Guidelines for the first-line treatment of RLS/WED, 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 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 RLS/WED.

The Task Force made the following prevention and treatment recommendations:

As a means to prevent augmentation, medications such as α2δ ligands should be considered for initial RLS/WED treatment; these drugs are effective and have little risk of augmentation. Patients with low iron stores should be given appropriate iron supplementation. If dopaminergic drugs are used, 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. 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 nighttime 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 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.

**Keywords:** Restless legs syndrome, Willis-Ekbom disease, augmentation, pharmacologic therapy, periodic limb movements of sleep, dopamine agents, alpha 2 delta ligands, α2δ ligands, opioids, algorithm, prevention, treatment.
1. Introduction

Dopaminergic drugs have been widely used over the last 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 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 management is 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 not expert 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, www.irlssg.org) appointed a Task Force together with the European RLS Study Group (EURLSSG, www.eurlssg.org) and the RLS Foundation (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 thirteen 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–Conflict of interest disclosures).
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.

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, CINAHL database. The electronic databases were consulted using the following search terms: (((restless* OR jitter* OR anxiet*) 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 articles attempting to determine the characteristics of augmentation. After assessing from title, abstract or full text of articles, a total of 45 articles for RLS/WED were eligible for inclusion in the above review (Table e-1).

3.2. Outcome measures
Table 1 shows the tools that are 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 6 and 12 months, and (3) more than 12 months, (4) uncontrolled open-label, case series with a duration between 6 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.

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 identified in this study was a worsening of symptom severity manifested by an earlier onset of symptoms in the afternoon or evening compared to 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 two hours 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 four-hour time advance of symptoms, or a smaller (two to four hour) 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 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 symptoms eventually improve. 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].

a. 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 6 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 symptoms pre-treatment, 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 (112ng/mL). Frauscher et al. reported an inverse correlation between serum ferritin levels and RLS/WED augmentation.

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 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.

b. 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-minute 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 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. Taken together, 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 six 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 or 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 (e.g., 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, all 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, with 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 frequently when other dopamine agonists such as ropinirole or pramipexole are given in the early evening or afternoon. Similarly 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 an improvement with decreased dose. Factors that exacerbate RLS/WED symptoms include: iron deficiency, poor medication adherence, sleep deprivation, lifestyle changes (e.g., 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 anti-histamines,
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 weeks and 30 weeks [15, 19-21], one controlled trial lasting > 1 year [2], seven uncontrolled studies lasting between 26 and 52 weeks [1, 14, 22-26], and 16 uncontrolled studies lasting > 1 year [9, 12, 27-40].

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 2-3 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 6 months on a fixed dose of pramipexole (either 0.5 or 0.25mg) [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

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 8 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 factor 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 involves reducing the dopaminergic load by using the lowest 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 consider using for initial RLS/WED treatment medications that, while effective, have little or no risk of augmentation. As the α2δ ligands (table 3) do not have this long-term risk, they should be considered for initial RLS/WED treatment.
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 4a and b), 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 (i.e., Europe) no such treatments are approved for RLS/WED.

a) 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 5). 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.

b) 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/week), or as preventive medications before predictable conditions of immobility (e.g., 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.

c) 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.

d) 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.

e) 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 licensed 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 6 provides the suggested initial dose for switching dopamine agonists.

RECOMMENDATION

• 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, should consider using for initial RLS treatment medications that, while effective, have little or no risk of augmentation.

• Hence, a treatment trial with \( \alpha_2 \beta \) ligands should be considered as an initial treatment as this class of drugs has shown in one-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 (e.g., Europe).

- Patients with low iron stores should be given appropriate iron supplementation.
- If dopaminergic drugs are appropriate or needed, 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.

6. TREATMENT OF AUGMENTATION (Figure 1, Table 7)

6.1. Elimination of exacerbating factors

The first step in treating augmentation consists in 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.

6.2. 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 what 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 Figure 1):

6.3. Continue current dopamine agonist therapy

Continue treatment with the same dopamine agonist according to one of three possibilities:

• 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.

