

New concepts in the management of restless legs syndrome

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ABSTRACT

Restless legs syndrome (RLS), also known as Willis-Ekbom disease (WED) is a neurological condition with an overall prevalence in adults of 5-10% in Europe and North America. It is characterised by strong feelings of restlessness and distressing paraesthesia-like sensations in the lower legs, particularly when at rest. The symptoms vary considerably in severity and frequency. RLS/WED has a variable clinical expression influenced by genetic, environmental, and medical factors. Research into the pathophysiology of RLS/WED has found that various genetic markers and existing dysfunctions in dopaminergic mechanisms and iron mechanisms play a central role. Until recently, the first line treatment of RLS/WED was with low dose dopamine agonists, with three drugs having been approved by the US Food and Drug Administration and the European Medicines Agency. However, the occurrence of dopaminergic augmentation and an overall increase in severity of symptoms during long term treatment with dopamine agonists is leading to a shift towards non-dopaminergic alternatives as initial treatments, and particularly to $\alpha 2\delta$ ligands. Recent international guidelines recommend, whenever possible, to start treatment with these drugs ($\alpha 2\delta$ ligands) to avoid augmentation from the start. Other (eg, glutamatergic or adenosine) neurotransmitters might also play an important role in causing RLS/WED and might thus lead to new treatments.

Introduction

Restless legs syndrome (RLS), also known as Willis-Ekbom disease (WED), was until recently a neglected condition. Only in the past few decades has research provided an insight into this common neurological disorder, which affects sleep and health.¹⁻³ It is characterised by strong feelings of restlessness and distressing paraesthesia-like sensations in the lower legs, particularly when at rest. Conversely, symptoms usually improve or resolve when the patient starts physical activity. The symptoms follow a circadian pattern and are worse in the evening. RLS/WED has been shown to be a major burden on those who have it. Reductions in health related quality of life scores are similar to or worse than those in patients with osteoarthritis, congestive heart failure, depression, or stroke.²⁻¹³

Improvements in the description of symptoms and in the understanding of the genetic background and pathophysiology of RLS/WED and the discovery of a distinctive response to specific therapeutic agents have contributed to building a body of knowledge such that today RLS/WED is accepted in the medical community as a real nosological entity.¹⁴

This review assesses the latest evidence on the diagnosis, pathophysiology, and treatment of RLS/WED. Until recently, dopaminergic agents were the first line treat-

GLOSSARY OF ABBREVIATIONS

EURLSSG—European Restless Legs Syndrome Study Group
GWAS—genome-wide association studies
IRLS—International Restless Legs Scale
IRLSSG—International RLS Study Group
IRP—iron regulatory protein
MRI—magnetic resonance imaging
PLMs—periodic leg movements
PLMS—periodic limb movements of sleep
RLSF—RLS Foundation
RLS—restless legs syndrome
SIT—suggested immobilisation test
sTR—soluble transferrin receptor
WED—Willis-Ekbom disease

ment for this disease, but we now know that these drugs can lead to augmentation of symptoms for many patients. Physicians need to be aware of the risks of treating RLS/WED patients with different drugs, and this is reflected in the most recent evidence based and expert consensus guidelines discussed below.

Epidemiology of RLS/WED

RLS/WED is a common condition, with considerable clinical variability. More than 50 population based prevalence

studies have shown that RLS/WED affects 5-10% of European and North American adults, with 2-3% experiencing moderate to severe symptoms.^{4 15} Women are affected about twice as often as men. The mean age of onset is during the third or fourth decade, but paediatric cases are not rare with overall paediatric prevalences of 2-4%.^{16 17}

Race/ethnicity, sex, and age

Few studies have examined the prevalence RLS/WED by race/ethnicity within the same population, and non-comparison reports have suggested that the proportion of people with RLS/WED, especially those experiencing symptoms at least once a month, is higher among white people than in other populations.¹²⁻²² In adults over the age of 35, RLS/WED occurs about twice as often in women as in men.^{3 23} However, virtually no sex difference is seen for adults under 35 years old. RLS/WED can begin at any time from childhood to virtually any age.^{24 25} The later in life RLS/WED starts, the more rapid the onset and the greater the likelihood that it is associated with another medical condition such as neuropathy, iron deficiency, or renal disease.

Incidence

Few studies have assessed the incidence of RLS/WED.^{22 26} They suggest that new cases are common, occurring in 0.8-2.2% of the general population annually; however, remission is also common.^{22 26} A study from Japan showed that frequency, but not severity, of RLS/WED symptoms may predict the persistence of the condition over time.²⁷

Main challenges in epidemiology

Although most studies performed over the past 10 years have used the same diagnostic criteria,²⁸ these have been used in a heterogeneous way. Therefore, no standardisation exists for how the essential diagnostic criteria are phrased, including a lack of translations into frequently spoken languages and consideration of culturally adapted versions. This might have contributed to the large variation in the prevalence of RLS/WED that has been reported in different countries and even within the same country.²⁹

Most published studies in the past 15 years have been cross sectional. This type of study is adequate for reporting the prevalence in general or specific populations, but it is not well suited to risk factor analysis. It does not enable a clear time sequence to be established between the onset of a given risk factor and the onset of RLS/WED, as both are assessed at the same point in time. More cohort studies in the field of RLS/WED epidemiology are needed to allow repetitive assessment of the same population over time, thereby providing better analysis of risk factors.³⁰

Furthermore, epidemiological research needs to converge with other aspects of RLS/WED research such as genetics, brain imaging, and pathophysiology; new findings and technical developments need to be integrated into epidemiological research. The identification of an increasing number of genetic loci related to RLS/WED

requires the collection of blood and DNA samples in large population based studies whenever possible. This allows for comparison of allele frequencies across populations and identification of genetic susceptibility factors that increase the probability of disease development. New imaging techniques, especially functional magnetic resonance imaging (MRI) methods, represent promising tools in the near future.

Prospective cohort studies are needed to assess RLS/WED in addition to other conditions, collecting family and medical history, images, biomaterials, risk factors, and diagnostic investigations repeatedly over time to analyse genetic susceptibility, potential biological pathways, functional and structural brain changes, comorbidity patterns, and patient reported outcomes in a broad number of phenotypes.

