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Original Article

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

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SUMMARY

A Task Force was established by the International Restless Legs Syndrome Study Group (IRLSSG) in conjunction with the European Restless Legs Syndrome Study Group (EURLSSG) and the RLS Foundation (RLS-F) to develop evidence-based and consensus-based recommendations for the prevention and treatment of long-term pharmacologic treatment of dopaminergic-induced augmentation in restless legs syndrome/Willis–Ekbom disease (RLS/WED).

The Task Force made the following prevention and treatment recommendations:

As a means to prevent augmentation, medications such as α2δ ligands may be considered for initial RLS/WED treatment; these drugs are effective and have little risk of augmentation. Alternatively, if dopaminergic drugs are elected as initial treatment, then the daily dose should be as low as possible and not exceed that recommended for RLS/WED treatment. However, the physician should be aware that even low dose dopaminergics can cause augmentation. Patients with low iron stores should be given appropriate iron supplementation. Daily treatment by either medication should start only when symptoms have a significant impact on quality of life in terms of frequency and severity; intermittent treatment might be considered in intermediate cases.

Treatment of existing augmentation should be initiated, where possible, with the elimination/correction of extrinsic exacerbating factors (iron levels, antidepressants, antihistamines, etc.). In cases of mild augmentation, dopamine agonist therapy can be continued by dividing or advancing the dose, or increasing the dose if there are breakthrough night-time symptoms. Alternatively, the patient can be switched to an α2δ ligand or rotigotine. For severe augmentation the patient can be switched either to an α2δ ligand or rotigotine, noting that rotigotine may also produce augmentation at higher doses with long-term use. In more severe cases of augmentation an opioid may be considered, bypassing α2δ ligands and rotigotine.

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1. Introduction

Dopaminergic drugs have been widely used over the past decades for the treatment of restless legs syndrome (RLS)/Willis–Ekbom disease (WED), a neurological sensorimotor disorder characterized by an irresistible urge to move the lower limbs especially at rest, and frequently accompanied by nocturnal dysesthesia.

Two decades ago the major problem with RLS/WED management was ensuring that physicians were aware of RLS/WED and able to identify and therefore treat patients with clinically significant symptoms. The first dopaminergic drug to be used for the treatment of RLS/WED was levodopa, and while the first trials were very promising, it soon became apparent that the treatment efficacy of levodopa diminished over time. Of more concern, augmentation, an iatrogenic and at times profound worsening of RLS/WED symptoms following persistent use was recognized [1]. The dopamine agonists ropinirole, pramipexole, and rotigotine, which have longer half-lives than levodopa, were approved for the treatment of RLS/WED between 2004 and 2008 following randomized controlled trials demonstrating their remarkable short-term efficacy for RLS/WED symptoms. However, despite the fact that most patients initially respond very well to dopamine agonists and that this class of drugs is generally well tolerated over the short-term, longer studies and clinical experience have demonstrated that treatment efficacy diminishes in many patients over time, and/or augmentation develops, albeit after a longer duration of treatment than with levodopa [2]. A recent US community-based study estimated that 76% of all patients treated with dopaminergic agents required either a dose increase and/or showed indications for partial or full augmentation, with a yearly incidence rate of approximately 8% [3].

Therefore, today, a major issue with RLS/WED concerns managing treatment over the long-term, and in particular preventing and treating augmentation, which has become a common and increasing challenge that hinders the successful long-term treatment of RLS/WED with dopamine agonists.

There are presently no official augmentation treatment guidelines, and this situation is particularly troublesome for primary care physicians and specialists without expertise in RLS/WED management. Currently, physicians find themselves in a situation similar to the early 1990s, not knowing how to optimally manage RLS/WED patients over the long-term. For this reason, the International RLS Study Group (IRLSSG, http://www.irlssg.org) appointed a Task Force together with the European RLS Study Group (EURLSSG, http://www.eurlssg.org) and the RLS Foundation (http://www.rls.org) to review the current evidence and reach a consensus on the prevention and treatment of RLS/WED augmentation.

2. Process and objectives

2.1. Task force

The Executive Committee of the IRLSSG, together with the EURLSSG and the RLS Foundation, established an international Task Force to develop recommendations for the prevention and treatment of RLS/WED augmentation. The 13 members of the Task Force (authors of the current recommendations) include neurologists, psychiatrists, pulmonologists, sleep specialists and pharmacologists from the USA, Europe and Japan, all with extensive experience in RLS/WED treatment. All members completed the IRLSSG conflict of interest statement (Appendix 1).

2.2. Objectives

The objectives of the Task Force were (1) to review the evidence on the prevalence, identification, prevention, and treatment of augmentation and, given the paucity of these data, to (2) complement these with consensus-based recommendations of RLS/WED experts.

3. Methods

3.1. Literature and search strategy

Published papers (meta-analysis, randomized trials, cohort studies, case–control studies, observational studies) were identified from the following sources published before 2 October 2014: Cochrane Database of Systematic Reviews (CSDR) in the Cochrane Library, Database of Abstract of Reviews of Effects (DARE) in the Cochrane Library, CENTRAL (Cochrane Central Register of Controlled Trial) in the Cochrane Library, National Library of Medicine's MEDLINE database, EMBASE database, and CINAHL database. The electronic databases were consulted using the following search terms: {[(restless* OR jitter* OR anxiety*) AND (limb* OR leg* OR tibia*) OR ekbom* OR "restless legs syndrome" OR "willis ekbom disease")] AND treat*}.