• If dividing or advancing the dose fails, then an alternative is to increase the dose, usually the earlier rather than the nighttime dose. If, however, the augmentation distress occurs mostly from symptoms breaking through at night then the nighttime 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.

• If these dose adjustments fail, a switch to another medication is recommended.

6.4. 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:

• an α2δ ligand (pregabalin, gabapentin enacarbil and gabapentin). Table 3 provides the α2δ ligand suggested doses,

or alternatively, depending on the patient’s clinical features,

• 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]

________________________________________

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

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 alternate approaches described below for severe augmentation should be attempted.

6.5. Severe augmentation

Severe augmentation is augmentation that either does not fulfill the criteria for mild augmentation, (e.g., 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:

a) 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 8 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.

b) 10-day washout

The patient is gradually weaned off the dopamine drug, followed by a washout period of approximately 10 days without any drugs. At the end of the washout period, a new drug may be introduced. The advantages of the 10-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 this often leads to transitory extremely severe RLS/WED symptoms and profound insomnia during the washout period that may last 4 or 5 days or longer. Education and counseling support is essential to help the patient with this process.

c) Consider an opioid

In patients with severe augmentation, such as symptoms with almost 24-hour duration, a low dose of an opioid (prolonged-release oxycodone [44] or methadone[12]) can be considered instead of an α2δ ligand (table 6). 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 (e.g., 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.

6.6. 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.
Practice points/Highlights

- Prevention of augmentation should be started by considering using medications such as α2δ ligands for initial RLS/WED treatment.

- If dopaminergic drugs are given, then the daily dose should be kept as low as possible and not exceed that recommended for RLS/WED treatment.

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

- Treatment of existing augmentation should be initiated with the elimination/correction of extrinsic exacerbating factors (low iron levels, antidepressants, antihistamines, etc.) where possible.

- 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 nighttime 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 to rotigotine, noting that rotigotine may also produce augmentation at higher doses with long-term use. In severe cases of augmentation a high-potency opioid may be considered, bypassing α2δ ligands and rotigotine.
Research agenda

In the future we should:

• 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.

• Perform controlled studies on the optimal management of patients with augmentation.

• Investigate the pathophysiology of augmentation.

• Assess methods to identify augmentation and those at risk of developing augmentation.
Table 1: Overview of tools used to assess augmentation in RLS/WED trials

<table>
<thead>
<tr>
<th>Method</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>Allen Earley criteria[1]</td>
<td>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.</td>
</tr>
<tr>
<td>NIH criteria[4]</td>
<td>Clinical criteria based on consensus. The primary features of augmentation were identified as a drug-induced shifting of symptoms to a period of time two hours earlier than was the typical time of daily onset prior to pharmacological intervention OR increased leg movements, decreased duration of treatment benefit, spread of the symptoms to more of the body, decreased time able to stay at rest without symptoms, paradoxical response to dose increase.</td>
</tr>
<tr>
<td>Max Planck Institute (MPI) criteria for diagnosing RLS augmentation[5]</td>
<td>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 (two to four hour) 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.</td>
</tr>
<tr>
<td>Augmentation severity rating scale (ASRS)</td>
<td>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.</td>
</tr>
</tbody>
</table>
### Table 2: Differential diagnosis of augmentation

<table>
<thead>
<tr>
<th></th>
<th>Augmentation</th>
<th>End of dose rebound</th>
<th>Tolerance</th>
<th>Natural Progression</th>
<th>Exacerbating factors*</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Worse than before treatment</strong></td>
<td>Yes</td>
<td>Yes, in early morning</td>
<td>No</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td><strong>Earlier onset</strong></td>
<td>Yes</td>
<td>Yes, in early morning</td>
<td>No</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td><strong>Spread to arms</strong></td>
<td>Yes</td>
<td>No</td>
<td>No</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td><strong>Breakthrough at night</strong></td>
<td>Yes</td>
<td>Yes, in early morning</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td><strong>Worse with increased dose</strong></td>
<td>Yes, but not immediately</td>
<td>No</td>
<td>No</td>
<td>No</td>
<td>No</td>
</tr>
<tr>
<td><strong>Improved with decreased dose</strong></td>
<td>Yes, but not always‡</td>
<td>No</td>
<td>No</td>
<td>No</td>
<td>No</td>
</tr>
</tbody>
</table>