Sources and selection criteria

We did a literature search using the PubMed database from its inception to 1 November 2016 and used the broad search term “restless legs syndrome”. We included systematic reviews, meta-analyses, and also original studies published in English. We included original studies if they had a duration of at least six months. We categorised studies according to the level of evidence (class I- IV) that they provided and according to the categorisation system used by the International RLS Study Group (IRLSSG) in its recent guidelines.³¹ Accordingly, the highest evidence (class I) is provided by studies with concealed randomisation, clearly defined primary endpoints and inclusion and exclusion criteria, dropouts accounted for and sufficiently low to minimise bias, and equivalent baseline characteristics among groups or appropriate statistical adjustment to account for any differences. A class II study was one that matched all but one of the criteria for a class I study. We considered effective any drug for which convincing evidence existed from at least one class I or two class II studies; we considered an intervention to be probably effective if one class II study supported its efficacy.

Clinical definition of RLS-WED

According to an international expert consensus, the diagnosis of RLS/WED is made on the basis of the presence of clinical symptoms.^{14 32} RLS/WED is mainly characterised by neurosensory symptoms, which are strong feelings of restlessness and distressing paraesthesia-like sensations in the lower legs.^{33 34} RLS/WED typically manifests when the patient is at rest, and a state of relaxation or comfort is associated with a greater likelihood of symptoms occurring. Conversely, symptoms usually improve or resolve when the patient begins physical activity; as symptoms arise, patients will experience an intense urge to move in order to relieve the discomfort felt.³⁵ In addition, the symptoms follow a circadian pattern and are worse in the evening.³⁶ RLS/WED has variable expression influenced by genetic, environmental, and medical factors. The symptoms vary considerably in frequency from less than once a month or year to daily; severity ranges from mildly annoying to disabling, and symptoms may also remit for differing periods of time.¹⁴

Box 1 | Diagnostic criteria for restless legs syndrome (RLS)/Willis-Ekbom disease (WED)

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
Sometimes the urge to move the legs is present without the uncomfortable sensations. The arms or other parts of the body may also be involved in addition to the legs.²³⁻⁴¹ Often the urge to move and the accompanying sensory symptoms are intermingled together and difficult to separate symptomatically or temporally. The sensations are described as painful in up to 30-50% of RLS/WED patients.³⁷⁻³⁹
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
When examined by means of objective tests, such as the suggested immobilisation test,⁴² patients with RLS/WED report pronounced sensory symptoms in the legs and the presence of periodic leg movements while both resting and awake, and these 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
RLS/WED patients generally feel at least some symptomatic relief almost immediately with the start of activity or very soon thereafter. Usually, the simple act of moving or walking suffices. Symptoms should generally not return or worsen with continued activity. When symptoms are very severe, relief through activity may not be noticeable but must have been previously present.³⁵⁻⁴³
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 day³³
Clinicians should ask about symptoms both at rest in the morning and during the evening and at night. The critical clinical question for this criterion involves ascertaining circadian differences in response of symptoms to rest. Patients with RLS/WED should report fewer symptoms when resting in the morning than in the evening or night. Patients with very severe RLS/WED, however, may have relentless symptoms persisting throughout the day and night without any noticeable circadian variation. In these cases, patients should be able to report that this circadian/evening-night-time increase in symptoms was previously present in the earlier course of the disease.
5. The occurrence of the above features is not solely accounted for by symptoms primary to another medical or behavioural condition (eg, neuropathy, myalgia, venous stasis, leg oedema, arthritis, leg cramps, positional discomfort, or habitual foot tapping)
These conditions, often referred to as “RLS/WED mimics,” have been commonly confused with RLS/WED, particularly in epidemiological surveys, because they produce symptoms that meet, or at least come very close to meeting, all of the above criteria.

Current diagnostic criteria

The first diagnostic definition of RLS/WED based on expert consensus and developed in 2003 following a workshop at the National Institutes of Health enabled a rapid development of research and treatments for RLS/WED over the subsequent decades.³³ Clinical experience accumulated since then has led to a recent update of these diagnostic criteria,¹⁴ which state that RLS/WED is diagnosed by ascertaining symptom patterns that meet the five essential criteria in box 1, using clinical specifiers where appropriate. These five essential criteria have to be met for a positive diagnosis.

Supporting features

RLS/WED has both a motor symptom—periodic leg movements (PLMs)—and several common clinical patterns that can support a diagnosis, particularly when diagnostic certainty is lacking.

Periodic leg movements

PLMs are repetitive, stereotyped, flexor withdrawal-like movements of the legs that occur during sleep and are thus called periodic limb movements of sleep (PLMS) (fig 1). PLMs can also occur during wakefulness. PLMS occur

in about 80-89% of RLS/WED patients seen in a clinic setting, and PLMs during wakefulness occur at a similar frequency.⁴⁴⁻⁴⁶ Contrary to initial expectations, PLMS are not the cause of sleep disturbance in RLS/WED—rather, they may reflect some RLS/WED biology partially independent of this. They occur with significant transient changes in electroencephalograms,⁴⁷⁻⁴⁹ heart rate,⁵⁰⁻⁵³ and blood pressure,⁵³⁻⁵⁶ which may reflect an underlying process that produces an increased risk of cardiovascular disease, which has been observed in RLS/WED patients in several but not all studies.⁵³⁻⁶⁰

PLMS, although fairly specific to RLS/WED, are not very sensitive,⁴⁴ as they occur in several other medical conditions,⁶¹⁻⁶⁵ and with many drugs,⁶⁶⁻⁶⁷ and are common among adults over the age of 45.⁶¹⁻⁷⁰ PLMS support a diagnosis of RLS/WED when present to a degree greater than expected for the patient's age in the absence of evidence for other disease states or drugs that could induce or aggravate PLMS.