The search strategy identified 2718 references (including possible duplicates). A further search with MeSH terms {("Restless Legs Syndrome"[Mesh]) AND ("Clinical Trials as Topic"[Mesh] OR "Therapeutics"[Mesh])} identified 538 references (including possible duplicates).

Inclusion criteria were articles in any language with mean patient follow-up > 6 months with any assessment of augmentation (clinical impression, NIH/MPI criteria), as well as any articles which attempted to identify the characteristics of augmentation (clinical identifiers, neurophysiological predictors). After assessing from title, abstract or full text of articles, a total of 45 articles for RLS/WED were eligible for inclusion in the review (Table 1).

3.2. Outcome measures

Table 1 shows the tools that were used to identify and assess augmentation.

3.3. Data extraction and evaluation of the evidence

Studies were divided into one of the following seven categories: (1) identifying augmentation, (2) controlled trials with a duration between six and 12 months, and (3) more than 12 months, (4) uncontrolled open-label, case series with a duration between six and 12 months, and (5) more than 12 months, (6) treatment of augmentation, and (7) treatment withdrawal.

3.4. Consensus-based clinical recommendations

Consensus was defined by at least 90% of the task force agreeing on a clinical recommendation. All task force members agree with the current recommendations.

3.5. Approval of treatment recommendations

Summaries of both the recommendations were prepared and first presented at the annual meeting of the IRLSSG on March 21, 2015, in Seoul, South Korea. In addition, an e-mail was sent to all IRLSSG and EURLSSG members as well as to the Medical Advisory Board of the RLS Foundation with a copy of the recommendations. Members were given an opportunity to comment on the recommendations from March 21 to May 11, 2015. The Executive Committee of the IRLSSG approved the final recommendations on May 12, 2015.

Table 1
Overview of tools used to assess augmentation in RLS/WED trials.

Method	Description
Allen Earley criteria [1]	First description of RLS/WED: augmentation was characterized as an earlier onset of symptoms in the afternoon, a shorter latency to onset of symptoms when at rest, a spreading of symptoms to the upper limbs and the trunk, an overall increase in the intensity of symptoms and a shorter effect of the medication.
NIH criteria [4]	Clinical criteria based on consensus. The primary features of augmentation were identified as a drug-induced shifting of symptoms to a period of time 2 h earlier than the typical time of daily onset prior to pharmacological intervention OR increased leg movements, decreased duration of treatment benefit, spread of the symptoms to other body parts, decreased amount of time that it is possible to stay at rest without symptoms, and paradoxical response to dose increase.
Max Planck Institute (MPI) criteria for diagnosing RLS augmentation [5]	Criteria developed based on empirical information from clinical studies with levodopa and short-acting dopamine agonists, not longer duration dopamine agents. The main criteria outlined in this definition are a four-hour time advance of symptoms, or a smaller (2- to 4-h) advance of symptoms expressed along with other required clinical indications, 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. A paradoxical response to treatment – an increase in severity with increasing dose of medication, and an improvement following decrease in medication – was considered an alternative key feature for diagnosis. The greater emphasis on time shift of symptoms may benefit longer-acting dopamine agonists, and this may explain the lower rate of augmentation found for these drugs.
Augmentation severity rating scale (ASRS)	Three items are used to assess the severity of augmentation: earlier onset of symptoms, shorter latency to symptom occurrence at rest, and spreading to other body parts. Augmentation severity is represented in a total score.

4. Identifying augmentation

4.1. Augmentation definition criteria

Augmentation was first described and defined in 1996 when it was reported in 73% of RLS/WED patients treated with carbidopa/levodopa. The main feature of augmentation identified in this study was a worsening of symptom severity manifested by an earlier onset of symptoms in the afternoon or evening compared with before treatment initiation, which was severe enough to warrant treatment modification in 50% of patients [1]. Other features of augmentation included a quicker onset of symptoms following rest, an increased intensity of symptoms, spread of symptoms to different body parts, and a shorter duration of the effect of the medication. Since 1996, several sets of criteria have been established to identify and evaluate augmentation. In a 2003 NIH-sponsored consensus conference [4], an operational definition of augmentation based on clinical experience was drafted, the primary feature of which was a drug-induced shifting of symptoms to a period of time 2 h earlier than was the typical time of daily onset prior to pharmacological intervention or the worsening of at least two features of RLS/WED beyond that expected just before or at the onset of treatment.

In 2006 the Max Planck Institute (MPI) criteria established an operational definition to assess the severity/clinical significance of augmentation [5]. The main criteria outlined in this definition were: a 4-h time advance of symptoms, or a smaller (2- to 4-h) advance of symptoms together with other required clinical features [5], 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. A paradoxical response to treatment – an increase in severity with increasing dose of medication, and an improvement following decrease in medication – was considered an alternative key feature for diagnosis.

4.2. Difficulties diagnosing augmentation

The existing criteria [4,5] were developed for use in clinical research. Since they require a baseline assessment, they are difficult to use in everyday clinical practice. Also, these criteria were not designed to identify initial symptoms of augmentation. Furthermore, the MPI criteria do not seem sufficiently sensitive to detect augmentation when medications are very long acting (such as rotigotine) or are given multiple times a day, since these criteria rely heavily on an anticipation in the time of onset of symptoms.

