SUMMARY OF RECOMMENDATIONS FOR THE LONG-TERM TREATMENT OF RLS/WED *from* AN IRLSSG TASK FORCE

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The task force is grateful to Catherine Friederich Murray for her assistance with writing this document.

The choice of treatment for restless legs syndrome (RLS; also known as Willis-Ekbom disease [WED]) should be based upon the risks and benefits associated with each treatment, the patient's response to previous treatment for RLS/WED, possible interaction with other treatments, the patient's comorbid conditions, and the patient's clinical status. Table 1 provides information for determining treatment choice based on the long-term benefits and risks of each major class of medications used to treat RLS/WED.

LEVELS OF EVIDENCE FOR EACH PHARMACOLOGIC TREATMENT OF RLS/WED

Several classes of drugs have been shown to be effective in the long-term treatment of RLS/WED. The following recommendations provide the levels of evidence in support of the use of these drugs for the long-term treatment of RLS/WED.

Non–Ergot-Derived Dopamine-Receptor Agonists

- Pramipexole is effective for the treatment of RLS/WED for up to 6 months (Level A). Pramipexole is probably effective for the treatment of WED for 1 year (Level B). Pramipexole is possibly effective for up to 10 years in the 10% to 40% of patients who tolerate the therapy and do not experience augmentation or tolerance (Level C).
- Ropinirole is effective for the treatment of RLS/WED for up to 6 months (Level A). Ropinirole is probably effective for the treatment of WED for up to 1 year (Level B). There is insufficient evidence documenting the effectiveness of ropinirole to make a recommendation beyond 1 year of treatment.
- Rotigotine is effective for the treatment of RLS/WED for up to 6 months (Level A). Rotigotine is probably effective for the treatment of WED for up to 5 years in the approximately 43% of patients who tolerate the therapy and do not experience augmentation or loss of efficacy (Level B).

Levodopa

- Levodopa-benserazide is probably effective for the treatment of RLS/WED for up to 2 years in the 24% to 40% of patients who tolerate the therapy and do not experience augmentation or loss of efficacy (Level B).

Ergot-Derived Dopamine-Receptor Agonists

- Pergolide should no longer be used for the treatment of RLS/WED, except for patients whose symptoms are refractory to all other treatments and in whom the benefits of this treatment outweigh the risks.
- Cabergoline should no longer be used for the treatment of RLS/WED, except for patients whose symptoms are refractory to all other treatments and in whom the benefits of this treatment outweigh the risks.

$\alpha_2\delta$ Ligands

- Gabapentin enacarbil is probably effective for the treatment of RLS/WED for up to 1 year (Level B). There is insufficient evidence documenting the effectiveness of gabapentin enacarbil to make a recommendation beyond 1 year of treatment.

- Pregabalin is effective for the treatment of RLS/WED for 1 year (Level A). There is insufficient evidence documenting the effectiveness of pregabalin to make a recommendation beyond 1 year of treatment.
- There is insufficient evidence documenting the effectiveness of gabapentin in the long-term treatment of RLS/WED to make any recommendation.

Opioids

- At the time of writing these recommendations, there was insufficient long-term evidence to make a recommendation for any one opioid. The high-potency opioids, eg, methadone and oxycodone, as a class of medications, however, can be considered possibly effective (level C) in the long-term treatment of RLS/WED refractory to other treatments. Caution should be taken to exclude sleep-related breathing disorders before treatment is initiated with opioids, particularly in older patients.

