Teaching Course 1

MDS-ES/EAN: Differential diagnosis of sleep related movement disorders - Level 3

RLS and PLM: Clinical and video-based characteristics of typical and atypical cases, and treatment complications

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Restless legs syndrome: Clinical and video-based characteristics of typical and atypical cases, and treatment complications
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The first criteria for the diagnosis of restless legs syndrome (RLS) were established in 1995, revised in 2003, and in 2014 a fifth criterion was added in order to improve specificity by excluding mimics (see table 1). All versions of the criteria have maintained the key features of the clinical picture: sensory symptoms—namely restlessness (urge to move) and unpleasant sensations (paraesthesias, pain)—and motor symptoms (periodic limb movements and other motor manifestations). These occur mostly in the legs during periods of rest and improve with movement, such as walking, and have a circadian aspect whereby symptoms are more pronounced in the evening and at nighttime.
**Table 1: International Restless Legs Syndrome Study Group (IRLSSG) consensus diagnostic criteria for restless legs syndrome/Willis–Ekbo disease (RLS/WED).**

RLS/WED, a neurological sensorimotor disease often profoundly disturbing sleep and quality of life, has variable expression influenced by genetic, environmental and medical factors. The symptoms vary considerably in frequency from less than once a month or year to daily, and severity from mildly annoying to disabling. Symptoms may also remit for various periods of time. RLS/WED is diagnosed by ascertaining symptom patterns that meet the following five essential criteria, adding clinical specifiers where appropriate.

### Essential diagnostic criteria (all must be met):

1. An urge to move the legs usually but not always accompanied by, or felt to be caused by, uncomfortable and unpleasant sensations in the legs.\(^a\,^b\)

2. The urge to move the legs and any accompanying unpleasant sensations begin or worsen during periods of rest or inactivity such as lying down or sitting.

3. The urge to move the legs and any accompanying unpleasant sensations are partially or totally relieved by movement, such as walking or stretching, at least as long as the activity continues.\(^c\)

4. The urge to move the legs and any accompanying unpleasant sensations during rest or inactivity only occur or are worse in the evening or night than during the day.\(^d\)

5. The occurrence of the above features is not solely accounted for as symptoms primary to another medical or a behavioral condition (e.g. myalgia, venous stasis, leg edema, arthritis, leg cramps, positional discomfort, habitual foot tapping).\(^e\)

### Specifiers for clinical course of RLS/WED:\(^f\)

A. Chronic-persistent RLS/WED: symptoms when not treated would occur on average at least twice weekly for the past year.

B. Intermittent RLS/WED: symptoms when not treated would occur on average <2/week for the past year, with at least five lifetime events.

### Specifier for clinical significance of RLS/WED:

The symptoms of RLS/WED cause significant distress or impairment in social, occupational, educational or other important areas of functioning by their impact on sleep, energy/vitality, daily activities, behavior, cognition or mood.

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\(^a\) Sometimes the urge to move the legs is present without the uncomfortable sensations and sometimes the arms or other parts of the body are involved in addition to the legs.

\(^b\) For children, the description of these symptoms should be in the child’s own words.
When symptoms are very severe, relief by activity may not be noticeable but must have been previously present.

When symptoms are very severe, the worsening in the evening or night may not be noticeable but must have been previously present.

These conditions, often referred to as “RLS/WED mimics,” have been commonly confused with RLS/WED particularly in surveys because they produce symptoms that meet or at least come very close to meeting criteria 1–4. The list here gives some examples that have been noted as particularly significant in epidemiological studies and clinical practice. RLS/WED may also occur with any of these conditions, but the RLS/WED symptoms will then be more in degree, conditions of expression or character than those usually occurring as part of the other condition.

The clinical course criteria do not apply for pediatric cases nor for some special cases of provoked RLS/WED such as pregnancy or drug-induced RLS/WED where the frequency may be high but limited to duration of the provocative condition.

**Diagnostic criteria led to change of therapy**

To differentiate between “typical” and “atypical” cases of RLS and to better separate RLS patients form so-called “mimics”, a new paragraph in the criteria, entitled “Specifiers for RLS” seeks to define a more homogeneous subgroup of patients for research and for treatment planning. These diagnostic criteria also differentiate between “chronic-persistent RLS” and “intermittent RLS”. Patients with the latter condition rarely seek medical attention and treatment is mostly not needed, therefore these patients are no longer included in any of the current therapeutic trials.