4.3. Paradoxical response

The complexity of these criteria gives an indication of the difficulties encountered in diagnosing augmentation in daily clinical practice. First, it is difficult to establish paradoxical response to treatment, which is considered a key diagnostic feature of augmentation: increasing doses of dopaminergic agents, especially if taken earlier in the day before RLS/WED onset, often improve symptoms, only for them to worsen again after some time on the higher dose. Conversely, with dose decrease most patients' symptoms initially worsen for several days to weeks due to withdrawal from the drug before eventually improving. Whereas with levodopa an improvement in symptom severity can be seen within a few days after discontinuing the drug, with dopamine agonists it can take several weeks to months for a patient to notice any significant improvement, during which time they must endure severe worsening of symptoms.

4.4. Identifying augmentation

Seven articles were reviewed specifically with regard to identifying augmentation [3,6–11].

4.4.1. Clinical identifiers of augmentation

Tzonova et al. performed a cross-sectional study among RLS/WED patients who had been treated with dopaminergic agents for a mean of six years, 41.3% of whom suffered daily daytime ('breakthrough') symptoms [11]. This study shows that despite an initial response to dopaminergic agents, with time, symptoms could no longer be completely managed, but only 5% of patients met augmentation criteria. The authors suggest that breakthrough crises could be early signs of augmentation. Beginning augmentation may be much more frequent in clinical series [3,12] and almost half of the patients on very-long-term treatment were unchanged or even worse at the end compared to the beginning of a very-long-term observational period [13]. The objectives of an observational cross-sectional community study completed by Allen et al. were to examine the potential risk factors or predictors of augmentation [3].

Five factors were found to reflect a likely increased risk of developing augmentation: (1) more frequent RLS/WED symptom pretreatment, (2) greater discomfort with RLS/WED symptoms before treatment, (3) comorbid asthma, (4) older age, and (5) longer treatment duration ($p < 0.05$). A retrospective assessment of augmentation and tolerance in patients treated with pramipexole reported that previous tolerance with levodopa increased the probability of

augmentation ($p < 0.05$) [14]. Ondo et al. performed a prospective observational study, and simple logistic regression revealed that a positive family history of RLS/WED, and fewer clinic visits all increased the probability of augmentation, with lack of any neuropathy being the strongest predictor ($p = 0.05$). Two studies have examined the relation between ferritin levels and RLS/WED risk of augmentation [6,10]. Trenkwalder et al. performed a retrospective analysis of pooled data from an earlier study with cabergoline and levodopa [15]. Mean serum ferritin values were lower at baseline in those who developed augmentation (85 ng/mL) compared to those without augmentation (112 ng/mL). Frauscher et al. reported an inverse correlation between serum ferritin levels and RLS/WED augmentation [6].

The task force also considered whether RLS/WED severity at baseline is linked to the likelihood of developing augmentation. It appears that more severe RLS/WED is a risk factor for augmentation, but this may result from tendency to use higher doses for more severe symptoms.

The above studies, while continuing to shed light on augmentation and how it manifests, do not allow the task force to make recommendations on the identification of augmentation in daily practice. Therefore, a consensus-based recommendation was agreed upon.

4.4.2. Neurophysiological predictors

Mitterling et al. conducted a prospective study to evaluate the possibility of establishing polysomnographic markers of augmentation [8]. While video polysomnography found no significant differences in PLM indices between the augmented and non-augmented groups, an unexpected relatively low median PLM during sleep (PLMS) index was found in augmented patients. A 60-min suggested immobilization test (SIT) was also performed before every sleep study and showed that only augmented patients had a substantial number of PLMs during the test. Augmented patients scored significantly higher on item 4 on the RLS-6 scale, which concerns RLS/WED daytime symptoms at rest. The authors conclude that augmentation of RLS/WED predominantly manifests during wakefulness [8]. Another study [7] also found no association between PLMs and augmentation. So, while conventional sleep studies do not seem useful to identify augmentation, immobilization tests might be promising, but further research is needed.

4.5. Consensus-based recommendation for the identification of augmentation

To facilitate the identification of augmentation in clinical practice, physicians might wish to consider that augmentation may be present whenever a patient who has been on stable treatment for at least 6 months requests more medication. The IRLSSG task force recommends four screening questions, that have yet to be validated, that may be used in clinical practice in patients currently under treatment with dopaminergic agents. An affirmative answer to any of these four questions should lead the physician to suspect that augmentation may be present:

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 to the original effective dose?
3 Has the intensity of symptoms worsened since starting the medication?
4 Have symptoms spread to other parts of the body (eg, arms) since starting the medication?

It is important to remember that augmentation may progress in a fluctuating manner over time. It needs to be differentiated from multiple augmentation mimics: natural progression of RLS/WED, fluctuations in disease severity, tolerance, end-of-dose rebound (Table 2), and worsening due to exacerbating factors. RLS/WED is thought to progressively worsen over time but unlike augmentation, symptoms show lasting improvement with increased dose [16]. Tolerance refers to a decrease in medication efficacy over time, thereby necessitating an increase in dosage in order to maintain the initial relief of symptoms. In contrast to augmentation, in the case of tolerance RLS/WED symptoms do not appear earlier in the day, nor do they become more severe than at baseline. However, data indicate that tolerance likely precedes or is a subtype of augmentation [14]. End-of-dose rebound occurs in up to 35% of RLS/WED patients and refers to the reappearance of symptoms in the early morning, the time at which the medication concentration is falling. It is therefore more common with drugs with a shorter half-life such as levodopa [17], or less frequent when other dopamine agonists such as ropinirole or pramipexole are given in the early evening or afternoon. Similar to augmentation, the symptoms of rebound are worse than at baseline, but there is no spread of symptoms to the arms, nor a worsening with increased dose, or conversely no improvement with decreased dose. Factors that may exacerbate RLS/WED symptoms include iron deficiency, poor medication adherence, sleep deprivation, lifestyle changes (eg, more sedentary lifestyle), appearance of other physiological or pathological conditions known to trigger or exacerbate RLS/WED (pregnancy, renal insufficiency, other sleep disorders particularly sleep-disordered breathing), and medications such as antihistamines, dopamine-receptor blockers, or serotonergic antidepressants [18].