In contrast, PLMs during relaxed wakefulness, as measured for example by the suggested immobilisation test (SIT), have high sensitivity and specificity for RLS/WED, particularly if evaluated multiple times and combined with subjective leg discomfort scores in the multiple suggested immobilisation test.⁴²⁻⁷¹ Measuring PLMs during wakefulness with the SIT is also a valid and reliable way to evaluate severity and treatment response of RLS/WED.³⁵

Dopaminergic treatment response

Most RLS/WED patients show at least some initial clinical benefit from dopaminergic drugs, such as levodopa and dopamine agonists. Large clinical trials with diverse patient populations show a good clinical response to dopamine agonist treatment in about 60-75% of participants.⁷² Thus, in general clinical practice, a failure to respond to dopaminergic treatment should raise some concern about the accuracy of diagnosis but does not necessarily exclude a diagnosis of RLS/WED. However, as non-response to dopaminergic drugs is possible but rare, compliance, dose, and concomitant drugs should be checked.

Family history

RLS/WED has been noted to occur commonly in families, indicating important genetic or shared environmental factors for the disease.⁴⁵⁻⁷⁴ The risk of RLS/WED is nearly six times higher among first degree relatives of RLS/WED patients than in other people.⁷⁵ In addition, twin studies have shown high concordance for RLS/WED.⁷⁶⁻⁷⁸ The presence of RLS/WED among first degree relatives is thus supportive of the diagnosis.

Lack of profound daytime sleepiness

Patients with moderate to severe RLS/WED have chronic short sleep times but generally do not report a level of daytime sleepiness that would be expected for the degree of sleep loss.²⁻⁸⁰ They will usually have slightly elevated but still normal Epworth Sleepiness Scale scores.²⁻⁸³ Thus, hyperarousal might be part of the pathophysiology of RLS/WED.⁸⁰ Profound sleepiness should prompt evaluation for another cause, such as sleep apnoea, narcolepsy, or a drug effect.⁸⁴

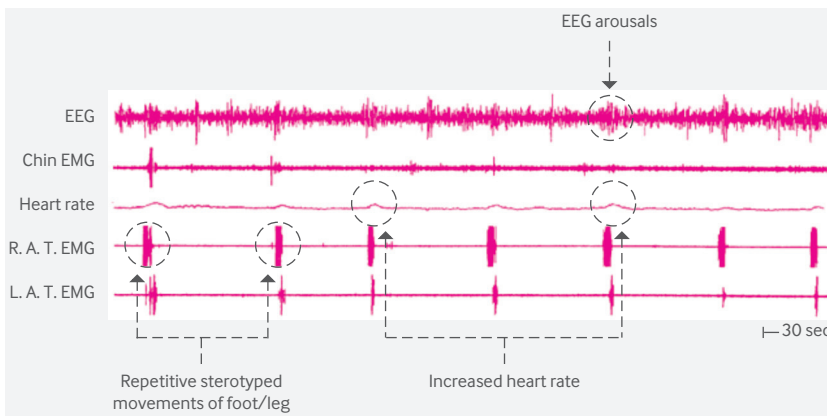


Fig 1 | Periodic leg movements (PLMs) during sleep. The presence of repetitive PLMs causes arousals seen on electroencephalography, which contribute to sleep fragmentation. In addition, repetitive sympathetic arousals are caused, which might lead in the long term to systemic hypertension and increased cardiovascular risk

Comorbid conditions

Previous classifications of RLS into primary and secondary types are being increasingly questioned, as these might suggest an inappropriate causal relation.⁸⁵ Although in certain conditions (eg, iron deficiency), treatment of the underlying disease may reduce or eliminate symptoms of RLS/WED, the term comorbid RLS/WED seems to be more appropriate for most other associations. RLS/WED might be seen as a continuous spectrum with a major genetic contribution at one end and a major environmental or comorbid disease contribution at the other.⁸⁵

Conditions most consistently associated with RLS/WED in cross sectional epidemiological studies are pregnancy, iron deficiency, chronic kidney failure, major depressive disorder, generalised anxiety disorder, panic disorder, and attention-deficit/hyperactivity disorder. In addition, some studies have found positive associations with cardiovascular disease, including coronary heart disease and stroke.⁵⁶⁻⁸⁶ Limited mortality data suggest an increased risk of death in women with RLS/WED and possibly increased mortality in RLS/WED patients with chronic kidney failure. However, causal inference has yet to be elucidated with all of these associations, and a recent review of RLS/WED associated with comorbidities identified an increased prevalence of RLS/WED only in iron deficiency and kidney disease.⁸⁵

Clinical course

A history of remission and relapse in symptoms should be noted as a possible indicator of the subsequent course of the condition. The typical pattern of an insidious onset with gradual progression over a period of years to a clinically significant disease occurs more frequently with early age of onset.^{24,25} However, in some cases, relatively rapid symptom development over months to a few years is reported with a variable degree of symptom progression after onset.⁸⁷

What do we know about the cause of RLS/WED?

Genetics

RLS/WED is a highly familial trait but genetically complex, with estimates of concordance between 54% and 69%

reported in twin studies.^{76,77} Genome-wide linkage analyses have identified at least eight major susceptibility loci for RLS/WED: RLS1 on chromosome 12q12-q21, RLS2 on 14q13-21, RLS3 on 9p24-p22, RLS4 on 2q33, RLS5 on 20p13, RLS6 on 19p13, RLS7 on 16p12.1, and RLS8 on 2p14.⁸⁸⁻⁹⁵ Recent genome-wide association studies (GWAS) of RLS/WED, in populations of primarily European ancestry, identified six additional loci associated with RLS/WED, which are represented by single nucleotide polymorphisms on chromosomes 2p14 (MEIS1 and an intergenic region 1.3 Mb downstream of MEIS1), 6p21.2 (BTBD9), 15q23 (MAP2K5/SKOR1), 9p24.1-p23 (PTPRD), and 16q12.1 (TOX3/BC034767).⁷⁴⁻⁹⁷

Despite these advances, further GWAS still need to be developed in RLS/WED. The published studies have rather small sizes (<6000 cases) compared with those for other complex disorders,⁹⁸ which is reflected in the number of risk loci identified. Moreover, variants across the entire frequency spectrum are expected to contribute to disease susceptibility, including also rare and low frequency variants,⁹⁹ which have not so far been assessed by GWAS of RLS/WED.