RLS is a condition that mainly occurs with various diseases including iron deficiency anaemia, multiple sclerosis, polyneuropathy, Parkinson’s disease, as well as common chronic diseases such as arterial hypertension, headache, or conditions such as inflammation, and pregnancy. Over time a differentiation of RLS into “primary, idiopathic” and “secondary, symptomatic” has been established without clear criteria for differentiating both. Although available evidence now encompasses a broad spectrum of pathophysiological, population-based (cross-sectional or longitudinal) studies, the question whether RLS is more a primary disorder or a comorbidity, remains unresolved. It is even likely that a cumulative number of diseases within a single patient increases the risk of the additional manifestation of RLS symptoms on the background of the genetic risk load, or vice versa.

To fulfill inclusion criteria for almost all randomised controlled trials (RCTs), a score of 15 or higher on the International RLS rating scale (IRLS) is required. This corresponds to at least moderate RLS, with an at least twice weekly occurrence of symptoms causing some distress in daily life. Nevertheless, this definition of clinical significance, which effectively limits which RLS patients should be treated, is subject to debate. “No consensus was reached in terms of the specific frequency and duration of RLS/WED to specify clinical significance”. At present, clinical trials in RLS continue to include only patients with moderate to severe RLS, and use the IRLS as the gold-standard. For clinical practice, only patients with an IRLS >15 should be treated with pharmacological agents.

**Treatment of RLS associated with other disorders: uraemia, iron deficiency, and pregnancy**

The prevalence of RLS increases with age, and is also often associated with one or even several other conditions. Most of these, such as diabetes, arterial hypertension, multiple sclerosis, or neurodegenerative diseases cannot be cured, and for some, such as spino-
cerebellar ataxias, there is no treatment available at all. RLS in uraemic patients is a frequent complaint in dialysis centres. Between 20-30% of patients on haemodialysis need a specific treatment for frequently severe RLS. After receiving a kidney transplant, within days patients recover almost completely from the disabling RLS symptoms; thus kidney transplantation is one of the rare obviously causal treatments of RLS, although RLS may reoccur occasionally in mild forms after some time. It should be mentioned that dose adjustments are important in uraemic conditions. A trial with the dopamine agonist rotigotine transdermal patch in uraemic patients is currently underway. However, there is still insufficient evidence for any specific therapeutic regimen for uraemic-associated RLS. Interestingly, uraemic RLS symptoms may be improved using non-pharmacological treatments such as exercise training for six months, which reduces both RLS as well as depression. A comprehensive overview of therapy in uraemic and further secondary RLS is given by Drs. Giannaki and Comella.

Iron deficiency and anaemia in RLS

Patients with low ferritin, either with or without anaemia, should first be treated with iron formulations before starting any dopaminergic therapy. There is a well-studied pathophysiological connection between iron and dopamine metabolism in RLS (see e.g. 5). The most widely used parameter to indirectly check brain iron status is serum ferritin, which should be at least 50mcg/l or higher, and in the author’s experience even closer to 100mcg/l to minimize the likelihood that iron deficiency underlies the RLS symptoms. Various iron formulations have been investigated in several trials including intravenous (i.v.) iron. According to evidence-based methods, there is no single efficacious iron formulation but several trials with various i.v. iron formulations have shown improvement of RLS symptoms after two to six weeks, with a special long-term effect of the treatment. However, not all patients with iron deficiency benefit from iron supplementation, and selection criteria are urgently needed to identify probable responders to iron i.v. treatment. The currently recommended treatment approach is to supplement iron in iron-deficient RLS patients, irrespective of associated anaemia. In a very recent RCT, efficacy was reached only after at least 8-12 weeks after giving a single infusion of 1.000mg iron ferric carboxymaltose i.v.. In this trial, response to iron treatment did not depend on baseline ferritin levels in non-anemic RLS patients.

Iron deficiency is obviously also a major contributing factor to RLS in pregnancy. An IRLSSG treatment algorithm recommends supplementing iron after excluding other sleep disorders, i.e., insomnia or sleep apnoea in pregnancy. Medications for RLS are risk/benefit rated for use during pregnancy and lactation “with the recommendation to first check serum ferritin levels, then start oral iron treatment when ferritin is below 75mcg/l, and i.v. iron when ferritin is below 30mcg/L”. For pregnant women with RLS and normal ferritin or for whom iron supplementation is not working sufficiently or fast enough, pharmacological treatment “can be considered”, in the following order: levodopa/carbidopa (100/25mg-200/50mg), clonazepam 0.25-1mg and, in very severe and refractory cases, low-dose oxycodone – although no trials are available for any of these agents in pregnancy and RLS.