4.6. Prevalence of augmentation with different dopaminergic drugs

To evaluate the frequency of augmentation the task force reviewed 28 studies: four controlled trials lasting between 26 and 30 weeks [15,19–21], one controlled trial lasting more than one year [2], seven uncontrolled studies lasting between 26 and 52 weeks [1,14,22–26], and 16 uncontrolled studies lasting more than one year [9,12,27–40].

Table 2
Differential diagnosis of augmentation.

	Augmentation	End of dose rebound	Tolerance	Natural progression	Exacerbating factors*
Worse than before treatment	Yes	Yes, in early morning	No	Yes	Yes
Earlier onset	Yes	Yes, in early morning	No	Yes	Yes
Spread to arms	Yes	No	No	Yes	Yes
Breakthrough at night	Yes	Yes, in early morning	Yes	Yes	Yes
Worse with increased dose	Yes, but not immediately	No	No	No	No
Improved with decreased dose	Yes, but not always†	No	No	No	No

* For example, low serum ferritin, medications, increased immobility.
† Eventually augmentation is overcome when the dose is decreased; and while augmentation symptoms can improve within 72 h on levodopa, it can take several weeks to several months to see an improvement with dopamine agonists.

Augmentation prevalence is difficult to evaluate as it varies according to the drug, its dose, the duration and type of study, the criteria used to evaluate augmentation, and the number of subjects. However, some degree of augmentation has been reported with the use of all investigated dopaminergic drugs as well as for the atypical opioid tramadol (which has some dopaminergic effect) [41]. However, despite multiple methodologies, and different levels of rigor in assessing augmentation, a clear difference between augmentation rates and the duration of studies can be seen: for short-term studies the augmentation rates are <10% [2,20,23,32,33], for studies lasting two to three years the augmentation rate increases to approximately 30% [3,9,14,38,39], while two of the three long-term (approx. 10 years) studies available reported augmentation in 42–68% of patients [12,36]. Furthermore, one randomized double-blinded control study showed a significant increase in rates of augmentation on pramipexole for 12 compared to six months on a fixed dose of pramipexole (either 0.5 or 0.25 mg) [2]. Based on this evidence, the Task Force concludes with reasonable certainty that the likelihood of augmentation increases with duration of treatment.

In the near absence of direct comparative studies for augmentation rates with different dopaminergic medications, the incidence rate appears to be highest during treatment with levodopa [1] and is higher for shorter-acting (pramipexole, ropinirole) [32,36,42] than longer-acting dopamine agonists (cabergoline, rotigotine) [37]. However, as mentioned above, such evidence is far from definite and it is unclear whether this finding is related to masking of earlier symptom onset by the longer-acting dopaminergic agents or if it is truly an augmentation-sparing effect. Hence, there is insufficient evidence that longer-acting drugs cause a lower incidence rate of augmentation.

5. Consensus-based recommendations

Most studies on the treatment of augmentation have a low class level of evidence. There are no controlled studies and decisions frequently had to be reached based on consensus provided by experts. Studies that investigated the prevention of augmentation have many limitations: these studies were sponsored, run and evaluated by the industry. Moreover, the definition of augmentation used in these studies was frequently very restrictive, and the duration of the studies was not long enough to see the full scope of augmentation.

5.1. Reducing impact of risk factors

Ten studies were reviewed concerning the treatment of augmentation. These studies were classified according to previously used criteria for treatment trials [43]. Two of these studies provide class IIIc evidence, while the remaining eight studies provide class IV evidence. These studies were generally open label designs that were insufficiently powered and had inadequate endpoints. It is therefore impossible to make recommendations on the treatment of augmentation based exclusively on empirical data.

Nevertheless, the task force agreed that treatment with *dopaminergic agents* poses the greatest risk for augmentation; that augmentation is likely exclusively related to the specific action of the dopaminergic system; and that this risk is strongly correlated with the *dose* and *duration* of treatment [2,3,12,36].

Therefore, the most effective preventive strategy would be to not use dopaminergic agents. However, should dopaminergic treatment be selected, then it is recommended that the dopaminergic load be kept low by using the minimum effective dose for the shortest required period of time. Other factors that are thought to contribute to an increased risk of augmentation include low iron stores [6,10]; greater severity of RLS/WED symptoms prior to initiation of treatment [1,3]; possibly, a family history of RLS or lack of neuropathy [9].

5.2. First-line treatment of de novo patients

The primary long-term concern with dopaminergic agents is the development of augmentation. While many short-term effects are apparent within days or weeks and thus become easy to identify, augmentation frequently develops gradually and insidiously. Furthermore, its similarity to natural progression of the disease might make it difficult to detect before it becomes a significant problem. For these reasons, preventive strategies need to be implemented to minimize, and if possible, avoid the dopaminergic load in every de novo patient. The physician, particularly if not very experienced in long-term management of RLS/WED, should keep dopaminergic load as low as possible in previously untreated RLS/WED patients, and should consider using treatment medications that, while effective, have little or no risk of augmentation for initial RLS/WED. As the α2δ ligands (Table 3) do not have this long-term risk, they may be considered for initial RLS/WED treatment. Similarly, other authors have recommended that treatment be initiated with α2δ ligands [44].

