms between 10 and 20 years of age and 18% of them had onset before 10 years of age [2].

Pediatricians need to be aware of RLS because it may be common, and when untreated, can cause significant functional impairment. Possible causes of under-recognition include the mild and intermittent nature of the symptoms at younger ages.

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Symptoms, Pathophysiology, and Diagnostic Criteria for RLS

According to Picchietti et al. [1, 2] RLS symptoms are usually underdiagnosed in children with attention deficit hyperactivity disorder (ADHD) because the complaint of RLS dysesthesia in children is usually mild and intermittent. RLS is usually progressive, and it is thus likely that these children will become more symptomatic in the future. Furthermore, in certain children, RLS symptoms may appear only when the children are sleep deprived or have received caffeine. The fact that the clinical presentation in children remains largely unknown may contribute to prevalence uncertainty because current diagnostic criteria may not capture all children affected [5].

RLS may lead to significant morbidity because of the associated sleep disturbance, which impact attention, working memory, higher order cognitive functions, academic achievement, mood, behaviour, quality of life and family well-being [2, 6].

The pathophysiology of RLS has been recently defined, with genetics, brain dopamine system, and iron having been found to play important roles [1, 7, 8].

The National Institutes of Health workshop and the International RLS Study Group (IRLSSG) defined the pediatric RLS diagnostic criteria for the first time in 2003 [5]. These criteria defined three possible forms of pediatric RLS: (1) definite; (2) probable; (3) possible RLS. The fast growing publications in the last decade since 2003 lead a group of researchers to redefine the criteria for pediatric RLS. A panel of seven pediatric RLS experts was approved in spring 2010 by the IRLSSG Executive Committee to provide recommendations on revision of the pediatric RLS diagnostic criteria. The pediatric RLS committee found broad consensus that adult and pediatric diagnostic criteria should be combined, with pediatric- specific terms and prompts considered by the diagnostician when the criteria are applied in clinical and research settings. See Table 1.2, which reports the updated integrated RLS diagnostic criteria [9].

However, the Pediatric Committee highlighted the peculiarity of the pediatric RLS and made special considerations summarized below:

(a) The child must describe the RLS symptoms in his or her own words of which the diagnostician should be aware
(b) Language and cognitive development determine the applicability of the RLS diagnostic criteria, rather than age
(c) A significant impact on sleep, mood, cognition, and function on behavioral and educational domains should be present
(d) The clinical course criteria do not apply for pediatric cases; it is not certain that at least twice weekly can be considered the best determinant of chronicity in pediatric cases.

It is mandatory to accurately investigate for the symptoms in children related to the urge and discomfort components that can be often missed in a regular visit but easily discovered when given the opportunity and the correct instruments to the child [10].

Furthermore, it is extremely important to evaluate family history of RLS: it is not uncommon, taking the history of the child, to discover that a component of the family was affected by RLS not being aware of it.

The differentiation pediatric RLS from other conditions or mimics could not be an easy step. [3, 4, 11–13]. Table 19.1 reports some of the common mimics of pediatric RLS [9].

As RLS symptoms occur during bedtime they are most likely to interfere with sleep onset and these symptoms may be confused with bedtime resistance and limit setting-type behaviors.

Unlike RLS, leg cramps are very painful, typically affect only one leg, and are restricted to specific muscle groups. Symptoms are not relieved by leg movements (LMs) and are alleviated by rest and alternate use of ice packs and warm compresses. Electrolyte disturbances and neuromuscular disorders may be an underlying etiology, especially in severe cases.

Table 19.1 Differential diagnosis of pediatric restless legs syndrome

Common mimics
• Positional discomfort
• Sore leg muscles
• Ligament sprain/tendon strain
• Positional ischemia (numbness)
• Dermatitis
• Bruises
• Growing pains
Less common mimics
• Leg cramps
• Arthritis
• Other orthopedic disorders
• Peripheral neuropathy
• Radiculopathy
• Myelopathy
• Myopathy
• Fibromyalgia
• Complex regional pain syndrome
• Drug-induced akathisia
• Sickle cell disease

From Picchietti DL et al. Pediatric restless legs syndrome diagnostic criteria: an update by the International Restless Legs Syndrome Study Group. Sleep Med (2013), http://dx.doi.org/10.1016/j.sleep.2013.08.778, with permission

Causes of secondary RLS include peripheral neuropathy and uremia. Medications, such as antidepressants, sedating antihistamines, and dopamine receptor antagonists, may worsen or precipitate cases of RLS.

It is important to evaluate the similarities and the differences between pediatric RLS and growing pains, a common benign condition in childhood characterized by intermittent bilateral leg pain that occurs in the late afternoon or evening [14]. A recent paper explored the relationship between pediatric RLS and growing pains showing the considerable overlap in the diagnostic criteria and the sharing of clinical symptoms. RLS and growing pains are common disorders, with criteria for definite RLS met by 1.9% of children ages 8–11 years and 2% of children and adolescents ages 12–17 years [2]. The prevalence of growing pains widely varies from study to study, but conservative estimates suggest a prevalence of 4.7% [15]. RLS and growing pains commonly occur together and the family histories of RLS and growing pains often are overlapping. Leg rubbing to obtain relief from leg discomfort is common to both disorders, though walking to obtain relief seems unique to RLS; on the other hand, childhood RLS has been reported to be painful in up to 45% of cases. Even experienced clinicians found difficult to differentiate the two conditions that could represent the different phenotypic expressions of the same disorder [16].