RLS associated with diseases such as multiple sclerosis, polyneuropathy, spinocerebellar ataxia, stroke, or cardiovascular disease is treated the same way and uses the same agents as in idiopathic RLS. However, patients with severe neurological or medical disorders have been explicitly excluded from RCTs. Therefore, our knowledge and recommendations for treatment are only based on case reports, patient cohorts, and clinical experience. As these patients are often severely affected by RLS, they need pharmacological treatment that should follow the guidelines for idiopathic RLS when possible. Any side effects of RLS medication should be monitored closely in these patients. For a comprehensive summary of treatment trials in secondary RLS see Comella.

Pharmacological treatment: general considerations
Since the 1990s, first L-dopa/DDCI, followed by various dopamine agonists, were used to treat restlessness, sensory and motor symptoms and sleep disturbance in patients with RLS. Dopamine agonists are licensed in many countries and became the most common therapy for RLS. Both RCTs and clinical practice have confirmed their efficacy.

Not only dopaminergic agents, but all currently known RLS therapies, seem to lose efficacy over time in some patients with severe RLS. Most often this leads physicians to add on various combination treatments with licensed or even non-licensed agents for improving RLS symptoms (personal observation). Therefore, we need to be cautious in starting any pharmacological treatment in RLS and should advise patients that no symptomatic therapies can cure RLS, and may not completely or permanently relieve RLS symptoms and sleep problems. At present, treatment guidelines based on long-term studies (when available) recommend starting with “either a dopamine-receptor agonist or an α-2-δ ligand as the first-line of treatment for most RLS patients, the choice of agent depending on the severity of patients’ RLS symptoms, cognitive status, history, and comorbid conditions”. (Allen 1 A small number of non-pharmacological treatment studies or cognitive behavioural therapies have triggered a new attitude towards more self-responsibility in RLS patients.

Dopaminergic therapy in RLS

Therapy with non-ergot dopamine agonists is currently recommended as a first line therapy or “Standard Therapy” as reflected in several guidelines. Accordingly, pramipexole, ropinirole, and rotigotine transdermal patches are licensed in many countries, including Europe, USA and Japan. Although levodopa/DDCI may still be used, it may be advisable to start with a dopamine agonist because the short half-life of levodopa and its pulsatile mode of action may lead to higher augmentation rates than those observed with other dopamine agonists, such as pramipexole or rotigotine. Although levodopa has been generally recommended for intermittent use in RLS, not one study has been performed to treat intermittent RLS as defined in the new classification criteria. Treating intermittent attacks of RLS or RLS in specific situations such as sitting in conferences or long-distance flights are well known clinical applications for 100/25mg levodopa/DDCI, although no controlled data are available. However, pramipexole, with its short-acting efficacy and rapid onset of action, has been used as well. Although the ergot-dopamine agonists pergolide and cabergoline have proved efficacious in RLS therapy, as in Parkinson’s disease therapy, they should now be avoided as first choice medications because of side effects such as valvular fibrosis, despite cabergoline being especially effective for RLS and possibly restituting reduced cortical excitability.

Practical use of dopamine agonists (DA)

Finding the lowest effective dose of dopamine agonists is the key objective of various trial designs. Only about 1/6 to 1/8 of the maximal doses used in Parkinson’s disease are recommended for RLS. When dose titrating rotigotine, for example, an increase from 2 to 3mg has not been shown to significantly increase its benefit. A five-year study of rotigotine included the dose of 4mg (finally not approved by the EMA) which increased augmentation rates compared to the 2mg or 3mg doses, but provided no further long-term efficacy. In this long-term trial, 57% of the patients discontinued participation during the five years, mostly due to application site reactions resulting from the transdermal patch. In trials with flexible doses, such as the ropinirole trials, a dose of ca. 2mg was selected as optimal by patients and investigators (licensed ropinirole dose for RLS: 0.25-4mg). Similar data are available for pramipexole (licensed pramipexole dose for RLS: 0.25-0.75mg). In clinical practice, a single dose of 0.25 pramipexole relieves RLS complaints in RLS patients not already experiencing augmentation or in those used to higher dopaminergic doses. Many trials using different designs confirm the efficacy of this low dose of pramipexole (0.25mg,
0.18mg respectively) compared to placebo both for alleviating periodic limb movements (PLM) and for subjective symptoms.32, 34-39 The only trial that was unable to show efficacy of 0.25mg pramipexole was a comparative multi-centre RCT using pramipexole at 0.25 and 0.5mg compared to 300mg pregabalin and placebo.40 This trial demonstrated, however, that this low dose of pramipexole had the same augmentation rate as placebo or pregabalin when evaluated for one-year of treatment.40

