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# *Restless legs syndrome*

Restless legs syndrome (RLS) was first described by the Swedish neurologist Karl-Axel Ekbom in 1945 and, as a consequence, RLS is also known as Ekbom's syndrome.

In recent years, there have been a number of controlled clinical studies investigating the pharmacological treatment of RLS. The present review describes the various new treatment options for RLS, using international recommendations as the starting point.

## Clinical symptoms and diagnosis of RLS

The diagnosis of RLS is based on clinical symptoms. These are characterised by unpleasant, painful, tingling sensations in the legs (and sometimes the arms) while at rest. Diurnal variations typically occur. The International Restless Legs Syndrome Study Group has determined that four essential diagnostic criteria are required to make the diagnosis of RLS (Table 1). There are also a number of other clinical features which can support the diagnosis (Table 1). The clinical spectrum is broad, with RLS symptoms predominating in some patients and sleep disturbances in others.

A number of other conditions can resemble RLS but require different diagnostic investigations and treatment, or no treatment at all (Table 2). About 80% of patients with RLS experience involuntary nocturnal motor phenomena known as periodic limb movements (PLMs) and in some cases nocturnal cramps as well. PLMs also occur in a wide range of other neurological disorders, mainly in Parkinson's disease but also in other neurodegenerative and hereditary conditions. PLMs can also occur in the absence of any other symptoms.

## Epidemiology

RLS is more common in women than in men. Estimates of prevalence have varied widely between different studies but the consensus indicates that 5 - 10% of the adult population have symptoms of RLS, with about 2% being severely affected. RLS seems to be a chronic condition and often becomes apparent before the age of 20. Prevalence increases with age.

Table 1: *Diagnostic criteria for RLS*

*Essential diagnostic criteria for RLS*

1. An urge to move the legs, usually accompanied by uncomfortable and unpleasant sensations in the legs; sometimes the arms or other body parts are involved.
2. The symptoms begin or worsen during periods of rest or inactivity such as lying or sitting.
3. The symptoms are partially or totally relieved by movement, such as walking or stretching, at least as long as the activity continues.
4. The symptoms are worse in the evening or night than during the day. In some severe cases, the worsening at night may not be noticeable.

*Supportive clinical features or RLS*

1. Positive family history.
2. Response to dopaminergic therapy.
   Periodic limb movements during wakefulness or sleep.
3. Chronic course
4. Sleep disturbances, including difficulty in maintaining sleep and daytime sleepiness.
5. Physical and neurological examinations are normal in primary RLS.

| Table 2: *Differential diagnosis of RLS* |
|---|
| • Peripheral neuropathy<br>• PLMs without RLS<br>• Spinal claudication<br>• Lumbar root problems<br>• Intermittent claudication<br>• Sleep-related phenomena such as nocturnal leg cramps, dystonia or sleep starts<br>• Sleep disturbances where sleep is disrupted as a result of age-related changes, nocturia, sleep apnoea, nocturnal dyspnoea or other sleep-related neurological or medical conditions<br>• Drug-related sleep disturbances<br>• Attention deficit hyperactivity disorder (ADHD) in children<br>• Akathisia |

**Aetiology**

RLS can be either primary or secondary. Secondary RLS is due to an underlying neurological or medical condition or to other causes such as drug treatment (Table 3). Primary (idiopathic) RLS has no known underlying cause. The aetiology involves both a genetic predisposition and other as yet unidentified factors. A family history of the condition is especially common in patients whose symptoms emerge before the age of 45.

**Pathogenesis**

Dopaminergic pathways, and in particular the nigrostriatal pathway, are believed to be involved in the pathogenesis of RLS. This hypothesis is supported by the results of pharmacological studies, which commonly show that dopamine agonists alleviate the symptoms of RLS and reduce the frequency of PLMs.

Iron deficiency and iron-deficiency anaemia are frequently associated with RLS. Decreased levels of ferritin in the blood and the cerebrospinal fluid have been found in patients with RLS, and there is an association between the reduction in ferritin levels and the severity of RLS symptoms.

**Treatment**

Treatment of RLS is symptomatic and includes both pharmacological and non-pharmacological strategies.

| Table 3: *Aetiological factors in RLS* |
|---|
| *Primary RLS*<br>• Unknown aetiology, perhaps hereditary<br>*Primary RLS*<br>• Pregnancy<br>• Iron deficiency<br>• Renal disease<br>• Diabetes<br>• Peripheral neuropathy<br>• Rheumatoid arthritis<br>• Neurodegenerative conditions such as Parkinson's disease<br>• Certain hereditary neurological diseases<br>• Drug-induced RLS: Dopamine antagonists (especially antipsychotics), selective serotonin reuptake inhibitors (SSRIs), sedating antihistamines, metoclopramide, lithium. Calcium antagonists may aggravate the symptoms of RLS. |

Non-pharmacological measures include:

1. Regular physical activity
2. Avoidance of coffee, nicotine and alcohol
3. Avoidance of, or reduction in the use of, drugs that can worsen RLS (antidepressants, antipsychotics, anti-nausea agents, dopamine antagonists and sedating antihistamines)
4. Iron supplements where necessary
5. Vitamin B supplements

No systematic studies have been carried out on these measures and the evidence on which the recommendations are based is weak. The value of iron supplementation is currently being investigated. Iron supplements are probably best given intravenously.

Pharmacological treatment is based on the use of:

1. Dopamine agonists
2. Antiepileptics
3. Low-potency opioids
4. Benzodiazepines
5. Other agents, including quinine

*Dopamine agonists*

Dopaminergic agents alleviate the symptoms of RLS, improve sleep maintenance and reduce the frequency of PLMs (Table 4). There may also be a reduction in daytime sleepiness but this effect is not consistent as some dopaminergic agents can actually increase daytime sleepiness.