Furthermore, growing pains differ from RLS in that the unpleasant sensations are not partially or totally relieved by movements of the lower extremities. Typically, children may awaken in the middle of the night complaining of a "throbbing" pain in the legs. Onset usually occurs during early to late childhood, and the location of the pain is prominent in the front of the thighs, calves, or behind the knees. Symptoms may be alleviated with massage, ice packs, warm compresses, and acetaminophen or ibuprofen. To better evaluate the similarities and differences between the two disorders, a genome wide association study of all genes with particular attention to those genes identified as related to RLS need be performed in growing pain children.

There are no specific tests for RLS and the diagnosis is made through a complete medical history and physical examination. An overnight sleep study may be recommended to evaluate for other sleep disorders, especially periodic limb movement disorder.

The RLS diagnosis in children is often hampered because children may be unable to provide a good description of the symptoms. This clinical criteria constitutes the first obstacle for the clinician who examines a child compelling for a sleep disorder suggestive for RLS: spontaneous verbal expression of symptoms can be very limited, especially in preschoolers.

Establishing a good relationship with the child will greatly enhance chances of accurately assessing sensory symptoms, while the parents can refer other symptoms. It is very important to avoid leading questions and facilitate expression of the sensation in the child's own words.

When exploring RLS diagnostic criteria in children, it is important to use age-specific vocabulary (e.g., "Do your legs bother you?") and encourage the child to report symptoms in his/her own words; to define "urge" to move, children use

more age-appropriate terms such as “need to move”, “want to move,” and “got to kick”.

Sensory symptoms are difficult to explain by children and simple description such as a funny feeling, pain, hurting, tickling, bugs, spiders, ants, goose bumps in the legs can be accepted.

Most children will not describe an ‘urge to move’ per se, but parents may report frequent stretching, kicking, pacing and running around and/or requests for leg massage. These symptoms may be perceived by parents as bedtime resistance behaviors: these children avoid being in bed and lying still as these symptoms may worsen by inactivity. Sometimes children may draw pins, needles, tiny sand particles, bugs, or a saw over their legs when asked to depict their symptoms.

The presence of RLS may be unrecognized, especially in infants and preschool children that may present clinically with sleep disturbance before the onset of any RLS feelings, months or years later [17]. Recently it has been described as typical of early RLS an awakening after 1–3 h of sleep accompanied from screaming, crying, kicking and slapping the legs or by verbally expressing that the legs ‘hurts’ [18].

RLS-related pain in children typically occurs from both knees down and especially involves the calves, although thigh pain may also appear. These pains can be symmetric or asymmetric. Partial or complete resolution by movement is a key feature when diagnosing RLS in children with pain complaints.

To decide on the appropriateness of a possible treatment, clinicians should assess not only the severity of symptoms but also the impact of RLS symptoms on sleep, cognition, and mood.

The above reported diagnostic criteria are intended for both clinical and research settings. However, due to some differences in the presentation of symptoms the pediatric RLS committee adopted two different diagnostic categories [9]:

Probable RLS

(a) The child meets all five essential criteria for RLS, except criterion 4 (occurrence only or worsening in the evening or night). A significant subset of children do not report worsening at evening and night, yet they meet all other diagnostic criteria and have supportive features for RLS including a positive family history [2, 17, 19].

Possible RLS

(b) The child is observed to have behavior manifestations of lower extremity discomfort when sitting or lying, accompanied by motor movement of the affected limbs. The discomfort is characterized by RLS criteria 2–5 (is worse during rest and inactivity, relieved by movement, worse in the evening or night, and is not solely accounted for as primary to another medical or a behavioral condition). This diagnosis is based on behavioral observations rather than direct report by the child or adolescent and is particularly

helpful for children younger than 6 years of age and in children with neurodevelopmental disabilities).

The diagnosis of pediatric RLS is mostly based on clinical symptoms but in order to support the diagnosis the clinician should evaluate the presence of Periodic Limb Movements during sleep (PLMS) >5 per hour and, most importantly, a family history showing the presence of: (a) RLS among first-degree relatives; (b) PLMS >5 per hour; (c) Periodic Limb Movements Disorder (PLMD) among first-degree relatives.

RLS and ADHD

In literature several studies have shown a strict association between RLS and ADHD or ADHD symptoms both in clinical and in community samples. Sleep disruption associated with RLS may lead to ADHD symptoms, RLS may mimic the symptomatology of ADHD, or it may be comorbid with idiopathic ADHD [20–25].

About 25% of adults and school-age children with RLS meet the criteria for ADHD, whereas 12–35% of children with ADHD met the criteria for RLS [21, 26]. Several different studies showed that diurnal manifestations of RLS mimic ADHD and that RLS/PLMs are more prevalent in ADHD children [23]; in particular up to 44% of ADHD children have RLS and up to 26% of RLS children have ADHD [27].

The exact relationship of ADHD, RLS, and PLMD is not clear but we can hypothesize different possible explanations of this association:

- RLS may might lead to symptoms of ADHD through sleep disruption, i.e. hyperactivity might lead to inattention through the mechanism of leg discomfort
- RLS may mimic ADHD symptomatology in restrictive situations such as when seated in a classroom, movie theater, airplane, or car
- RLS and ADHD may coexist as comorbid disorders
- RLS, PLMD, and ADHD share a common dopamine dysfunction, which could be genetically determined, at least in subgroup of patients and respond to dopaminergic agents.

For these reasons, the association between RLS and ADHD symptoms may have relevant implications for treatment when these conditions coexist [27]. For example, stimulant medication has been found to not adversely affect RLS or PLMS and conversely may improve sleep and diminish ADHD symptoms [1].

Both ADHD and RLS have been found to be associated with iron deficiency (ID) [27]: The hypothesis of ID is not incompatible with the hypothesis of dopaminergic hypoactivity, since iron is a cofactor for tyrosine hydroxylase, the rate-limiting enzyme for dopamine synthesis. Children with ADHD are more likely to have ID and treatment with supplemental iron has been reported to help reduce

their PLMD symptoms, improve sleep quality and subsequently decrease ADHD symptoms.