No difference in clinical efficacy could be identified in a comparative trial of pramipexole and ropinirole when using equivalent low dosages.41 Clinical experience may slightly favour pramipexole for short-term effectiveness. In a mixed treatment comparison in 15 trials, rotigotine was found to be slightly better than ropinirole in reducing RLS severity after 12 weeks of treatment.42 Further comparative analysis in 35 RCTs showed that the ergot-agonists cabergoline and pergolide had greater treatment effects than non-ergot dopamine agonists, while pramipexole was more effective than levodopa.

All dopamine agonists were given as single doses in the evening or at night in clinical trials. Although divided doses are frequently used in clinical practice, such a regimen with a need for earlier treatment during the day might be the first step towards starting augmentation. If RLS symptoms are primarily troublesome during the daytime with overall severe RLS, an agent with a long half-life or a 24h effect covering daytime symptoms, such as a rotigotine transdermal patch, is recommended.21, 23, 27 This may also be favourable for avoiding early augmentation in these severe cases, although prospective comparative data on dopamine agonists are not available.

**Side Effects of dopamine agonists**

The side effects of all dopamine agonists include nausea, gastrointestinal complaints, leg swelling, and daytime sleepiness. All patients need to be carefully advised about possible compulsive behaviours such as pathological gambling, shopping, eating, or hypersexuality during treatment with a dopamine agonist. Even at the low dosages used in RLS patients, these side effects can lead to serious problems and are well described.43, 44 Patients at risk show a history of psychiatric disease, alcohol or addiction problems.

Daytime drowsiness sometimes extending into so-called sleep attacks are a well-known side effect of dopamine agonists.45 It is less well known, and often underestimated, that dopamine agonists may conversely interfere with deep sleep and also lead to increased wakefulness at night. Therefore, these drugs can actually cause insomnia despite successful alleviation of RLS symptoms. Skin reactions should be mentioned as a possible side effect of rotigotine patches, as they occur in up to 16% of RLS patients when pooled data are analysed.17 Treatment must be stopped when skin reactions such as erythema at the application site increase over time. Changing a dopamine agonist to avoid a certain side effect in an individual patient is helpful in some cases (Glass IV evidence).

**Alpha-2-delta-ligands**

Pregabalin, an analogue of gamma-aminobutyric acid and the structurally related compound gabapentin, are known as α-2-δ ligands and are licensed for treatment of neuropathic pain and seizures, and pregabalin, is also licensed for anxiety disorders.47 Pregabalin has been shown to be effective in improving RLS symptoms, especially sleep and PLMS as revealed by polysomnography.52
The major problem with gabapentin is its unreliable plasma level after intestinal absorption, and 600 mg/day is recommended, as higher dosages were not considered to provide additional benefits and have been associated with more adverse side effects, such as somnolence and dizziness. Gabapentin-enacarbil, which has a more stable effect, is not approved in Europe.

Pregabalin has recently been reported to significantly improve RLS symptoms as measured on the IRLS at a mean single dose of 123mg. Higher doses of 300-600mg improved several sleep parameters, such as sleep stages and sleep continuity, but not sleep efficiency—though several side effects have been reported, predominantly dizziness, unsteadiness, and daytime sleepiness. These findings suggest that pregabalin may directly improve sleep itself in RLS patients (apart from its effects on motor dysfunction). Pregabalin has a wide range of effects on psychiatric and pain disorders and might therefore be less specific in treating RLS motor symptoms compared to a dopaminergic agent, but more appropriate in improving sleep and insomnia. A large RCT compared a dose of 300mg pregabalin with two doses of pramipexole for short-term and long-term efficacy as well as for the development of augmentation. On the IRLS, pregabalin was shown to be as efficacious in reducing RLS severity—for those patients who could tolerate the 300mg—as pramipexole 0.5mg, and superior to placebo. Pramipexole 0.25mg was not reported to be more efficacious than placebo in this trial (see comment under pramipexole), but augmentation rates did not differ statistically between pregabalin (2.1%) and low-dose pramipexole (5.3%), whereas 0.5mg pramipexole compared to 300mg pregabalin showed augmentation rates of 7.7% versus 2.1% after 52 weeks. The percentage of 2.1% augmentation during pregabalin treatment likely reflects fluctuations of severity rather than true augmentation.