However, the question is what percentage of total RLS/WED heritability can be explained by these six associated loci, or by the currently known associated markers and risk alleles? Six risk markers that have been evaluated in two cohorts from Canada and the US,^{95,100} in both case-control groups and extended family based associations, account for less than 10% of the total heritability. Until the precise variants responsible for the association are identified, these measurements should be regarded as only approximations; they presumably will have higher penetrance and odds ratios.¹⁰⁰

Dopaminergic dysfunction

The most compelling argument in favour of a dopaminergic dysfunction is the striking improvement in symptoms with dopaminergic drugs.³¹ However, the mechanism of this improvement has never been fully elucidated. Brain imaging of the nigrostriatal system has yielded conflicting results,¹⁰¹ and the substantia nigra does not show cell loss at autopsy.¹⁰² Most studies using single photon emission computed tomography scanning to assess dopamine transporter density have shown normal results, but a positron emission tomography study showed a decreased number of dopamine transporters,¹⁰³ possibly reflecting a decreased number of membrane bound dopamine transporters. Alternatively, this could also be a reflection of increased extracellular dopamine.

The number of D2/D3 receptors may be decreased in the mesolimbic areas, as shown by raclopride binding.¹⁰⁴ Also, lesioning of the A11 area that gives rise to a dopaminergic pathway projecting to the spinal cord results in overactivity in mice.¹⁰⁵ However, an autopsy study did not show a dramatic cell loss in the A11 hypothalamic region of patients with RLS/WED.¹⁰⁶

Neurophysiological studies have shown altered spinal excitability with decreased inhibition.¹⁰⁷

Iron deficiency

Iron deficiency has also repeatedly been shown to be associated with RLS/WED.¹⁰⁸ In idiopathic RLS/WED,

central nervous system iron storage may be impaired, whereas the systemic iron may be normal. Brain MRI studies of patients with RLS/WED have shown decreased iron in the midbrain, and a correlation between decreased brain iron and RLS/WED severity has been reported.¹⁰⁹ An autopsy study found that H-ferritin was markedly reduced, whereas L-ferritin was present but had a different morphology.¹⁰² Another autopsy study found that iron regulatory protein (IRP) 1 concentrations were decreased in the brains of patients with RLS/WED, whereas IRP2 was upregulated.¹¹⁰

The mechanism by which iron deficiency leads to dopaminergic dysfunction is unclear. Iron has a complex effect on dopaminergic function. It is a cofactor for tyrosine hydroxylase and is integral to D2 receptor function.^{102 111}

Role of opiates and other neurotransmitters

Other systems, such as the opiate, glutamate, adenosine, and hypocretin systems,¹¹²⁻¹¹⁴ might also be involved and might thus be future targets of drug action.

Diagnosis of RLS/WED

Update on recent diagnostic criteria

The diagnosis of RLS/WED is based on the presence of all five diagnostic criteria described in box 1,¹⁴ and supportive criteria should be assessed as well. Clinical diagnosis may yield 16% false positives and 15-20% false negatives.¹¹⁵⁻¹¹⁷ Even when structured interviews are used, the positive predictive value of the diagnostic criteria does not exceed 86%.¹¹⁸ Thus, additional objective testing might be necessary in one in seven patients. This might include polysomnography,¹¹⁹ SIT,³⁵ and/or actigraphy.¹²⁰

Additional medical evaluation

Several relatively simple procedures may help to exclude secondary causes of RLS/WED, particularly iron deficiency and peripheral neuropathy.¹²¹

Basic laboratory evaluation

Laboratory parameters include complete blood cell count, markers of kidney and liver function, iron metabolism, inflammation, endocrine function (glucose, thyroid hormones), and vitamins (B₁₂, D, and folic acid). Basic biochemistry is also needed, with determination of plasma concentrations of glucose, creatinine, urea, potassium, calcium, and sodium.

For iron metabolism, two variables are of special interest:

- Serum ferritin—low concentrations of serum ferritin may precede a decrease in serum iron concentration. Serum ferritin concentrations below 50 ng/mL (<50 µg/L) have been associated with RLS/WED, even in the absence of decreased haemoglobin or serum iron concentrations.^{122 123}
- The concentration of the soluble transferrin receptor (sTR) reflects the total body mass of cellular transferrin receptor.¹²⁴ A high sTR concentration is considered to be the initial response to declining body iron supply.¹²⁵

Urinary evaluation

In addition to urinalysis, a 12 or 24 hour urine collection for creatinine clearance should be done to determine the glomerular filtration rate in patients at risk of kidney disease. Alternatively, kidney function can be determined by using measures of serum creatinine. Declining renal function is associated with increasing prevalence of RLS/WED.¹²⁶

Electromyography and nerve conduction studies

RLS/WED is not uncommon in several neurological conditions such as spinal cord dysfunction (Charcot-Marie-Tooth type 2, spinocerebellar ataxias).^{127 128} Electromyography and nerve conduction studies should be used primarily when peripheral neuropathy is suspected on clinical grounds.¹²⁹

Other investigations

In certain cases, extensive complementary tests (MRI, special cerebrospinal fluid and serum determination, venous ultrasonography of the legs) should be carried out to confirm the existence of other factors and conditions that may contribute to so called “comorbid RLS/WED,” such as lumbosacral radiculopathy, Lyme disease, monoclonal gammopathy of undetermined significance, myelopathy, or myelitis, or to make a differential diagnosis from others diseases, such as deep venous thrombosis or chronic venous insufficiency.

Update on management

Treatment for RLS/WED should be started when the symptoms impair the patient’s quality of life, daytime functioning, social functioning, or sleep. Consideration should be given to fully replenishing iron stores and maximising non-drug treatments before starting treatment, although patients who are diagnosed as having RLS/WED will have already tried and tested many non-drug options by the time they seek medical assistance (eg, activities that keep them concentrated, avoidance of caffeine and alcohol, hot baths). Use of drugs that are known to exacerbate RLS/WED symptoms should also be reconsidered—these include antihistamines, dopamine antagonists, anti-nausea drugs, antidepressants, serotonergic reuptake inhibitors, neuroleptics, β blockers, some anticonvulsants, and lithium.¹³⁰ Furthermore, measures (including oral iron supplements and, in some cases, intravenous iron administration) should taken to ensure that ferritin concentrations are raised above 50 ng/mL.