Furthermore, preliminary observational data suggest that RLS in parents of children with ADHD predicts lifetime occurrence of ADHD and anxiety disorders, especially agoraphobia, implying a genetically conveyed vulnerability for psychiatric disorders and RLS in families with ADHD [28]: a shared dysfunction in dopaminergic, adrenergic and serotoninergic neurotransmitter systems may explain this association.

It has been further demonstrated that ADHD symptom severity was higher in children with ADHD when RLS is present as comorbid disorder [29]. In children diagnosed with both RLS and ADHD, previously unsuccessfully treated with psychostimulants, low doses of dopaminergic agents (levodopa, pergolide, and ropinirole) has been effective [27] and also those children benefits of the concurrent administration of iron supplementation [30].

RLS and PLMS

Different reports showed that RLS and PLMS may occur in children [31, 32]. The relationship between RLS, PLMS, and PLMD is complex. Most individuals with RLS have PLMS [33] and PLMS are considered to be supportive of an RLS diagnosis in children and represents an objective measure for RLS and be an endophenotype for certain RLS cases [34]. Furthermore, PLMD is considered as a diagnostic entity related to RLS, particularly for children and that PLMD evolves to RLS in children over time [32]. Often a diagnosis of PLMD precede the diagnosis of RLS in young children less than 6 years of age who do not yet have well-developed language skills and therefore cannot adequately describe the sensory component of RLS and the development of a clear sensory component could appear only in early adolescence [32]. The clinical picture of an RLS child could be extremely variable: a child can have RLS with PLMS, but he or she cannot have RLS and PLMD.

The role and clinical significance of periodic leg movements during sleep (PLMS) are still under debate [35]; however, they remain the most important and constant objective finding in RLS and PLMD in adults.

Different studies have shown that periodicity of LMs develops with age and is unusual in normal children or children with RLS [36, 37] because LMs tend to show clear-cut periodicity in subjects with RLS only after the second decade and in normal controls after the fourth decade of life. Furthermore PLMS index increased up to age ages 15–25 years then plateaued until age 65 years when there was another increase, [2] periodicity index progressively increased up to the age of 35 years and then remained stable up to age 85, and [3] time of night decrement was evident at 15–75 years of age but not <15 or >75 years [36].

So, the classical PLMS Index does not seem to be sufficiently specific for the diagnosis and clinical significance of RLS. Ferri et al. [38] have suggested a new approach for the detection and analysis of LMs recorded from the anterior tibialis muscles during sleep in patients with RLS, with particular attention to their quantity, duration, amplitude and periodicity. They also have suggested that a synthesis of the features of LMs during sleep can be achieved by considering three main parameters including the total number of LMs per hour of sleep, the periodicity of the LMs and the distribution of the LMs throughout the night.

Furthermore, Manconi et al. [39] showed that only a subset of LMs during sleep corresponding to the periodic component of the whole leg motor activity during sleep (with intermovement intervals 6–46 s and duration of 2–4 s) responded to pramipexole treatment while the non periodic isolated LMs did not.

The primary findings of a recent study conducted from Ferri et al. [40] in a clinical sample of children with ADHD were an increased PLMS index in ADHD children compared to controls but a low periodicity index and little time of night decrement in both groups. For children the intermovement intervals may be short and variable in contrast to the typical 15–40 s intervals in adults [41–43]. However, although this was within the PLMS range, the peak was not prominent and most of the activity was quite irregular with lack of the fixed stereotypic pattern characteristic of adult RLS.

Treatment

Pediatric RLS therapy is really important since RLS's associated sleep disturbances might determine significant developmental-behavioural and cardiovascular morbidity and impacts family well-being. Positive parental involvement and support is another important aspect in the treatment of pediatric RLS, nonetheless because RLS is highly familial and it is not unusual for a parent to be affected.

Treatment reviews and algorithms for RLS and PLMD have been recently published for adults but not for children [44]. For pediatric RLS and PLMD, the focus of treatment is not only to reduce leg symptoms but mainly to improve sleep. In patients who are thought to have secondary RLS, screening for renal disease, thyroid dysfunction, vitamin B12 and folic acid deficiency (peripheral neuropathy) should be considered.

Non-pharmacologic Interventions

Establishing healthy sleep habits is an important aspect of a comprehensive treatment plan. In milder cases, these interventions alone can be sufficient. Adequate sleep duration, regular bed timings and routine principles of good sleep hygiene are important.

Daily exercises in the daytime (avoid vigorous exercise and mind-stimulating activities around bedtime) can improve sleep quality and help to reduce RLS symptoms. Good sleep hygiene practices can be helpful for children with RLS. These include enforcing a regular sleep-wake schedule; avoiding caffeine, heavy meals, fluids, or exercise within a few hours of bedtime, and discouraging non-sleep-inducing activities such as watching television or playing games near bedtime. For legs symptoms relief, the use of local comfort aids is helpful: apply a heating pad, cold compress, or consider rubbing legs but also consider massage, acupressure, walking, stretching, or other relaxation techniques.

It is important to identify medications or other factors that could aggravate RLS and PLMD and examine ways of discontinuing these medications. For instance, selective serotonin reuptake inhibitors (SSRIs), tryciclic antidepressants (TCAs), metoclopramide, diphenhydramine, nicotine, caffeine, and alcohol has all been shown to either promote or aggravate RLS and PLMD.