The side effect profiles for all α-2-δ ligands are similar, the most prominent being dizziness and unsteadiness, accompanied by daytime sleepiness and fatigue. All these side effects are dose-dependent. In clinical practice, the most common problem in RLS patients is dizziness and daytime sleepiness when an effective dose of pregabalin is given at night, especially in the elderly, and therefore doses should be increased carefully, starting with 50mg at night.

**Dopaminergic-induced augmentation**

Accompanying the success of RLS therapy, a major problem known as augmentation increasingly dominates dopaminergic RLS therapy. The current definition of augmentation is as follows:

**Table 2: Key features of augmentation in RLS.**

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<tr>
<th>Augmentation is the shifting of symptoms to a period of time 2 h or earlier than was the typical period of daily onset of symptoms before pharmacologic intervention.</th>
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<tr>
<td>An increased overall intensity of the urge to move or sensation is temporally related to an increase in the daily medication dosage.</td>
</tr>
<tr>
<td>A decreased overall intensity of the urge to move or sensations is temporally related to a decrease in the daily medication dosage. The latency to RLS symptoms at rest is shorter than the latency with initial therapeutic response or before treatment was instituted. The urge to move or sensations are extended to previously unaffected limbs or body parts.</td>
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<tr>
<td>The duration of treatment effect is shorter than the duration with initial therapeutic response.</td>
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<tr>
<td>Periodic limb movements while awake either occur for the first time or are worse than with initial therapeutic response or before treatment was instituted.</td>
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From a clinical standpoint it is of the utmost importance that augmentation be suspected during dopaminergic therapy and carefully monitored for by using the following modified criteria: a) the patient complains of either an increase in disease severity or declares a need for higher dosages or both, b) onset of symptoms is earlier by at least 2 hours over 24h, c) the patient increases the dosages of his/her self-medication.

Any increase in a dopaminergic dose above the maximum licensed dosage for RLS and approaching the dosage limit for Parkinson’s, is highly indicative of augmentation and should be managed by dose reduction.

Management of augmentation

Mild augmentation starts very gradually and is almost indistinguishable from increasingly severe RLS. Therefore, any patient wishing to increase their treatment dosage should be carefully informed about the U-shaped dose response curve of dopaminergic therapy and that pharmacological therapy is not only unable to totally eliminate RLS symptoms but may even worsen them. Reducing the dosage to the licensed level or even below is step 1, followed by requiring some days of patience to tolerate possible short-lived withdrawal symptoms (step 2a) or switching to a dopamine agonist with a longer half-life such as rotigotine (step2b) (for which first favourable data are available). In step 3, if augmentation is severe and cannot be resolved by step 1 or 2, a low-dose of an opioid may be given in addition to reducing the dopaminergic. Patients with very severe RLS, may require an opioid during augmentation and continue RLS therapy with opioid monotherapy (see opioids). An ultimate, very effective therapy is the intrathecal application of morphine in rare cases.

Although often recommended, dopaminergic therapy need not always be completely discontinued, as some patients still require a small dose (lowest dosage of any dopamine agonist) after having been treated for many years with dopaminergic agents (data on file, not published). In this context, a fast tapering off of dopaminergics or even drug holidays can also lead to dopamine withdrawal syndrome. Therefore, a slow reduction from high doses of dopamine agonists may be better tolerated than an abrupt cessation. Lower doses may be simply stopped before switching to an alternative drug. Switching treatment during acute augmentation from a standard formulation of an agonist to a sustained release formulation may produce a favourable outcome as shown recently for pramipexole (study duration up to 13 months). Similar data are available for switching from any dopaminergic formulation to rotigotine transdermal patches with their more continuous dopaminergic delivery during acute augmentation. Both overnight switching and overlapping treatments with both substances were reported to work in the open study AURORA. For pramipexole and ropinirole sustained-release formulations, however, it should be mentioned, that they have never been studied in RCTs and they have not been approved for RLS therapy.