Several drugs have been evaluated over the short term, under controlled conditions for RLS/WED. However, as RLS/WED is often a lifelong disease, only those drugs that have been studied over periods longer than six months and have been approved in the EU, the US, and Japan are mentioned here (with the exception of oxycodone extended release, which is not approved in Japan).³¹

Dopaminergic agents

Pramipexole

Pramipexole has been shown to be effective for the treatment of RLS/WED for up to six months on the basis of the results of a class I, 26 week, double blind, randomised,

placebo controlled study of pramipexole (0.125-0.75 mg) versus placebo in 331 RLS patients. It reported an improvement in International Restless Legs Scale (IRLS) score of 13.8 (SE 0.8) for pramipexole compared with 11.1 (SE 0.8) for placebo, as well as improvements in the Clinical Global Impression scale in 68.5% versus 50% of patients ($P=0.001$) and in the Patient Global Impression scale in 62.3% versus 44.0% ($P=0.001$).¹³¹ Pramipexole is probably effective for one year on the basis of class II evidence (no placebo in long term phase) from a 52 week, double blind, randomised controlled study in 719 patients (0.25 and 0.5 mg/day), which reported a change in IRLS score compared with placebo of -0.6 (pramipexole 0.25) and -3.2 (pramipexole 0.5) (both $P<0.05$).¹³² The most frequently reported adverse events associated with the use of pramipexole include sleepiness, nausea, and insomnia.³¹

Ropinirole

Ropinirole has been shown to be effective for the treatment of RLS/WED for six months on the basis of the results of a class I evidence from a randomised, double blind, placebo controlled study of 404 patients with severe idiopathic RLS/WED (median dose 1.8 mg/day). The adjusted mean treatment difference in IRLS score was -2.5 ($P<0.05$) at 26 weeks, and change from baseline was -20.4 at week 67 for remaining patients ($P<0.05$). It is probably effective for one year on the basis of the results from two open label prospective studies (median ropinirole doses of 1.6 or 2.0 mg/day).^{133 134} In the first study, the IRLS total score improved by 12 versus baseline at week 52.¹³³ The second study found that mean IRLS baseline scores improved at the end of the double blind phase by 15.9 (SE 0.76) for ropinirole and by 13.4 (0.77) for placebo ($P<0.05$), with an improvement by 20.4 (0.55) during the open label phase.¹³⁴ The most frequently reported adverse events include nausea, headache, fatigue, dizziness, and vomiting.³¹

Rotigotine

Rotigotine is considered effective for the treatment of RLS/WED for six months on the basis of class I evidence from two double blind, randomised studies that showed that doses of 2 mg and 3 mg were superior to placebo in patients with moderate to severe idiopathic RLS/WED.^{135 136} The improvements in IRLS total score compared with placebo were 11.1 for 0.5 mg ($P=0.068$), 11.2 for 1 mg ($P=0.054$), 13.5 for 2 mg ($P<0.001$), and 14.2 for 3 mg ($P<0.001$). The most frequently reported adverse events are application site reactions, nausea, headache, and fatigue.³¹

Non-dopaminergic agents

$\alpha 2\delta$ ligands

Gabapentin enacarbil—Although seven double blind studies have evaluated the efficacy of gabapentin enacarbil in treating RLS/WED, all of which showed an average improvement in symptom severity at doses between 600 and 1200 mg per day,¹³⁷⁻¹⁴³ only one of these class I studies met our minimum six month study duration criterion. This study reported that gabapentin enacarbil (1200 mg/

day) improved IRLS score at 24 weeks by 15.5 and that relapse was less common in the active treatment arm compared with placebo (9% v 23%; $P=0.02$).¹³⁸

Pregabalin—At a dose of 150-450 mg/day, pregabalin is considered effective for the treatment of RLS/WED for one year on the basis of class I evidence from one randomised, double blind study that evaluated the efficacy of pregabalin and the incidence of augmentation over 52 weeks in 719 patients. Pregabalin significantly reduced the IRLS score compared with pramipexole at 52 weeks (-3.8 and -3.1 , respectively; $P<0.001$). The rate of augmentation over a period of 40 or 52 weeks was significantly lower with pregabalin than with pramipexole at a dose of 0.5 mg (2.1% v 7.7%; $P=0.001$) but not at a dose of 0.25 mg (2.1% v 5.3%; $P=0.08$).¹⁴⁴

Opiates

Oxycodone extended release

Oxycodone is considered effective in treatment resistant RLS/WED on the basis of one class II study that consisted of a high quality 12 week, randomised, double blind, placebo controlled phase ($n=304$) followed by a 40 week open label extension ($n=197$). Prolonged release oxycodone-naloxone (5.0 mg/2.5 mg twice daily up-titrated to a maximum dose of 40 mg/20 mg twice daily) was shown to be effective in RLS/WED refractory to other treatments.¹⁴⁵ Improvement in IRLS score at 12 weeks was significantly greater for prolonged release oxycodone-naloxone (-16.6) than for placebo (-9.5) ($P<0.001$), and this beneficial effect continued throughout the extension phase, (IRLS -5.7 at week 40 compared with baseline).

Methadone

Two low quality studies have shown sustained therapeutic benefit of methadone over two to 10 years in RLS/WED patients refractory to other treatments.^{31 146 153} A retrospective, 10 year, longitudinal assessment of dopamine agonists and methadone for the treatment of RLS found that patients taking methadone did not discontinue treatment or develop augmentation during this time.¹⁴⁷ A case series reported that at least 75% of patients ($n=29$) being treated with methadone (mean 15.5 mg/day) experienced a reduction in RLS symptoms.¹⁴⁸

Which treatment works best?