Iron Hypothesis

The most common cause of secondary RLS in children appears to be iron deficiency (ID): ID is prevalent in human infants, especially in the late infancy/toddler period and there is mounting evidence that ID affects motor activity [45]. Typically, iron stores increase slowly with supplemental iron over weeks to months, and buildup is delayed by physical growth. The level of iron stores in humans is easily measured by serum ferritin that is the best indicator of early iron deficiency, but can be a challenging marker to interpret: cut-off values differ across centres and literature sources, and as an acute-phase reactant, false elevations can occur from infection or inflammation [46]. Saturation of peripheral iron stores typically occurs at ferritin levels of 80–100 ng/mL. Current evidence suggests that achieving and maintaining serum ferritin above 50 ng/mL can be of benefit [32, 46]. In children, therapeutic iron has been found to be of benefit for RLS, PLMS, and ADHD [29, 30, 47, 48].

The dopaminergic theory of RLS further support the ID hypothesis since iron is fundamental for the biosynthesis of dopamine and it is necessary for tyrosine hydroxylation, which is a rate-limiting step for dopamine production. Iron deficiency has been well documented from brain autopsy, magnetic resonance imaging and cerebrospinal fluid studies of adults with RLS [18, 49, 50].

Some authors have postulated that increased leg activity during the period of IDA might indicate a shared underlying mechanism with RLS [51, 52]. Peirano et al. [52] found that that 10-year-old children who experienced IDA in infancy showed a mild but significant increase of tibialis anterior EMG activity during sleep when compared to age-matched normal controls. The activity is characterized by a slightly but significantly higher periodicity due to a selective increase of muscle activations separated by an interval ranging approximately 10–50 s. Taken all together, these findings point to the possibility that long-term consequences of IDA in infancy, despite iron therapy, can be detected during sleep.

Whether increasing peripheral iron stores increases brain iron stores has not yet been definitively determined. The only placebo-controlled trial involving children

with RLS was an RCT for ADHD [30] included 23 children with ADHD and serum ferritin levels <30 ng/mL, randomized with a 3:1 ratio to oral iron (ferrous sulfate: 80 mg/day; $n = 18$) or placebo ($n = 5$). After 12 weeks, although the reduction on the CPRS index score and on the CTRS index score failed to reach significance ($p = 0.055$ and $p = 0.076$, respectively), the authors found a significant decrease in the clinical global impression severity scale ($p < 0.01$).

A general recommendation for iron supplementation when ferritin level is <50 μg/L is to start with 3 mg elemental iron/kg/day or ferrous sulfate at a dose of 50–65 mg of elemental iron for three months and then recheck ferritin level. To enhance absorption, iron should ideally be taken in the morning on an empty stomach with a source of vitamin C such as orange juice. Some foods (e.g. milk, cereals, fiber, eggs) may decrease iron absorption for 2 h.

Children need monitoring over time for symptom recurrence. Although the risk of iron overload is very low parents should be asked for a personal and family history of hemochromatosis or unexplained liver disease, and it is recommended to measure transferrin saturation and ferritin levels at baseline and at least twice yearly while on iron. Finally consider that it may take weeks or months of treatment with iron supplementation to detect improvements in RLS symptoms.

Pharmacologic Treatment

Recently consensus-based guidelines for pharmacological treatment of adult RLS have been published [53, 54] but no specific papers or guidelines are available for children. Currently, either the US Food and Drug Administration or the European Medicines Agency (EMEA) have not approved medications for RLS in children.

However, several papers in literature have demonstrated the efficacy of specific pharmacological agents in children with moderate-to-severe RLS symptoms and PLMD who did not respond to the sleep hygiene and nutritional measures.

In children medication should be combined with non-pharmacological measures to achieve optimal results and should involve a detailed discussion of risks versus benefits with the family [1, 55].

Pharmacologic treatments for RLS have been serendipitously discovered and developed for adults and then applied to children. For the past decades a series of clinical studies investigated the therapeutic value and limitations of these medications whose effectiveness and safety are now better understood. The paucity of large-scale treatment studies may imply a difficulty in recruiting sufficient paediatric sample sizes that meet diagnostic criteria.

The best initial form of treatment is to reduce factors or conditions that may worsen or precipitate RLS and evaluate for the presence of iron deficiency. Careful monitoring for adverse events and periodic reassessment of treatment are recommended and family understanding of the pathology is crucial. When starting a drug for RLS in children it is prudent to begin with the lowest possible dose and slowly titrate upwards with close monitoring for adverse effects.

Dopaminergic Agents

Dopaminergic medications are considered the first line of treatment for RLS: these agents include carbidopa/levodopa and the selective dopamine agonists (pramipexole, ropinirole, pergolide). The use of dopaminergic medications has proved successful in numerous case reports and small open-label studies of children with RLS with and without ADHD, but no large-scale double-blind, placebo-controlled trial with dopaminergic medications in children has been performed [29, 56–63].

The use of dopaminergic medications is associated with an improvement in RLS symptoms and reduction of PLMS and associated arousals. In children with ADHD and RLS and PLMD, the use of dopaminergic medications can result in improvements and even resolution of ADHD symptoms.

Some studies exists about dopaminergic treatment in children with RLS, although with intrinsic limitations in methodology due to sample size, open labeling and absence of randomization: cardibopa/L-dopa and pergolide showed to improve sleepiness in 43% of ADHD patients [64], although the same authors in a successive recent study found that L-DOPA had no effect on Conners' scales, sleep, or psychometric tests when all patients treated with the drug were compared to those on placebo or when patients with ADHD only were compared to those with ADHD and RLS/PLMS, indicating that L Dopa had effect on RLS/PLMS but not on ADHD symptoms [65].

Ropinirole was found effective in a case of RLS comorbid with depression, without side effects [59] and pramipexole has been successful in open studies, eliminating clinical symptoms [17, 66, 67]. Adjunctive therapy with iron in selected patients may improve resolution of symptoms [68].

In case of comorbid depression or anxiety, the adult literature indicates improved results with treatment of disordered sleep and the preference of noradrenergic medication (such as bupropion) over serotonergic medication for depression [69, 70].