Before an initial treatment is selected, the long-term risk of augmentation has to be weighed against the short- and intermediate-term side effects and benefits associated with each treatment option (see Tables 4 and 5), the patient's response to previous treatment for RLS/WED, possible interaction with other treatments, and the patient's comorbid conditions and clinical status. It should be noted that application site reactions to rotigotine transdermal patches are consistently high in RLW/WED [37].

In addition, the use of non-dopaminergic options as a first-line treatment is limited by the fact that in some regions of the world (ie, Europe) no such treatments are approved for RLS/WED.

5.2.1. Adjusting daily treatment of RLS/WED to prevent augmentation

If a patient is already being treated with a dopaminergic agent, the lowest possible cumulative daily dopaminergic dose should be used to control the majority of bothersome RLS/WED symptoms, and the total daily dose should not exceed maximum recommended levels (pramipexole, 0.5–0.75 mg; ropinirole, 4 mg; rotigotine, 3 mg; Table 6). However, even low-dose dopaminergic treatments have a risk of augmentation [2]. Physicians should explain to patients that the goal of treatment is not to completely eradicate symptoms but to ensure they do not interfere with quality of life. If symptoms become bothersome, the dose can be increased cautiously, but this will increase the risk of developing augmentation. A non-dopaminergic agent can be added if concerns about dose of the dopaminergic drug occur. These therapeutic decisions should also be based on other factors related to patient characteristics such as age, previous episodes of augmentation, and vulnerability to class-related side effects.

Table 3
α2δ ligand suggested doses*.

	Starting dose		Usual effective daily dose
	<65 years	>65 years	
α2δ ligands			
Approved (USA, Japan as of 2015)			
Gabapentin enacarbil	600 mg	300 mg	600–1200 mg
Not approved			
Pregabalin	75 mg	50 mg	150–450 mg
Gabapentin*	300 mg	100 mg	900–2400 mg

* Long-term studies have not been performed with gabapentin in RLS/WED and absorption is variable, thereby complicating dosing.

Table 4
Factors that affect selection of an agent for initial treatment in patients with restless legs syndrome/Willis–Ekbom disease (adapted from Garcia-Borreguero et al. [43]).

Factor that impacts the choice of agent	Treatment choice
Time of day (daytime symptoms)	Preferably a long-acting agent Twice-a-day dosing of a short-acting agent
Sleep disturbance disproportionate to other symptoms of RLS/WED, eg, severe insomnia	$\alpha_2\delta$ ligand
Comorbid insomnia	$\alpha_2\delta$ ligand
Pregnancy risk	Avoid both DAs and $\alpha_2\delta$ ligands Consider the use of iron
Impaired renal function	Select a drug that is not renally excreted or reduce dose of renally excreted drugs
Increased risk of falls	Dopamine-receptor agonist
Painful restless legs	$\alpha_2\delta$ ligand
Comorbid pain syndrome	$\alpha_2\delta$ ligand
History of impulse control disorder	$\alpha_2\delta$ ligand
History of alcohol or substance abuse	Dopamine-receptor agonist or $\alpha_2\delta$ ligand
Very severe symptoms of RLS/WED	Dopamine-receptor agonist
Excess weight, metabolic syndrome	Dopamine-receptor agonist
Availability or cost of drug	Dopamine-receptor agonist or $\alpha_2\delta$ ligand
Comorbid depression	Dopamine-receptor agonist
Comorbid generalized anxiety disorder	$\alpha_2\delta$ ligand
Higher potential for drug interactions	Select drug that is not hepatically metabolized
Symptomatic PLMS	Dopamine-receptor agonist

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

The daily treatment of RLS/WED should be deferred as long as possible until symptoms occur almost daily. However, a number of factors make this goal difficult to achieve. First, in patients with intermittent RLS/WED the emergence of symptoms is often unpredictable. Second, many patients find that it is more effective to take medication prior to onset of symptoms, preventing their occurrence, rather than waiting until after symptom onset. Nevertheless, the goal of intermittent dosing should be pursued, especially if symptoms are infrequent (<1–2 per week), or as preventive medications before predictable conditions of immobility (eg, long car or plane trips, medical procedures). Levodopa may be used for intermittent treatment at most two to three times a week, but should not be used for daily treatment, given the high risk of augmentation with this medication.

5.2.3. Using longer acting dopamine agonists

As mentioned above, longer-acting dopaminergic agonists may cause less augmentation than shorter-acting dopamine agonists. As with all other dopamine agonists, the dose of longer-acting dopamine agonists should never be increased above recommended levels (rotigotine, 3 mg) for the treatment of RLS/WED.

5.2.4. Fluctuating RLS/WED symptoms

Longitudinal studies demonstrate that RLS/WED symptom intensity fluctuates and that some patients appear to go into spontaneous remission. Therefore, in patients with a history of notable fluctuating RLS/WED symptoms, the clinician may consider it appropriate to intermittently attempt to reduce the dose or even discontinue the drug in order to ensure that the patient is being treated with the lowest effective dose. If implemented, the patient should be made aware that withdrawal symptoms may be severe and may occur for several days or even weeks after dose reduction and this has to be distinguished from the requirement for continued medication treatment or a true worsening of RLS/WED symptoms.