RECOMMENDATIONS REGARDING CHOICE OF AGENTS

Choice of Initial Treatment

- Either dopamine-receptor agonists or the $\alpha_2\delta$ ligands are first-line treatment for patients with RLS/WED.
- The choice of the initial treatment should be based on the individual clinical features of RLS/WED in a given patient. Some recommendations based on clinical experience are provided in Table 2.
- Medication administration should be related to the timing of the onset of clinically significant symptoms that cannot be effectively managed behaviorally. Each medication has a specific time of onset, which need to be taken into account when prescribing treatment.
- Patients with clinically significant daytime symptoms should be treated with a long-acting agent. Multiple daily doses of a short-acting agent can also be tried. Frequent monitoring for loss of efficacy or the development or progression of augmentation is recommended for all dopaminergic agents.
- The use of $\alpha_2\delta$ ligands should be considered for initial treatment for patients with severe sleep disturbance (disproportionate to other RLS/WED symptoms), comorbid insomnia, RLS/WED-related or comorbid pain, a previous history of an impulse control disorder (ICD) or comorbid generalized anxiety disorder.
- Dopamine-receptor agonists should be considered for initial treatment for patients with very severe symptoms, excessive weight, comorbid depression, or increased risk of falls.
- In general, pharmacologic treatment should be avoided for RLS/WED symptoms occurring during pregnancy; both dopamine-receptor agonists and $\alpha_2\delta$ ligands should be avoided. Consideration should be given to fully replenishing iron stores prior to pregnancy and maximizing nonpharmacologic treatments. Published literature about the practical treatment of RLS during pregnancy is very limited.
- The availability and cost of drugs may need to be considered in making the choice of the initial treatment.

- Combination treatments of a dopamine-receptor agonist and an $\alpha_2\delta$ ligand should be considered for patients with symptoms that cannot be controlled with a low-dose monotherapy of either treatment class. There is a need for more clinical studies of combination treatments.

RECOMMENDATION REGARDING LOSS OF EFFICACY AND AUGMENTATION

Loss of efficacy and *augmentation* are the main causes of treatment failure that emerge later in the course of treatment.

For Both Augmentation and Loss of Efficacy

- The patient's serum ferritin level should be measured, and, if the concentration is lower than 75 μg/mL, supplementation with orally administered iron is recommended unless poorly tolerated or contraindicated.
- It is important to ask the patient about any lifestyle changes, changes in medical factors (use of dopamine-receptor antagonists or antidepressants), or other extrinsic factors (sleep deprivation, blood loss, alcohol use) that might have contributed to an earlier onset or an increase in the severity of symptoms. Any extrinsic factors exacerbating RLS expression should be adjusted as much as possible to reduce the need for medication changes.

For Loss of Efficacy

- Loss of efficacy commonly occurs for all drugs in the long-term treatment of RLS/WED. If loss of efficacy occurs, doses of the current agent should only be adjusted above the approved levels with caution and with monitoring for adverse effects, development of augmentation, or progressive loss of efficacy. Instead, consideration should be given to adding another medication or changing medications.
- For patients experiencing loss of efficacy under monotherapy, a drug of another class (either dopamine-receptor agonists or $\alpha_2\delta$ ligands) could either be added without increasing the dose of the current drug or, alternatively, substituted for the current drug.

For Augmentation

- Augmentation is a major clinical problem that emerges with the long-term treatment of RLS/WED. It can produce a severe exacerbation of RLS/WED symptoms and is thus something to be carefully assessed and managed.
- Some degree of augmentation has been reported with the use of all investigated dopaminergic drugs and also for tramadol. In the virtual absence of direct comparative studies, the incidence rate seems highest during treatment with levodopa and is higher for shorter-acting (pramipexole, ropinirole) than longer-acting (rotigotine, cabergoline) dopamine-receptor agonists. However, it is unclear whether this finding is related to masking of earlier symptom onset by the longer-acting dopaminergic agents or is truly an augmentation-sparing effect.
- The risk of augmentation increases with longer duration of treatment and possibly with higher dose. It is unclear whether the apparent relationship between dose and

augmentation rate is, in fact, secondary to patient characteristics such as disease duration or severity. Nevertheless, it is recommended that dose increases be carefully considered, particularly if they exceed usually accepted or approved dose levels. They should be limited to breakthrough of clinically important symptoms that cannot be managed behaviorally and should be balanced against the option of adding an alternate type of medication.