*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 hours on levodopa, it can take several weeks to several months to see an improvement with dopamine agonists.
<table>
<thead>
<tr>
<th>α2δ ligands</th>
<th>Starting dose</th>
<th>Usual effective daily dose</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt; 65 yrs</td>
<td>&gt; 65 yrs</td>
<td></td>
</tr>
<tr>
<td>Gabapentin enacarbil</td>
<td>600 mg</td>
<td>300 mg</td>
</tr>
<tr>
<td>Approved (USA, Japan as of 2015)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pregabalin</td>
<td>75 mg</td>
<td>50 mg</td>
</tr>
<tr>
<td>Gabapentin*</td>
<td>300 mg</td>
<td>100 mg</td>
</tr>
</tbody>
</table>

* Long-term studies have not been performed with gabapentin in RLS/WED and absorption is variable, thereby complicating dosing.
Table 4a: Factors that Affect Selection of an Agent for Initial Treatment in Patients With Restless Legs Syndrome/Willis-Ekbom Disease (adapted from [43])

<table>
<thead>
<tr>
<th>Factor That Impacts the Choice of Agent</th>
<th>Treatment Choice</th>
</tr>
</thead>
</table>
| 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, e.g., severe insomnia | α2δ Ligand |
| Comorbid insomnia                      | α2δ Ligand |
| Pregnancy risk                         | • Avoid both DAs and α2δ 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                  | α2δ Ligand |
| Comorbid pain syndrome                 | α2δ Ligand |
| History of impulse control disorder    | α2δ Ligand |
| History of alcohol or substance abuse  | Dopamine-receptor agonist or α2δ 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 α2δ ligand |
| Comorbid depression                    | Dopamine-receptor agonist |
| Comorbid generalized anxiety disorder  | α2δ Ligand |
| Higher potential for drug interactions | • Select drug that is not hepatically metabolized |
| Symptomatic PLMS                       | • Dopamine-receptor agonist |
Table 4b: Common adverse at 52 weeks (adapted from Allen et al. [2])

<table>
<thead>
<tr>
<th>Event</th>
<th>Pregabalin 300 mg</th>
<th>Pramipexole 0.25 mg</th>
<th>Pramipexole 0.5 mg</th>
</tr>
</thead>
<tbody>
<tr>
<td>Serious adverse events — no.</td>
<td>11</td>
<td>20</td>
<td>12</td>
</tr>
<tr>
<td>Patients with serious adverse events — no. (%)</td>
<td>9 (4.9)</td>
<td>12 (6.7)</td>
<td>9 (5.0)</td>
</tr>
<tr>
<td>Patients with adverse events — no. (%)</td>
<td>155 (85.2)</td>
<td>142 (79.8)</td>
<td>140 (77.8)</td>
</tr>
<tr>
<td>Discontinuations due to adverse events— no. (%)</td>
<td>50 (27.5)</td>
<td>33 (18.5)</td>
<td>43 (23.9)</td>
</tr>
<tr>
<td>Suicidal ideation— no.</td>
<td>6</td>
<td>3</td>
<td>2</td>
</tr>
</tbody>
</table>