The side effects of dopaminergic agents are limited, particularly at the low dosages usually prescribed for RLS treatment; in particular, inappropriate sleepiness and sleep attacks, or compulsive behavior have not been seen. Compared with the adverse reactions of levodopa, including tolerance, rebound, and augmentation phenomena in RLS, pramipexole had one of the best profiles.

Recent meta-analyses have found pramipexole to be effective and well tolerated in adult patients [53, 54].

In the clinical practice of treating children with PLMS and RLS, nausea is the most common side effect of dopaminergic treatment. Sensitivity to side effects makes it necessary to initiate therapy at very low doses and increase as tolerated every few days.

The maximum dose of L-Dopa is determined individually by side effects, but most patients require form 75 mg to 1.5 g. In children pramipexole is titrated slowly beginning with the lowest dose: the 0.125 mg tablet may be gradually increased to 0.250 mg per day.

An important adverse effects reported with these agents include is augmentation, characterized by the paradoxical worsening of RLS symptoms after starting dopaminergic medication; as the dose is increased, the symptoms of RLS worsen and start appearing earlier than the anticipated time of onset, sometimes occurring in the daytime and at times also appearing in the upper extremities. However, no reports of augmentation have been reported in children treated for RLS.

Gabapentin

Gabapentin, gabapentin enacarbil and pregabalin are alpha 2 delta ligands which may potentiate neuronal GABA synthesis and modulate glutamate synthesis trough Ca-channels opening regulation, and are FDA-approved drugs for treatment of moderate to severe RLS in adults.

Different studies have shown good effects of these drugs in improving sleep quality and reducing the sensory symptoms of RLS in adults [71–75].

Gabapentin has a good tolerability profile and few adverse side effects (emotional liability and edema) but it has also improved sleep quality of patients enhancing slow-wave sleep and reducing sleep-onset latency [76]. In our opinion it should be considered as the first choice for children requiring RLS therapy at variable dosage of 100–500 mg at bedtime. To our knowledge no studies have been published with the use of pregabalin in children with RLS.

Benzodiazepines

Before FDA approval of dopaminergic agonists for the treatment of RLS in adults, clonazepam was the most commonly used medication because of its noted effects in controlling myoclonic jerks and myoclonus after anoxia. The first published papers on the use of clonazepam for RLS were case reports in 1979 and 1980 [77, 78]. Clonazepam has a very long half-life of more than 40 h, which may results in next day sedation [79]. The side effects include mental confusion, muscle relaxation, and depression, but in context with RLS and ADHD it may also aggravate hyperactivity in some children.

As was demonstrated by Saletu et al. [80], clonazepam tends to improve sleep and reduce arousals due to PLMS in RLS patients, but it was not effective in reducing the motor and sensory abnormalities associated with RLS. Hence it was concluded that clonazepam had therapeutic effect on insomnia but not on the limb movements according to a more recent study by Manconi et al. [81].

Short-acting agents like triazolam, zalepon, temazepam and zolpidem (an imidazopyridine) were effective for sleep onset insomnia but the intermediate acting agent like temazepan was recommended if the patient awakens later at night. Overall, evidence recommends clonazepam as an option as an adjunctive medication and it is typically used to decrease RLS sensations and improve the quality of sleep in children.

Clonidine

Clonidine, a short acting alpha-2 agonist, is a commonly used medication for children's sleep and results particularly useful when there are severe sleep-onset problems and in comorbid ADHD related insomnia. In one randomized, double-blind, placebo-controlled trial clonidine has been effective for RLS sensory symptoms in adults without side effects [82, 83].

It has been particularly useful in children with insomnia associated with hyperactivity. This effect is thought to be mediated by its antiadrenergic effect that the decrease of overactivity of the sympathetic nervous system. Clonidine is widely used as needed drug because it is well tolerated by children, soporific, and rapidly effective [76].

Conclusions

It has been recently proposed [84] a neurobiological hypothesis that divides RLS into individual features: primary sensory-motor symptoms, PLMS, and sleep disturbance; subtyping RLS (and consequently individual patients) as a sleep disorder, a movement disorder, or a chronic pain disorder may optimize patient care.

The observation that dopaminergic agents are only effective on the periodic component of the LMs and are not changing the altered sleep architecture, associated to the lack of periodicity in children raises an interesting question on what types of medication would be most effective to treat RLS-related sleep disturbance in the pediatric population: due to the mentioned poor periodicity of LMs a dopaminergic treatment may not be the primary options.

This postulation is consistent with recent findings in adult RLS, in which a single oral dose of the dopamine agonists either pramipexole or ropinirole) were not found to improve sleep and NREM sleep instability [85], while clonazepam [81] and gabapentin [80] did it.

Confirming this result, a recent review study [44] on 62 trials comparing dopaminergic and non dopaminergic medications (anticonvulsants, opioids and iron) showed that changes in the IRLS score and Clinical Global Impression score in the substance groups were comparable concluding that, besides dopaminergics, other treatments show efficacy and may be well-tolerated alternatives for the treatment of RLS. Therefore, the treatment of RLS/PLMS should consider a combination of drugs targeting LM activity and NREM sleep instability at the same time as a valid treatment for sleep disturbances in ADHD children.

The action of drugs for RLS/PLMS on sleep stabilization could also prevent cardiovascular and neurocognitive consequences in adults and children: it has been hypothesized that RLS/PLMS, when comorbid with ADHD, might also indicate an increased cardiovascular risk during pharmacological treatment via an autonomic nervous system dysfunction modulated by reciprocal NREM sleep instability and PLMS/RLS interactions [86]. Therefore effective treatment of RLS/PLMS might

lead not only to improvement of ADHD symptoms severity, but also to decrease of cardiovascular risk during treatment with ADHD drugs in the subgroup of individuals with ADHD-PLMS/RLS.