- If bothersome earlier onset of symptoms occurs with augmentation when the patient is taking a short-acting dopaminergic medication, a dose of the current medication can be added earlier, with possible reduction of the latter dose or the medication changed to a single dose of a longer-acting dopaminergic or other medication. If the total dopaminergic dose is increased, careful monitoring for progressive augmentation is needed.
- For severe or progressive augmentation, the dopamine-receptor agonist should be discontinued and an $\alpha_2\delta$ ligand, an opioid, or possibly another (perhaps longer-acting) dopamine-receptor agonist substituted.

RECOMMENDATIONS FOR OTHER TREATMENT-RELATED PROBLEMS EMERGING DURING LONG-TERM THERAPY

For ICDs

- ICDs develop in 6% to 17% of patients with RLS/ WED who are taking dopamine-receptor agonists. ICDs may occur more often with higher doses of drugs and may be more likely to occur in women.
- Patients should be questioned about ICDs at each visit. If an ICD is present, the drug should be discontinued or at least the dose decreased to a level at which ICDs cease. Other non-dopaminergic drugs should be substituted or added.

For Comorbid Insomnia

- If problems of insomnia or inadequate sleep develop or persist on the current medication then a short-acting GABA-active hypnotic or if not already used an $\alpha_2\delta$ ligand can be added.

For Severe RLS Refractory to Standard Treatments

- In the long-term care of severe RLS that is refractory to standard treatments, consider, where available, the use of low-dose methadone.

Table 1—Benefits and Risks of Each Pharmacologic Treatment of RLS/WED

	L-dopa	Non-ergot DA		Ergot-based DA	$\alpha_2\delta$ Ligand	Opioid	Clonazepam
		Short-acting	Long-acting				
The potential of the drug to cause the following adverse events							
Augmentation	+++	++	+	++	0	NK	0
LoE	+++	++	NK	++	+	+	NK
ICD	0	+	0/+	NK	0	0	0
EDS	DK	++	+	++	+++	+	++
Negative mood	0	0	0	0	+	+	++
Weight gain	0	0	0	0	++	0	0
General toxicity[a]	+	+	++	+++	+	++	+
The potential of the drug to have positive effect on these parameters							
Subjective nighttime sleep	0	+	+	+	++	++	++
Classic nighttime WED symptoms	+	++	++	++	++	++	0
QoL	NK	++	++	++	++	NK	NK
Pain reduction	+	+	+	+	++	+++	0

Abbreviations: RLS/WED refers to restless legs syndrome/ Willis-Ekbom disease; DA, dopamine-receptor agonist; LoE, loss of efficacy; ICD, impulse control disorders; EDS, excessive daytime sleepiness; QoL, quality of life; NK, not known.

+++, is very likely to affect this parameter; ++, is somewhat likely to affect this parameter; +, is slightly likely to affect this parameter; 0 , has no affect on this parameter.

Table 2—Factors That Affect Selection of an Agent for Initial Treatment in Patients With RLS/WED

Factor **That Impacts** the **Choice** of **Agent**	**Treatment Choice**
Time of day (daytime disturbance)	• Preferably a long-acting agent • Twice-a-day dosing of a short-acting agent
Sleep disturbance disproportionate to other symptoms of RLS/WED, eg, very severe and symptomatic 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
Increased risk of falls	Dopamine-receptor agonist
Painful restless legs	$\alpha_2\delta$ Ligand
Comorbid pain syndrome	$\alpha_2\delta$ Ligand
History of ICD	$\alpha_2\delta$ Ligand
History of alcohol or substance abuse	Dopamine-receptor agonistor $\alpha_2\delta$ ligand
Very severe symptoms of RLS/WED	Dopamine-receptor agonist
Excess weight, metabolic syndrome, or obstructive sleep apnea	Dopamine-receptor agonist
Availability or cost of drug	Dopamine-receptor agonistor $\alpha_2\delta$ ligand
Comorbid depression	Dopamine-receptor agonist
Comorbid generalized anxiety disorder	$\alpha_2\delta$ Ligand
Daytime sleepiness	• Investigate the cause
Higher potential for drug interactions	• Select drug that is not hepatically excreted

Abbreviations: RLS/WED refers to restless legs syndrome/Willis-Ekbom disease; ICD, impulse control disorder.

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