**Common adverse events — no. (%) appearing in > 8% of patients**

<table>
<thead>
<tr>
<th>Event</th>
<th>Pregabalin 300 mg (%)</th>
<th>Pramipexole 0.25 mg (%)</th>
<th>Pramipexole 0.5 mg (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dizziness</td>
<td>39 (21.4%)</td>
<td>15 (8.4%)</td>
<td>17 (9.4%)</td>
</tr>
<tr>
<td>Somnolence</td>
<td>32 (17.6%)</td>
<td>12 (6.7%)</td>
<td>14 (7.8%)</td>
</tr>
<tr>
<td>Fatigue</td>
<td>23 (12.6%)</td>
<td>19 (10.7%)</td>
<td>22 (12.2%)</td>
</tr>
<tr>
<td>Headache</td>
<td>22 (12.1%)</td>
<td>30 (16.9%)</td>
<td>35 (19.4%)</td>
</tr>
<tr>
<td>Nasopharyngitis</td>
<td>19 (10.4%)</td>
<td>20 (11.2%)</td>
<td>17 (9.4%)</td>
</tr>
<tr>
<td>Weight gain</td>
<td>16 (8.8%)</td>
<td>12 (6.7%)</td>
<td>12 (6.7%)</td>
</tr>
<tr>
<td>Constipation</td>
<td>14 (7.7%)</td>
<td>3 (1.7%)</td>
<td>2 (1.1%)</td>
</tr>
<tr>
<td>Nausea</td>
<td>11 (6.0%)</td>
<td>18 (10.1%)</td>
<td>26 (14.4%)</td>
</tr>
<tr>
<td>Back pain</td>
<td>10 (5.5%)</td>
<td>16 (9.0%)</td>
<td>13 (7.2%)</td>
</tr>
<tr>
<td>Influenza</td>
<td>9 (4.9%)</td>
<td>13 (7.3%)</td>
<td>3 (1.7%)</td>
</tr>
<tr>
<td>Vomiting</td>
<td>3 (1.6%)</td>
<td>4 (2.2%)</td>
<td>10 (5.6%)</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>7 (3.8%)</td>
<td>9 (5.1%)</td>
<td>10 (5.6%)</td>
</tr>
</tbody>
</table>
Table 5: Suggested initial dose and maximum recommended dose for dopamine agonists

<table>
<thead>
<tr>
<th></th>
<th>Initial dose</th>
<th>Max. Recommended dose</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pramipexole</td>
<td>0.125 mg/day</td>
<td>0.75 mg/day</td>
</tr>
<tr>
<td>Ropinirole</td>
<td>0.25 mg/day</td>
<td>4 mg/day</td>
</tr>
<tr>
<td>Rotigotine</td>
<td>1 mg/day</td>
<td>3 mg/day</td>
</tr>
</tbody>
</table>
Table 6: Suggested initial dose for switching dopamine agonists

<table>
<thead>
<tr>
<th></th>
<th>Rotigotine</th>
<th>Pramipexole ER*</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Pramipexole</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>0.25 mg</td>
<td>2 mg</td>
<td>0.375 mg</td>
</tr>
<tr>
<td>0.50 mg (or higher)</td>
<td>3 mg</td>
<td>0.75 mg</td>
</tr>
<tr>
<td><strong>Ropinirole</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>0.5-1.0 mg</td>
<td>2 mg</td>
<td>0.375 mg</td>
</tr>
<tr>
<td>2 mg or higher</td>
<td>3 mg</td>
<td>0.75 mg</td>
</tr>
</tbody>
</table>