Two types of drugs have been extensively investigated for the treatment of RLS/WED: dopamine agonists and $\alpha 2\delta$ ligands. Both have been shown to be clinically effective in treating sensory symptoms.¹⁴⁹ Dopamine agonists are more effective in treating PLMs, whereas $\alpha 2\delta$ ligands are effective in consolidating sleep.¹⁴⁹ In fact, electroencephalographic arousals associated with PLMs respond equally well to both types of drugs.¹⁵⁰ However, several large retrospective cohort studies have examined augmentation rates during long term treatment (5-10 years) with dopaminergic agonists, showing rates of dopaminergic augmentation and no improvement in more than 40% of patients.¹⁴⁷⁻¹⁵²

Because of the link between dopaminergic treatment and a progressive loss of response, the most recent international guidelines recommend that whenever

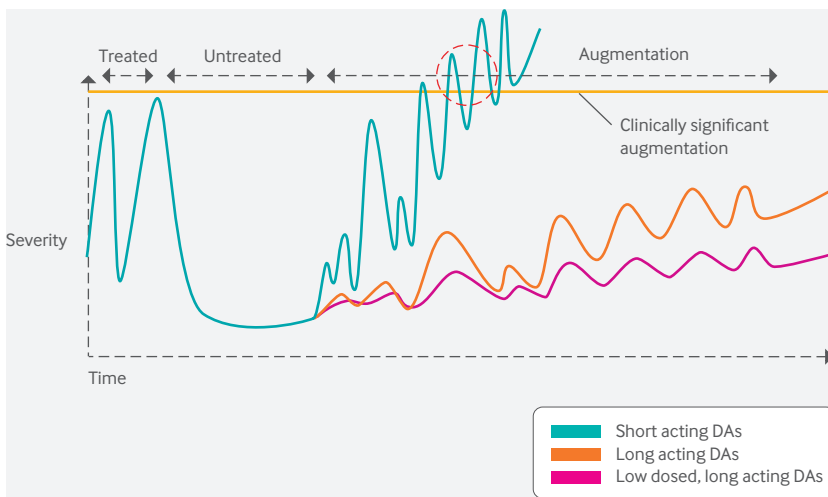


Fig 2 | Therapeutic response during treatment with dopamine agonists. At the beginning of treatment with dopamine agonist, pre-existing fluctuations in symptom severity cease and initial therapeutic benefit is obtained. However, with longer duration of treatment these fluctuations will eventually re-emerge until the severity matches or even exceeds that before any treatment had been started. This process is called dopaminergic augmentation and can take a variable amount of time to occur. There is general agreement that treatment with long acting dopamine agonists delays the process somewhat. Certainly, the use of low doses delays the process further, prolonging therapeutic response

possible the initial treatment of choice should be an $\alpha 2\delta$ ligand.^{153 154} The most effective preventive strategy involves not using dopaminergic agents unless absolutely necessary. Should a dopaminergic treatment be needed to manage the symptoms effectively, the dopaminergic load should be reduced by using the lowest effective dose for the shortest possible period of time. In addition, a long acting dopamine agonist might be preferable owing to its likely lower risk of augmentation. The only $\alpha 2\delta$ ligand approved for RLS/WED is gabapentin enacarbil, and it is not yet available in Europe.

Furthermore, recent studies have reported on the efficacy of opioids for the treatment of RLS/WED, when resistant to dopamine agonists.¹⁵⁵ Recent guidelines have taken these new data into account and highlight that a low dose of an opioid (prolonged release oxycodone¹⁴⁵ or methadone¹⁴⁷) may be considered in patients with very severe augmentation.^{153 156}

Long term treatment of RLS/WED

During long term treatment of RLS/WED, plasma ferritin concentrations should be kept over 50-75 $\mu\text{g}/\text{mL}$, by using oral iron if necessary. Drugs that are known to exacerbate RLS/WED, such as antidepressants, antihistamines, or dopamine blockers, should obviously be avoided unless strictly necessary. Patients should be encouraged to have good sleep hygiene with regular bedtimes.

If a patient is already being treated with a dopaminergic agent, the lowest possible cumulative daily dose should be used to control the most bothersome RLS/WED symptoms, and the total daily dose should never exceed maximum recommended levels (pramipexole 0.5 mg, ropinirole 4 mg, rotigotine 3 mg).¹⁵³ However, even low dose dopaminergic treatments carry a risk of augmentation.¹⁴⁴ Physicians should explain to patients that the goal of treatment is not to eradicate symptoms

completely but to ensure that they do not interfere with quality of life.¹⁵³ If symptoms become bothersome, the dose can be increased cautiously, but this will increase the risk of development of augmentation.¹⁵³ A non-dopaminergic agent can be added if concerns about the dose of the dopaminergic drug occur.¹⁵³

Intermittent (non-daily) treatment of RLS/WED to prevent augmentation

Starting daily treatment of RLS/WED should be deferred as long as possible until symptoms occur almost daily. The goal of intermittent dosing should be pursued, especially if symptoms are infrequent (<1-2/week), or as preventive therapy before predictable conditions of immobility (eg, long car or plane trips, medical procedures).

Using longer acting dopamine agonists

Longer acting dopaminergic agonists may cause less augmentation than shorter acting dopamine agonists (fig 2). Nevertheless, whether this is because long acting dopamine agonists may be actually masking the development of augmentation (by treating the typical first symptom of earlier onset of symptoms) remains controversial, making it difficult to know whether they actually cause less frequent augmentation problems.

Fluctuating RLS/WED symptoms

Longitudinal studies show that the intensity of RLS/WED symptoms fluctuates and that some patients seem to go into spontaneous remission.^{22 27} Therefore, in patients with a history of notable fluctuating RLS/WED symptoms, intermittently attempting to reduce the dose or even discontinue the drug may be appropriate to ensure that they are being treated with the lowest effective dose.¹⁵³

Switching to an alternative dopaminergic agent

Switching from one dopamine agonist to another is generally not considered useful for preventing (or treating) augmentation, except for switching from levodopa to a longer acting formulation of a licensed dopamine agonist.¹⁵⁷

Augmentation

Augmentation, the main complication of treatment, was first described and defined in 1996 when it was reported in 73% of RLS/WED patients treated with carbidopa/levodopa. In this report, the main feature of augmentation was identified as a worsening of symptom severity manifested by an earlier onset of symptoms in the afternoon or evening compared with before the start of treatment, which was severe enough to require modification treatment in 50% of patients.¹⁵⁸ Since then, a substantial effort has been made to further refine criteria that identify and evaluate augmentation. A consensus conference sponsored by the National Institutes of Health in 2003 developed an operational definition of augmentation based on clinical experience,³³ and this was followed by the Max Planck Institute's operational criteria in 2006 (box 2).¹⁵⁹ More recently, a task force established by the IRLSSG in conjunction with the European Restless Legs Syndrome Study Group (EURLSSG)

Box 2 | Max Planck Institute criteria for augmentation¹⁵⁹

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 previous 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 with 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 if measured by polysomnography or the suggested immobilisation test)
- d. Duration of relief from treatment is shorter.