Opioids

Opioids were already being used for treating RLS in the 1990s when Walters et al. proved the efficacy of oxycodone in RLS-subjective symptoms and PLMS in a small RCT. Several opioids have been used since, e.g. methadone in very severe RLS and even in a retrospective evaluation of a 10-year long-term treatment. Various opioids, including tramadol and oxycodone, seem to be beneficial as shown in a retrospective study. The first large multi-centre RCT using a fixed combination of prolonged release oxycodone/naloxone improved symptoms in patients with severe and very severe RLS, who had failed to respond to previous, mostly dopaminergic, treatments. In the first part of this randomized, placebo-controlled 12-week study, oxycodone/naloxone was given twice daily starting at a lowest dose of 5/2.5mg and titrating up to optimal doses and a mean dosage of approx. 10/5mg oxycodone/naloxone twice daily to arrive at a stable plasma level. Even in very severely
affected RLS patients with daytime symptoms, a significant improvement was achieved on the IRLS compared to placebo (change: 8.15 points) after 12 weeks, with a sustained efficacy during the long-term extension of 40 and 52 weeks. Sleep and quality of life also improved. Addiction and withdrawal problems did not occur. The most common side effects were constipation, somnolence and nausea. Despite an elaborate algorithm to detect augmentation, this phenomenon was not observed during the study. Currently, the combination of prolonged release oxycodone/naloxone at the assigned dosages is approved for RLS therapy in Europe. Further trials may be needed to place this combination treatment within the context of RLS therapy in general and to better explore its efficacy on sleep and sleep architecture.

**Other substances**

Other agents used in the past, or currently employed in various combinations, such as benzodiazepines, zolpidem, valproic acid, carbamazepine, magnesium, clonidine or various vitamins, have not proved to be effective over time\(^\text{27, 51}\) and will not be reviewed here. Treatment with iron is mostly beneficial and is reviewed in the first section. In individual patients, benzodiazepines or zolpidem may be useful when administered intermittently during severe augmentation (personal observation), and especially clonazepam may induce a sleep-stabilizing effect,\(^\text{71}\) but no data on a beneficial long-term therapy are available for any of these substances. But one should be aware that zolpidem and zopiclone may induce restless nocturnal eating, a common feature of RLS with sleep deprivation.\(^\text{72}\)

**Combination treatment**

Currently, there are no trials that investigate combined treatment approaches in RLS. As there is an increasing demand for combination therapy, and as it is already used in clinical practice, we will briefly discuss the most widely used combinations. Since augmentation depends mainly on the dosage of the dopaminergic agent, one possible combination therapy consists of a low-dosed dopamine agonist, i.e. pramipexole 0.18 (0.25) mg, combined with either an \(\alpha\)-2-\(\delta\) ligand or with oxycodone/naloxone. Patients with so-called “break-through” symptoms\(^\text{73}\) during the day may benefit from pregabalin at night to treat the sleep problems and insomnia and intermittent use of either L-dopa/DDCI or a short-acting dopamine agonist (pramipexole, ropinirole).\(^\text{24}\) Patients with severe RLS and predominantly motor symptoms both during daytime or at night (including high numbers of PLM) may benefit from a rotigotine transdermal patch for a 24h dopaminergic effect combined with opioids.

**International recommendations and guidelines**

A meta-analysis, evidence-based medicine (EBM) criteria and practice recommendations are available for the treatment of RLS. The published EBM guidelines\(^\text{27}\) assessing RCTs in RLS do not include recent trials and available therapies, and are currently being updated. For long-term therapy, a meta-analysis and consensus recommendations from the IRLSSG are available,\(^\text{51}\) as are published guidelines of how to treat RLS patients with augmentation.\(^\text{74}\) The American Academy of Sleep Medicine (AASM) clinical practice recommendations based on EBM ratings were published in 2012 and recommend non-ergot dopamine agonists as first-line therapy.\(^\text{17}\) Current American Academy of Neurology (AAN) recommendations have recently been published and recommend both dopamine agonists and \(\alpha\)-2-\(\delta\) ligands as first line therapy.\(^\text{75}\)
References