In the past two decades several papers have been published on pediatric RLS and PLMD, showing the relatively high prevalence and raising awareness on the effects of these disorders on quality of life. The new diagnostic criteria for children and the growing body of knowledge on comorbid disorders (like growing pains), as well as the genetics study will contribute to discover valid treatments for children suffering from these disorders.

References

1. Picchietti MA, Picchietti DL. Advances in pediatric restless legs syndrome: iron, genetics, diagnosis and treatment. Sleep Med. 2010;11:643–51.
2. 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.
3. Turkdogan D, Bekiroglu N, Zaimoglu S. A prevalence study of restless legs syndrome in Turkish children and adolescents. Sleep Med. 2011;12:315–21.
4. 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.
5. 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.
6. Pearson VE, Allen RP, Dean T, et al. Cognitive deficits associated with restless legs syndrome (RLS). Sleep Med. 2006;7:25–30.
7. Stefansson H, Rye DB, Hicks A, et al. A genetic risk factor for periodic limb movements in sleep. N Engl J Med. 2007;357:639–47.
8. Clemens S, Rye D, Hochman S. Restless legs syndrome: revisiting the dopamine hypothesis from the spinal cord perspective. Neurology. 2006;67:125–30.
9. Picchietti DL, et al. Pediatric restless legs syndrome diagnostic criteria: an update by the International Restless Legs Syndrome Study Group. Sleep Med. 2013;. doi:10.1016/j.sleep.2013.08.778.
10. Picchietti DL, Arbuckle RA, Abetz L, Durmer JS, Ivanenko A, Owens JA, et al. Pediatric restless legs syndrome: analysis of symptom descriptions and drawings. J Child Neurol. 2011;26:1365–76.
11. Benes H, Walters AS, Allen RP, Hening WA, Kohnen R. Definition of restless legs syndrome, how to diagnose it, and how to differentiate it from RLS mimics. Mov Disord. 2007;22(Suppl. 18):S401–8.
12. 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.
13. 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.
14. Evans AM. Growing pains: contemporary knowledge and recommended practice. J Foot Ankle Res. 2008;1:4.
15. Peterson HA. Growing pains. Pediatr Clin North Am. 1986;33:1365–72.

16. Walters AS, et al. Restless legs syndrome (Willis–Ekbom disease) and growing pains: are they the same thing? A side-bysidecomparison of the diagnostic criteria for both and recommendations for future research. Sleep Med. 2013;14(12):1247–52.
17. Picchietti DL, Stevens HE. Early manifestations of restless legs syndrome in childhood and adolescence. Sleep Med. 2008;9:770–81.
18. Tilma J, Tilma K, Norregaard O, Ostergaard JR. Early childhood-onset restless legs syndrome: symptoms and effect of oral iron treatment. Acta Pediatrica. 2013;102:221–6.
19. Picchietti DL, Rajendran RR, Wilson MP, Picchietti MA. Pediatric restless legs syndrome and periodic limb movement disorder: parent–child pairs. Sleep Med. 2009;10:925–31.
20. Picchietti DL, Walters AS. Restless legs syndrome and periodic limb movement disorder in children and adolescents: Comorbidity with attention-deficit hyperactivity disorder. Child Adoles Psych Clinics North Am. 1996;5:729–40.
21. Picchietti DL, England SJ, Walters AS, et al. Periodic limb movement disorder and restless legs syndrome in children with attention-deficit hyperactivity disorder. J Child Neurol. 1998;13:588–94.
22. Picchietti DL, Underwood DJ, Farris WA, et al. Further studies on periodic limb movement disorder and restless legs syndrome in children with attention-deficit hyperactivity disorder. Mov Disord. 1999;14:1000–7.
23. Chervin RD, Archbold KH, Dillon JE, et al. Associations between symptoms of inattention, hyperactivity, restless legs, and periodic leg movements. Sleep. 2002;25:213–8.
24. Lewin DS, Di Pinto M. Sleep disorders and ADHD: Shared and common phenotypes. Sleep. 2004;27:188–9.
25. Sadeh A, Pergamin L, Bar-Haim Y. Sleep in children with attention deficit hyperactivity disorder: a meta-analysis of polysomnographic studies. Sleep Med Rev. 2006;10:381–98.
26. Zak R, Fisher B, Couvadelli BV, et al. Preliminary study of the prevalence of restless legs syndrome in adults with attention deficit hyperactivity disorder. Percept Mot Skills. 2009;108:759–63.
27. Cortese S, Konofal E, Lecendreux M, et al. Restless legs syndrome and attention-deficit/hyperactivity disorder: A review of the literature. Sleep. 2005;28(8):1007–13.
28. Steinlechner S, Brueggermann N, Sobottka V, Benthien A, Behn B, Klein C, Schmid G, Lencer R. Restless legs syndrome as a possible predictor for psychiatric disorders in parents of children with ADHD. Eur Psychiatry Clin Neurosci. 2011;261(4):285–91.
29. Konofal E, Arnulf I, Lecendreux M, Mouren MC. Ropinirole in a child with attention-deficit hyperactivity disorder and restless leg syndrome. Pediatr Neurol 2005;32:350e1.
30. Konofal E, Lecendreux M, Deron J, et al. Effects of iron supplementation on attention deficit hyperactivity disorder in children. Pediatr Neurol. 2008;38:20–6.
31. Picchietti DL, Underwood DJ, Farris WA, Walters AS, Shah MM, Dahl RE, et al. Further studies on periodic limb movement disorder and restless legs syndrome in children with attention deficit/hyperactivity disorder. Mov Disord. 1999;14:1000–7.
32. Picchietti MA, Picchietti DL. Restless legs syndrome and periodic limb movement disorder in children and adolescents. Semin Pediatr Neurol. 2008;15(2):91–9.
33. 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.
34. Winkelmann J, Polo O, Provini F, Nevsimalova S, Kemlink D, Sonka K, Högl B, Poewe W, Stiasny-Kolster K, Oertel W, de Weerd A, Strambi LF, Zucconi M, Pramstaller PP, Arnulf I, Trenkwalder C, Klein C, Hadjigeorgiou GM, Happe S, Rye D, Montagna P. Genetics of restless legs syndrome (RLS): State-of-the-art and future directions. Mov Disord. 2007;22 (Suppl 18):S449–58.
35. Ferri R, Fulda S, Manconi M, Hoegl B, Ehrmann L, Ferini-Strambi L, Zucconi M. Night-to-night variability of periodic leg movements during sleep in restless legs syndrome and periodic limb movement disorder: comparison between the periodicity index and the PLMS index. Sleep Med. 2013;14:293–6.