5.2.5. Switching to an alternate 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 approved dopamine agonist. Physicians may wish to consider long-acting formulations of dopamine agonists as an alternative to reduce the risk of augmentation, although there is no evidence that this will ultimately delay or prevent augmentation. Table 7 provides the suggested initial dose for switching dopamine agonists.

Table 5
Common adverse at 52 weeks (adapted from Allen et al. [2]).

Event	Pregabalin 300 mg	Pramipexole 0.25 mg	Pramipexole 0.5 mg
Serious adverse events, no.	11	20	12
Patients with serious adverse events, no. (%)	9 (4.9)	12 (6.7)	9 (5.0)
Patients with adverse events, no. (%)	155 (85.2)	142 (79.8)	140 (77.8)
Discontinuations due to adverse events, no. (%)	50 (27.5)	33 (18.5)	43 (23.9)
Suicidal ideation, no.	6	3	2
Common adverse events, no. (%) appearing in >8% of patients			
Dizziness	39 (21.4%)	15 (8.4%)	17 (9.4%)
Somnolence	32 (17.6%)	12 (6.7%)	14 (7.8%)
Fatigue	23 (12.6%)	19 (10.7%)	22 (12.2%)
Headache	22 (12.1%)	30 (16.9%)	35 (19.4%)
Nasopharyngitis	19 (10.4%)	20 (11.2%)	17 (9.4%)
Weight gain	16 (8.8%)	12 (6.7%)	12 (6.7%)
Constipation	14 (7.7%)	3 (1.7%)	2 (1.1%)
Nausea	11 (6.0%)	18 (10.1%)	26 (14.4%)
Back pain	10 (5.5%)	16 (9.0%)	13 (7.2%)
Influenza	9 (4.9%)	13 (7.3%)	3 (1.7%)
Vomiting	3 (1.6%)	4 (2.2%)	10 (5.6%)
Diarrhea	7 (3.8%)	9 (5.1%)	10 (5.6%)

Table 6
Suggested initial dose and maximum recommended dose for dopamine agonists.

	Initial dose	Max. recommended dose
Pramipexole	0.125 mg/day	0.75 mg/day
Ropinirole	0.25 mg/day	4 mg/day
Rotigotine	1 mg/day	3 mg/day

Table 7
Suggested initial dose for switching dopamine agonists.

	Rotigotine	Pramipexole ER*
Pramipexole		
0.25 mg	2 mg	0.375 mg
0.50 mg (or higher)	3 mg	0.75 mg
Ropinirole		
0.5–1.0 mg	2 mg	0.375 mg
2 mg or higher	3 mg	0.75 mg

* The incidence rate of augmentation has not been assessed with pramipexole extended release.

6. Recommendations

Because a substantial number of patients on dopaminergic treatment will develop augmentation, the physician, particularly if not very experienced in long-term management of RLS/WED, may consider using for initial RLS/WED treatment medications that, while effective, have little or no risk of augmentation.

Hence, a treatment trial with α2δ ligands may be considered as an initial treatment as this class of drugs has been shown in 1-year studies to have no significant risk of augmentation. However, as with any other treatment, their profile of short- and intermediate-term side effects should be considered in selecting the most appropriate drug. This recommendation is also limited by lack of availability or regulatory approval for α2δ ligands in certain regions of the world (eg, Europe).

Alternatively, if dopaminergic drugs are elected as initial treatment, the daily dose should not exceed that recommended for RLS/WED treatment. Daily treatment with dopaminergic drugs should start only when symptoms have a clear impact on quality of life in terms of frequency and severity; intermittent treatment might be considered in milder cases.

Patients with low iron stores should be given appropriate iron supplementation.

7. Treatment of augmentation (Fig. 1, Table 8)

7.1. Elimination of exacerbating factors

The first step in treating augmentation consists of the elimination and/or correction of any exacerbating factors.

The patient's serum ferritin level should be measured, and, if the concentration is <50–75 μg/mL, or if transferrin saturation is less than 20%, supplementation with orally administered iron is recommended unless poorly tolerated or contraindicated. Intravenous (IV) iron can also be considered.

It is important to ask the patient about any lifestyle changes (sleep deprivation, alcohol use, decreased mobility), or changes in medical factors (use of dopamine antagonists, antihistamines or antidepressants, recent opioid discontinuation, blood loss) that can contribute to an earlier onset or an increase in the severity of RLS/WED symptoms.

Any extrinsic factors exacerbating RLS/WED expression should be adjusted as much as possible to reduce the need for RLS/WED medication changes.