Augmentation requires criteria A+B, A+C, or A+B+C to be met

and the RLS Foundation (RLSF) developed evidence based and consensus based recommendations for the prevention and long term treatment of dopaminergic induced augmentation in RLS/WED.

Augmentation manifests as a frequently fluctuating but slowly progressive increase in symptom severity and is difficult to differentiate from the symptoms of RLS/WED itself.¹⁵³ Its progressive nature means that it does not become evident immediately after the start of treatment. However, its likelihood increases with the duration and dose of treatment, as has been shown in a study that compared two doses of pramipexole.¹⁴⁴ All this makes augmentation hard to prevent. Furthermore, a recent study suggests that the risk of impulse control disorder is greatly increased in patients during augmentation.¹⁶⁰

The worsening of RLS/WED that occurs during augmentation probably reduces the response rate to future non-dopaminergic agents such as $\alpha 2\delta$ ligands, although insufficient data are available to establish this.

The recent IRLSSG/EURLSSG/RLSF guidelines seek to facilitate the identification of augmentation in clinical practice by recommending that physicians consider the presence of augmentation whenever a patient who has been on stable treatment for at least six months requests additional therapy.¹⁵³ Four screening questions, which have yet to be validated, may be used for this purpose in patients treated with dopaminergic agents. An affirmative answer to any of these four questions should lead the physician to suspect the presence of augmentation:

1. Do RLS/WED symptoms appear earlier than when the drug was first started?

2. Are higher doses of the drug now needed, or do you need to take the medicine earlier, to control the RLS/WED symptoms compared with the original effective dose?

3. Has the intensity of symptoms worsened since you started the treatment?

4. Have symptoms spread to other parts of the body (eg, arms) since you started the treatment?¹⁵³

However, initial symptoms of augmentation deserve special attention by clinicians, particularly because preventive measures can still be taken at this stage. Classic features of initial augmentation are breakthrough crises during the daytime, increase in symptom frequency or symptom intensity, shorter duration of treatment effects, symptoms in previously unaffected body parts, worsening of sleep efficacy or sleep quality, increased PLMs during sleep or wakefulness, need for additional treatment, or overall decrease in therapeutic efficacy.^{161 162}

Implications for initial treatment and prevention and treatment of augmentation

As augmentation is probably exclusively related to the specific action of the dopaminergic system, and this risk is strongly correlated with the dose and duration of treatment,¹⁴⁴⁻¹⁶³ the most effective strategy to prevent augmentation would be not to use dopaminergic treatment or at least to keep the dopaminergic load as low as possible.¹⁵³ Other factors that have been reported to contribute to an increased risk of augmentation include low iron stores, greater severity of RLS/WED symptoms before starting treatment, and a family history of RLS/WED or lack of neuropathy.¹²³⁻¹⁶⁵ Figure 3 shows the augmentation treatment algorithm as established in the international guidelines of the IRLSSG.¹⁵³

Ensuring response over the long term

The consensus is that the most effective strategy that should be taken to avoid development of augmentation in RLS/WED patients is not to use dopaminergic agents. However, should these agents be the preferred treatment choice for other reasons, the dopaminergic load should be kept as low as possible by using the minimum effective dose for the shortest required period of time.¹⁵³ Furthermore, should daily treatment be needed, then starting with a long acting dopamine agonist could be considered, as these types of drugs probably carry a lower risk of augmentation.

If a patient develops augmentation while taking dopaminergic treatment, the ultimate goal should be to eliminate this dopaminergic treatment, or at the very least to ensure the lowest possible dopamine dose so as to minimise the risk of further augmentation. If this proves too difficult, recent guidelines recommend combination treatment with a low dose dopamine agonist and an $\alpha 2\delta$ ligand.¹⁵³

Tolerance, impulse control disorders, somnolence, weight gain

In addition to augmentation, long term clinical experience has also shown the significance of other problems encountered when treating RLS/WED patients; these