36. Ferri R, Manconi M, Lanuzza B, Cosentino FI, Bruni O, Ferini-Strambi L. Age-related changes in periodic leg movements during sleep in patients with restless legs syndrome. Sleep Med. 2008;9:790–8.
37. Whittom S, Dauvilliers Y, Pennestri MH, Vercauteren F, Molinari N, Petit D, Montplaisir J. Age-at-onset in restless legs syndrome: a clinical and polysomnographic study. Sleep Med. 2007;9(1):54–9.
38. Ferri R, Zucconi M, Manconi M, Plazzi G, Bruni O, Ferini-Strambi L. New approaches to the study of periodic leg movements during sleep in restless legs syndrome. Sleep. 2006;29: 759–69.
39. Manconi M, Ferri R, Feroah TR, Zucconi M, Ferini-Strambi L. Defining the boundaries of the response of sleep leg movements to a single dose of dopamine agonist. Sleep. 2008;31: 1229–37.
40. Ferri R, Fulda S, Manconi M, Hoegl B, Ehrmann L, Ferini-Strambi L, Zucconi M. Night-to-night variability of periodic leg movements during sleep in restless legs syndrome and periodic limb movement disorder: comparison between the periodicity index and the PLMS index. Sleep Med. 2013;14:293–6.
41. 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.
42. Ferri R, Bruni O, Novelli L, Picchietti MA, Picchietti DL. Time structure of leg movement activity during sleep in attention-deficit/hyperactivity disorder and effects of levodopa. Sleep Med. 2013;14:359–66.
43. 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.
44. Hornyak M, Scholz H, Kohnen R, Bengel J, Kassubek J, Trenkwalder C. What treatment works best for restless legs syndrome? Meta-analyses of dopaminergic and non-dopaminergic medications. Sleep Med Rev. 2014;18(2):153–64.
45. Felt BT, Lozoff B. Brain iron and behavior of rats are not normalized by treatment of iron deficiency anemia during early development. J Nutr. 1996;126(3):693–701.
46. Panagiotou JP, Douros K. Clinicolaboratory findings and treatment of iron-deficiency anemia in childhood. Pediatr Hematol Oncol. 2004;21:519–32.
47. Silber MH, Ehrenberg BL, Allen RP, et al. An algorithm for the management of restless legs syndrome. Mayo Clin Proc. 2004;79:916–22.
48. Kryger MH, Otake K, Foerster J. Low body stores of iron and restless legs syndrome: a correctable cause of insomnia in adolescents and teenagers. Sleep Med. 2002;3:127–32.
49. Simakajornboon N, Gozal D, Vlasic V, et al. Periodic limb movements in sleep and iron status in children. Sleep. 2003;26:735–8.
50. Connor JR. Pathophysiology of restless legs syndrome: evidence for iron involvement. Curr Neurol Neurosci Rep. 2008;8:162–6.
51. Connor JR, Wang X-S, Allen RP, et al. Altered dopaminergic profile in the putamen and substantia nigra in restless leg syndrome. Brain. 2009;132:2403–12.
52. Peirano PD, Algarin CR, Chamorro RA, Reyes SC, Duran SA, Garrido MI, et al. Sleep alterations and iron deficiency anemia in infancy. Sleep Med. 2010;11(7):637–42.
53. 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.
54. Aurora RN, Kristo DA, Bista SR, Rowley JA, Zak RS, Casey KR, Lamm CI, Tracy SL, Rosenberg RS. 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: an American Academy of Sleep Medicine Clinical Practice Guideline. Sleep. 2012;35(8):1039–62.