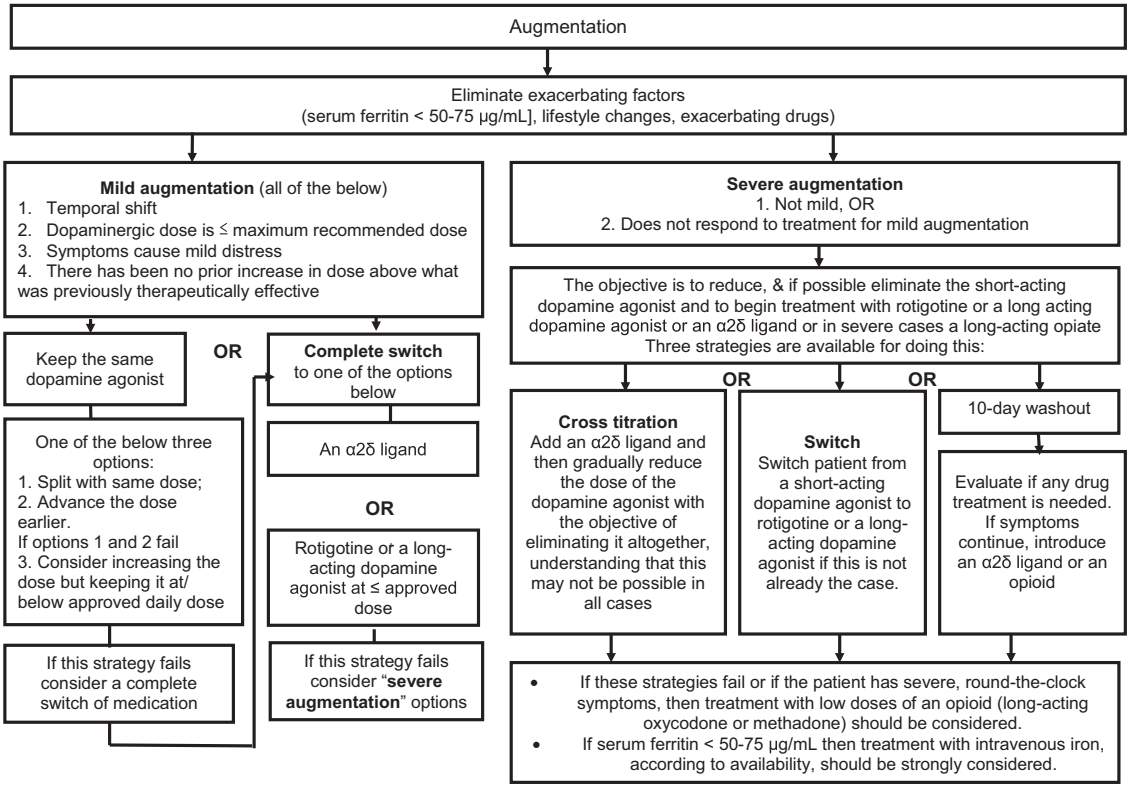

Fig. 1. Augmentation treatment algorithm.

Table 8
Treatment of augmentation: evidence.

Study	Drug	Design	Duration	Definition of augmentation	No. of patients	Results	Class of evidence*
Maestri et al. [7]	Pramipexole ER	Open, case series	Mean follow-up 13 months	MPI	24	Resolution of symptoms	IIIc
Godau et al. [45]	Rotigotine	Retrospective, case series	12 months	Clinical	28	Resolution of augmentation within one month for 27/28 patients. Discontinuation rate: 14.3%	IIIc
Silver et al. [12]	Methadone	Open, retrospective, case series	Up to ten years	NIH	76	Resolution of symptoms	IIIc
Ondo [46]	Methadone	Open, retrospective, case series	23 months (range: 4–44 months)	Clinical: greater intensity and earlier onset of symptoms	27 (eight patients intolerable augmentation when on DAs)	8/8 patients with augmentation showed a good response (3–5/5 grade). Efficacy rated as follows: 5, complete relief of RLS symptoms and excellent nocturnal sleep; 4, complete relief but continued subjective sleep problems; 3, 75–99% improvement; 2, 25–74% improvement; 1, 1–24% improvement; and 0, no improvement	IV
Miranda [47]	Rotigotine	Open, prospective case series	18 months	No adequate definition	10	Resolution of symptoms	IV
Stiasny-Kolster et al. [48]	Pramipexole low dose	Open, prospective case series	1–11 days	Patients. did not respond to levodopa, no further specification	17	Good general response	IV
Kurlan [49]	Gabapentin, clonazepam tramadol	Retrospective, case series	1–43 weeks	NIH	14	Mean time to resolution: GBP ($N = 4$): 2.6 w (1–6 w); Clonazepam ($N = 3$): 14.9 weeks (1–43 weeks); Tramadol ($N = 3$): 22.3 weeks (10–31 weeks)	IV
Winkelmann et al. [50]	Pergolide	Open, prospective	Six months	Clinical	15	All showed improvement at mean dose of 0.4 mg	IV
Earley et al. [51]	Pergolide	Open, retrospective case series	18 months (1–39 months)	Clinical	26	Response rate 83% (19/23RLS patients) or (19/26 patients with either RLS [$N = 23$] or PLMS [$N = 3$])	IV

* Classified according to previously used criteria for treatment trials [43].

7.2. Mild augmentation

Augmentation exists along a continuum of severity and is arbitrarily considered mild if all of the following are present: symptoms manifest predominantly as a temporal shift of symptoms to earlier in the day compared to before starting treatment; dopaminergic monotherapy is at a total daily dose at or below maximum recommended levels; symptoms cause only mild distress; and there has been no prior increase in total dose above that which was previously therapeutically effective.

In cases of mild augmentation, the physician can choose one of two strategies based on the individual characteristics of the patient (see Fig. 1).

7.2.1. Continue current dopamine agonist therapy

Continue treatment with the same dopamine agonist according to one of three possibilities: (1) As a first approach the total dose should be kept the same, but either divided or the time of the dose should be advanced to before symptom onset. (2) If dividing or advancing the dose fails, then an alternative is to increase the dose, usually adding or increasing the earlier rather than the night-time dose. If, however, the augmentation distress occurs mostly from symptoms breaking through at night then the night-time dose could be increased. Make sure that the maximum recommended dose is not exceeded and that the patient is carefully monitored for continued augmentation. Only one total daily dose increase should be performed. (3) If these dose adjustments fail, a switch to another medication is recommended.