* the incidence rate of augmentation has not been assessed with pramipexole extended release
<table>
<thead>
<tr>
<th>Study</th>
<th>Drug</th>
<th>Design</th>
<th>Duration</th>
<th>Definition of augmentation</th>
<th>N° patients</th>
<th>Results</th>
<th>Class of evidence*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Maestri M et al. 2014[7]</td>
<td>Pramipexole ER</td>
<td>Open, case series</td>
<td>Mean follow-up of 13 months</td>
<td>MPI</td>
<td>24</td>
<td>Resolution of symptoms</td>
<td>IIc</td>
</tr>
<tr>
<td>Ondo W, 2005[48]</td>
<td>Methadone</td>
<td>Open, retrospective, case series</td>
<td>23 m (range: 4-44)</td>
<td>Clinical: greater intensity &amp; earlier onset of symptoms</td>
<td>27 (8 patients intolerable augmentation when on DAs)</td>
<td>8/8 patients with augmentation showed a good response (8-5/5 grade). Efficacy rated as follows: 5, complete relief of RLS symptoms &amp; excellent nocturnal sleep; 4, complete relief but continued subjective sleep problems; 3, 75% to 99% improvement; 2, 25% to 74% improvement; 1, 1% to 24% improvement; and 0, no improvement</td>
<td>IV</td>
</tr>
<tr>
<td>Miranda CM. 2013[47]</td>
<td>Rotigotine</td>
<td>Open, prospective case series</td>
<td>18 m</td>
<td>No adequate definition</td>
<td>10</td>
<td>Resolution of symptoms</td>
<td>IV</td>
</tr>
<tr>
<td>Stiasny-Kolster K, et al. 2004[48]</td>
<td>Pramipexole low dose</td>
<td>Open, prospective case series</td>
<td>1-11 days</td>
<td>Patients, did not respond to levodopa, no further specification</td>
<td>17</td>
<td>Good general response</td>
<td>IV</td>
</tr>
<tr>
<td>Kurlan R, 2013 [49]</td>
<td>Gabapentin, clonazepam, tramadol</td>
<td>Retro., CS</td>
<td>1-43 weeks</td>
<td>NIH</td>
<td>14</td>
<td>Mean time to resolution: GBP (n=4): 2.6 w (1–6w); Clonazepam (n=3): 14.9 w (1–43w); Tramadol (n=3): 22.3 w (10–31w)</td>
<td>IV</td>
</tr>
<tr>
<td>Winkelmuller I, et al. 1998[50]</td>
<td>Pergolide</td>
<td>Open, prospective</td>
<td>6 months</td>
<td>Clinical</td>
<td>15</td>
<td>All showed improvement at mean dose of 0.4 mg</td>
<td>IV</td>
</tr>
<tr>
<td>Earley CJ, et al. 1996[51]</td>
<td>Pergolide</td>
<td>Open, retrospective, case series</td>
<td>18 m (1-39 months)</td>
<td>Clinical</td>
<td>26</td>
<td>Response rate 83% (19/23RLS patients) or (19/26 patients with either RLS (n=23) or PLMS (n=3))</td>
<td>IV</td>
</tr>
</tbody>
</table>

* classified according to previously used criteria for treatment trials. [43]
### Table 8: Opioid suggested doses

<table>
<thead>
<tr>
<th></th>
<th>Starting dose</th>
<th>Usual effective daily dose</th>
</tr>
</thead>
<tbody>
<tr>
<td>Oxycodone prolonged release (may be combined with naltrexone)</td>
<td>5-10 mg</td>
<td>10-40 mg</td>
</tr>
<tr>
<td>Methadone</td>
<td>2.5 mg</td>
<td>5-30 mg</td>
</tr>
</tbody>
</table>
Evaluate if any drug treatment is needed. If symptoms continue, introduce an α₂δ ligand or an opioid.

- If these strategies fail or if the patient has severe, round-the-clock symptoms, then treatment with low doses of an opioid (long-acting oxycodone or methadone) should be considered.
- If serum ferritin < 50-75 µg/mL then treatment with intravenous iron, according to availability, should be strongly considered.

The objective is to reduce, & if possible eliminate the short-acting dopamine agonist and to begin treatment with rotigotine or a long acting dopamine agonist or an α2δ ligand or in severe cases a long-acting opiate.

Three strategies are available for doing this:

• Cross titration
  Add an alpha-2-delta ligand and then gradually reduce the dose of the dopamine agonist with the objective of eliminating it altogether, understanding that this may not be possible in all cases

• Switch
  Switch patient from a short-acting dopamine agonist to rotigotine or a long-acting dopamine agonist if this is not already the case.

• 10-day washout

Complete switch to one of the options below

- An α2δ ligand
- Rotigotine or a long-acting dopamine agonist at ≤ approved dose

If this strategy fails consider "severe augmentation" options

One of the below three options:
1. Temporal shift
2. Dopaminergic dose is ≤ maximum recommended dose
3. Symptoms cause mild distress
4. There has been no prior increase in dose above what was previously therapeutically effective

Mild augmentation (all of the below)

1. Temporal shift
2. Dopaminergic dose is ≤ maximum recommended dose
3. Symptoms cause mild distress
4. There has been no prior increase in dose above what was previously therapeutically effective

Severe augmentation
1. Not mild, OR
2. Does not respond to treatment for mild augmentation

Keep the same dopamine agonist

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References