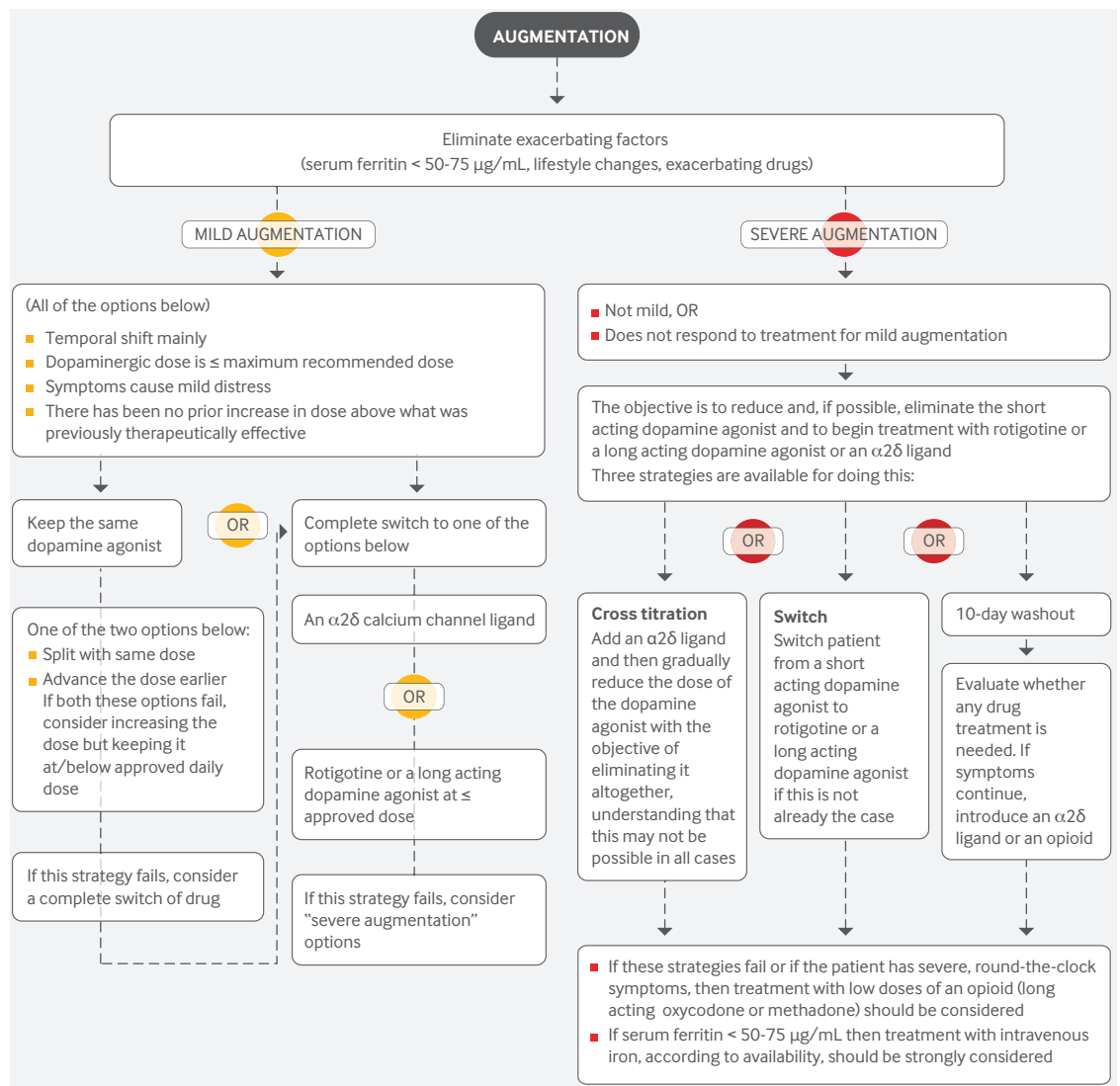


Fig 3 | Augmentation treatment algorithm¹⁵³

include weight gain, impulse control disorders (ICDs), mood disturbances, loss of efficacy, and somnolence. The IRLSSG treatment guidelines recommend that treatment choices should take these potential problems into account (table).³¹

ICDs have been reported to develop in 6-17% of patients with RLS/WED who are being treated with dopamine agonists.¹⁶⁶ ICDs are thought to occur more often with higher doses of dopaminergic agents and in women.³¹ Patients should be questioned about ICDs at each visit. If ICD that interferes with the patient's daily activities is present, the drug should be discontinued or at least the dose should be decreased to a level at which ICDs cease. Other non-dopaminergic drugs should be substituted or added.

Guidelines

Guidelines for the management of RLS/WED include those from the American Academy of Neurology (2016),¹⁶⁷ the Movement Disorders Society (2008),¹⁶⁸ the American Academy of Sleep Medicine (2012),¹⁶⁹ the European Federation of Neurological Societies/European

Neurological Society (2012),¹⁷⁰ and the International Restless Legs Study Group (2013, 2015, and 2016).³¹⁻¹⁵³

All recommend the use of drug strategies for moderate to severe RLS/WED. Guidelines published in the past five years not only include short term studies but also focus more on long term studies. As some of the complications, particularly augmentation, can be seen after prolonged use and become a crucial factor in deciding the first line treatment, more recent guidelines focus more on this aspect.³¹⁻¹⁵³ The 2013 IRLSSG guidelines offer a detailed description of all long term studies published before then,³¹ but they did not include a long term study on oxycodone extended release,¹⁵⁵ which was published after 2013. In 2016 augmentation guidelines included a change in the recommended first line treatment of RLS (to α2δ ligands),¹⁵³ following the results of a long term comparison between a dopamine agonist and an α2δ ligand.¹⁴⁴

Emerging treatments

Because of the risk of augmentation from all dopaminergic drugs during long term treatment, most new trials are now focusing on non-dopaminergic treatment options.

Clinical consensus on benefits and risks of each drug treatment for restless legs syndrome/Willis-Ekbom disease³¹

Effect	Levodopa	Non-ergot DA		Ergot based DA	α ₂ δ ligand	Opioid	Clonazepam
		Short acting	Long acting				
Potential to cause adverse events							
Augmentation	+++	++	+	++	0	NK	0
Loss of efficacy	+++	++	NK	++	+	+	NK
Impulse control disorders	0	+	0/+	NK	0	0	0
Excessive daytime sleepiness	DK	++	+	++	+++	+	++
Negative mood	0	0	0	0	+	+	++
Weight gain	0	0	0	0	++	0	0
General toxicity	+	+	++	+++	+	++	+
Potential to have positive effect							
Subjective night-time sleep	0	+	+	+	++	++	++
Classic night-time RLS/WED symptoms	+	++	++	++	++	++	0
Quality of life	NK	++	++	++	++	NK	NK
Pain reduction	+	+	+	+	++	+++	0

DA=dopamine receptor agonist; NK=not known; RLS/WED=restless legs syndrome/Willis-Ekbom disease. 0= has no effect on this parameter; +=slightly likely to affect this parameter; ++=somewhat likely to affect this parameter; +++=very likely to affect this parameter.

FUTURE RESEARCH QUESTIONS

- A need exists for prospective cohort studies to assess RLS/WED in addition to other conditions, to collect:
 - Family information
 - Images
 - Biomaterials
 - Medical histories
 - Risk factors
- Diagnostic investigations repeated over time are needed to analyse:
 - Genetic susceptibility
 - Potential biological pathways
 - Functional and structural brain changes
 - Comorbidity patterns
 - Patient reported outcomes in a broad variety of phenotypes
- Such approaches would have great potential to elucidate causative factors for RLS/WED and advance knowledge from the current status of associated risk factors to specific causes

Future studies will include intravenous iron treatments and substances that act on adenosine and on glutamate.¹⁷¹

Conclusion

RLS/WED was once a neglected condition, but intense research efforts over the past few decades have increased clinicians' awareness and understanding of the disease. Major research efforts over the past decades have yielded important advances in our knowledge of the genetics and pathophysiology. From a therapeutic perspective, although initial treatment with dopaminergic drugs was promising, the rates of long term treatment failure are high. α₂δ ligands and opiates might be helpful in filling the gap, but a need still exists for the development of new drugs that act on other neurotransmitter systems central to the pathophysiology of RLS/WED.

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