55. Garcia-Borreguero D, Kohnen R, Silber MH, Winkelman JW, Earley CJ, Högl B, Manconi M, Montplaisir J, Inoue Y, Allen RP. 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(7):675–84.
56. Pelayo R, Dubik M. Pediatric sleep pharmacology. Semin Pediatr Neurol. 2008;15(2):79–90.
57. Walters AS, Mandelbaum DE, Lewin DS, et al. Dopaminergic Study Group. Dopaminergic therapy in children with restless legs/periodic limb movements in sleep and ADHD. Pediatr Neurol. 2000;22:182–6.
58. Kotagal S, Silber MH. Childhood-onset restless legs syndrome. Ann Neurol. 2004;56(6):803–7.
59. Starn AL, Udall JN Jr. Iron deficiency anemia, pica, and restless legs syndrome in a teenage girl. Clin Pediatr (Phila). 2008;47(1):83–5.
60. Cortese S, Konofal E, Lecendreux M. Effectiveness of ropinirole for RLS and depressive symptoms in an 11-year-old girl. Sleep Med. 2009;10(2):259–61.
61. Picchietti DL, Walters AS. Moderate to severe periodic limb movement disorder in childhood and adolescence. Sleep. 1999;22(3):297–300.
62. Guilleminault C, Palombini L, Pelayo R, et al. Sleepwalking and sleep terrors in prepubertal children: what triggers them? Pediatrics. 2003;111(1):e17–25.
63. Martinez S, Guilleminault C. Periodic leg movements in prepubertal children with sleep disturbance. Dev Med Child Neurol. 2004;46(11):765–70.
64. Hening WA, Allen RP, Early CJ, Picchietti DL, Silber MH. An update on the dopaminergic treatment of restless legs syndrome and periodic limb movement disorder. Sleep 2004;27:970e99.
65. Picchietti DL, Underwood DJ, Farris WA, Walters AS, Shah MM, Dahl RE, Trubnick LJ, Bertocci MA, Wagner M, Hening WA. Further studies on periodic limb movement disorder and restless legs syndrome in children with attention-deficit hyperactivity disorder. Mov Disord. 1999;14(6):1000–7.
66. England SJ, Picchietti DL, Couvadelli BV, Fisher BC, Siddiqui F, Wagner ML, Hening WA, Lewin D, Winnie G, Cohen B, Walters AS. L-Dopa improves Restless Legs Syndrome and periodic limb movements in sleep but not attention-deficit-hyperactivity disorder in a double-blind trial in children. Sleep Med. 2011;12(5):471–7.
67. Benbir G, Guilleminault C. Pramipexole: new use for an old drug—the potential use of pramipexole in the treatment of restless legs syndrome. Neuropsychiatr Dis Treat. 2006;2(4):393–405.
68. Guilleminault C, Palombini L, Pelayo R, Chervin RD. Sleepwalking and sleep terrors in prepubertal children: what triggers them? Pediatrics. 2003;111(1):e17–25.
69. Amos LB, Grekowicz ML, Kuhn EM, Olstad JD, Collins MM, Norins NA, D'Andrea LA. Treatment of pediatric restless legs syndrome. Clin Pediatr. 2014;53(4):331–6.
70. Picchietti D, Winkelman JW. Restless legs syndrome, periodic limb movements in sleep, and depression. Sleep. 2005;28:891–8.
71. Kim SW, Shin IS, Kim JM, et al. Bupropion may improve restless legs syndrome: a report of three cases. Clin Neuropharmacol. 2005;28:298–301.
72. Garcia-Borreguero D, Stillman P, Benes H, Buschmann H, Ray Chaudhuri K, Gonzalez Rodríguez VM, Högl B, Kohnen R, Carlo Monti G, Stiasny-Kolster K, Trenkwalder C, Williams A-M, Zucconi M. Algorithms for the diagnosis and treatment of restless legs syndrome in primary care. BMC Neurol. 2011;11:28.
73. Happe S, Sauter C, Klosch G, et al. Gabapentin versus ropinirole in the treatment of idiopathic restless legs syndrome. Neuropsychobiology. 2003;48(2):82–6.
74. Cundy KC, Sastry S, Luo W, et al. Clinical pharmacokinetics of XP13512, a novel transported prodrug of gabapentin. J Clin Pharmacol. 2008;48(12):1378–88.

75. Kushida CA, Becker PM, Ellenbogan AL, et al. XP052 Study Group. A randomized, double-blind, placebo-controlled trial of XP13512/GSK1838262 in patients with RLS. Neurology. 2009;72(5):439–46.
76. Bogan R, Bornemann MA, Kushida CA, et al, XP060 Study Group. Long-term maintenance treatment of RLS with gabapentin enacarbil: a randomized control study. Mayo Clin Proc. 2010;85(7):693–4.
77. Durmer JS, Quraishi GH. Restless legs syndrome, periodic leg movements, and periodic limb movement disorder in children. Pediatr Clin N Am. 2011;58:591–620.
78. Matthews WB. Treatment of restless legs syndrome with clonazepam. Br Med J. 1979;1:751.
79. Oshtory MA, Vijayan N. Clonazepam treatment of insomnia due to sleep myoclonus. Arch Neurol. 1980;37:119–20.
80. Buchfuhrer MJ. Strategies for the treatment of restless legs syndrome. Neurotherapeutics. 2012;9(4):776–90.
81. Saletu M, Anderer P, Saletu-Zyhlarz GM, Parapatics S, Gruber G, Nia S. Comparative placebo-controlled polysomnographic and psychometric studies on the acute effects of gabapentin versus ropinirole in restless legs syndrome. J Neural Transm. 2010;117:463–73.
82. Manconi M, Ferri R, Zucconi M, Bassetti CL, Fulda S, Aricò D, Ferini-Strambi L. Dissociation of periodic leg movements from arousals in restless legs syndrome. Ann Neurol. 2012;71(6):834–44.
83. Prince JB, Wilens TE, Biederman J, et al. Clonidine for sleep disturbances associated with attention-deficit hyperactivity disorder: a systematic chart review of 62 cases. J Am Acad Child Adolesc Psychiatry. 1996;35(5):599–605.
84. Newcorn JH, Schulz K, Harrison M, et al. Alpha 2 adrenergic agonists. Neurochemistry, efficacy, and clinical guidelines for use in children. Pediatr Clin North Am. 1998;45: 1099–122.
85. Allen RP, Barker PB, Horská A, Earley CJ. Thalamic glutamate/glutamine in restless legs syndrome: increased and related to disturbed sleep. Neurology. 2013;80(22):2028–34.
86. Ferri R, Manconi M, Aricò D, Sagrada C, Zucconi M, Bruni O, Oldani A, Ferini-Strambi L. Acute dopamine-agonist treatment in restless legs syndrome: effects on sleep architecture and NREM sleep instability. Sleep. 2010;33(6):793–800.

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