7.2.2. Complete switch

The physician may consider that the existing augmentation, although not severely distressing, is a harbinger of more severe augmentation and that it is appropriate to switch drugs earlier rather than later. It must be considered that addressing the augmentation problem earlier may make the switch easier and less stressful for the patient.

The patient can either be switched to: (1) an α2δ ligand (pregabalin, gabapentin enacarbil and gabapentin[1]) (Table 3 provides the α2δ ligand suggested doses); or alternatively, depending on the patient's clinical features, (2) to rotigotine (other non-approved extended release oral dopamine agonists such as the extended release formulation of pramipexole remains relatively untested, but could eventually be considered as a second line option) [7].

For switching to an α2δ ligand, one option is to taper off the dopaminergic agent with a brief period in which the patient is off all medications. Alternatively, the non-dopaminergic agent can be added prior to or during the dopaminergic taper.

[1] Long-term studies have not been performed with gabapentin in RLS/WED and absorption is variable, thereby complicating dosing.

As augmentation or withdrawal may take days to weeks to resolve, evaluation of the efficacy of the new non-dopamine drug must wait until after this withdrawal period.

If this strategy fails, then alternative approaches described below for severe augmentation should be attempted.

7.3. Severe augmentation

Severe augmentation is augmentation that either does not fulfill the criteria for mild augmentation (eg, the total agonist dose exceeds recommended levels or the symptoms cause more than mild distress), or does not respond to treatment of mild augmentation as outlined above.

Initially, one of the following approaches should be selected. It should be noted that most of these approaches have not been adequately substantiated by published data and are largely based on the experience of individual centers.

7.3.1. Substitution or cross titration

The patient can be switched either to an α2δ ligand or to rotigotine. Other long-acting DAs might also need to be investigated in the future. In very severe cases a high-potency opioid should be considered (see Table 9 for suggested doses), bypassing α2δ ligands and rotigotine (see below). If the patient is switched to rotigotine, then the shorter-acting dopamine agonist can be discontinued and the rotigotine dose adjusted within approved dosage ranges. If the α2δ ligand is selected, it should be titrated to an effective dose (so the patient is temporarily on two RLS/WED medications). At that point, the dopamine agonist dose should be gradually reduced, warning the patient that a withdrawal is expected with temporary worsening of symptoms.

The ultimate objective is to eliminate dopaminergic treatment, or at the very least ensure the lowest possible dopamine dose so as to minimize the risk of further augmentation. If the attempt to eliminate all dopaminergic treatment fails, combination therapy with a low-dose dopamine agonist and an α2δ ligand can be maintained.

7.3.2. 10-day washout

The patient is gradually weaned off the dopamine drug, followed by a washout period of approximately ten days without any drugs. At the end of the washout period, a new drug may be introduced. The advantages of the ten-day washout are that it enables the physician to evaluate both the degree of RLS/WED symptoms on no medication and the benefits of any new drug treatment. In occasional cases, no continuing drug treatment is needed and this would not be known without a period off any treatment. The disadvantage is that this often leads to transitory extremely severe RLS/WED symptoms and profound insomnia during the washout period that may last four or five days or longer, and may need the reintroduction of low-dose dopamine agonists. Education and counseling support is essential to help the patient with this process.

7.3.3. Consider an opioid

In patients with severe augmentation, such as symptoms with almost 24 h duration, a low dose of an opioid (prolonged-release oxycodone [52] or methadone [12]) can be considered instead of an α2δ ligand (Table 7). These drugs should also be considered if the above approaches fail. There are, however, special considerations regarding opioids, and the physician should assess risk of addiction (family or personal history of alcohol or drug abuse, psychiatric comorbidities), risk of non-medical use, or comorbid medical issues (eg, pre-existing severe constipation, sleep apnea, prolonged QT_c). When patients are chosen appropriately, low-dose opioid therapy is typically very effective and safe even when used for long-term therapy (based on considerable clinical experience). Educating the patient about the demonstrated efficacy and safety of these medications at the doses used in RLS/WED is essential. If the physician is uncomfortable prescribing opioids, then they should refer the patient to a physician experienced in managing RLS/WED.

Table 9
Opioid suggested doses.

	Starting dose	Usual effective daily dose
Oxycodone prolonged release (may be combined with naltrexone)	5–10 mg	10–40 mg
Methadone	2.5 mg	5–30 mg

7.4. Iron therapy

If serum ferritin levels are <50–75 μg/mL or transferrin saturation is less than 20%, then treatment with oral or intravenous iron, depending on the clinical situation, should be strongly considered. This can be undertaken in combination with any of the other options.

8. Research agenda

In the future we should (1) perform comparative controlled long-term (>10 years) trials using standardized augmentation criteria to provide more accurate augmentation rates and to determine the percentage of patients who will develop augmentation on dopamine agonist therapy over the very long-term; (2) perform controlled studies on the optimal management of patients with augmentation; (3) investigate the pathophysiology of augmentation; and (4) assess methods to identify augmentation and those at risk of developing augmentation.

Conflict of interest

No financial support for this endeavor was requested nor received from any entity. No industry representatives participated in any way in the development of these recommendations and none were privy to this document before publication. See also Appendix 1.

The ICMJE Uniform Disclosure Form for Potential Conflicts of Interest associated with this article can be viewed by clicking on the following link: http://dx.doi.org/10.1016/j.sleep.2016.01.017.

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