The data presented in Table 4 are based on evidence of variable strength, however. Whereas several randomised, double-blind studies have been carried out demonstrating the effectiveness of levodopa, ropinirole, pramipexole and pergolide in RLS, only one double-blind study has been published on bromocriptine. Table 4 gives the absolute values for number of PLMs per hour of sleep from selected studies on gabapentin and the dopamine agonists ropinirole, pergolide, pramipexole and bromocriptine. PLM frequency is a variable which reflects changes in nocturnal motor phenomena only and does not take into account subjective changes in RLS symptoms. It was not possible to extract efficacy information on a number-needed-to-treat basis since all the studies considered were small and the periods of treatment were relatively short.

Table 4: *Absolute values for PLM frequency from selected studies*

| Drug studied | Number of PLMs per h of sleep (active treatment) | Number of PLMs per h of sleep (placebo treatment) | Study design |
|---|---|---|---|
| Gabapentin (n = 22) | 11.1 ± 3.3 | 20.8 ± 3.3 | Placebo-controlled, crossover |
| Ropinirole | 19.8 (0 - 44.4) (n = 9) | 76.4 (37.3 - 115.5) (n = 13) | Placebo-controlled |
| Pergolide (n = 29) | 5.7 ± 5.7 | 55.0 ± 42.6 | Placebo-controlled, crossover |
| Pramipexole (n = 10) | 1.7 ± 3.1 | 68.0 ± 39.7 | Placebo-controlled, crossover |
| Bromocriptine (n = 4) | 37.8 ± 27.5 | 85.5 ± 65.7 | Placebo-controlled, crossover |

Experience of long-term treatment is limited. In one study, symptoms improved in both the placebo group and the active treatment group and, after two to three months' treatment, the symptom scores in the two groups were similar. As RLS symptoms are variable in nature, it is not impossible that some of the clinical effect was due to this variability. In a recently-published study, by contrast, it was found that dopamine agonists are generally effective but that they are associated with a higher incidence of augmentation in familial and non-neuropathic RLS.

In view of this, it is advisable to a) consider monitoring the spontaneous course of the disorder for two to three months before starting pharmacological treatment, b) ensure that treatment is accompanied by regular assessment and c) conduct a withdrawal trial after an appropriate interval.

No studies comparing the efficacy of different dopamine agonists have been carried out, but there are clear differences between the various substances as regards side-effects. Augmentation occurs in more than 50% of patients on levodopa, for instance, so its use in RLS must be treated with reservation and ropinirole, pergolide, pramipexole or bromocriptine should be preferred for first-line therapy. Augmentation can also occur with partial dopamine agonists, however. The reported incidence with pramipexole is about 8% but it can be higher, especially in patients who have previously experienced the phenomenon during levodopa treatment. Augmentation can occur with other dopamine agonists but, as the studies on this subject have been of relatively short duration, the evidence is limited.

The other side-effects of dopamine agonists are typical dopaminergic effects such as initial nausea, vomiting, dizziness, headache and tiredness. These are classified as "common", indicating a placebo rate-subtracted incidence of > 1%. No studies have been carried out which directly compare the incidence of side-effects associated with different dopamine agonists. At higher doses, confusion, vivid dreams and hallucinations may occur, though these are rare during RLS treatment as the doses used are usually low. Valvular heart disease has been observed in up to a third of Parkinson's disease patients taking pergolide, and this should be borne in mind when using the drug in a benign condition such as RLS.

*Antiepileptics*

Gabapentin has been shown in double-blind controlled studies to be effective in alleviating RLS symptoms and reducing nocturnal PLMs. It is particularly indicated in cases where pain is a predominant feature. Its side-effects include somnolence, ataxia, dizziness, tiredness, headache, nausea and vomiting.

Valproic acid and carbamazepine have also been suggested for the treatment of RLS, primarily on the basis of experience from uncontrolled studies. In one study comparing slow-release valproic acid 600 mg with levodopa, decreases in the duration and intensity of RLS symptoms were more pronounced with valproic acid than with levodopa, and valproic acid was also associated with fewer arousals than levodopa. In an earlier double-blind study, carbamazepine was found to have an effect that was comparable to placebo. There have been no studies comparing individual antiepileptics with one another or with dopaminergic agents.

*Opioids*

The evidence base for the use of opioids in RLS is limited. There is one controlled study in which a combination of dextropropoxyphene and levodopa was found to reduce RLS symptom severity and PLMs.

*Benzodiazepines*

Benzodiazepines (triazolam, temazepam, clonazepam) and benzodiazepine analogues (zolpidem) have no effect on RLS or PLMs although they do have a transient symptomatic effect in sleep disturbances. The studi-

es which have been carried out are based primarily on case series. Caution should be exercised in using benzodiazepines in view of the risk of dependence and side-effects. There are no studies indicating that these agents have any lasting effect in RLS.

*Quinine and other drugs*

Quinine is indicated for the relief of nocturnal leg cramps, whilst barbiturates have also been used. However, there is no documented evidence to indicate that either quinine or barbiturates have any effect in RLS.

**Augmentation**

Augmentation is a troublesome phenomenon which affects up to 70% of patients on levodopa and whose occurrence is related to the dosage used and the length of treatment. It refers to the worsening of RLS and the accompanying motor symptoms during treatment. The key features of augmentation are as follows:

1. Onset of symptoms earlier in the day
2. Shorter latency period to symptoms
3. Increased symptom severity
4. Shorter duration of treatment effect
5. Spread of symptoms to other parts of the body, including the arms

The mechanisms underlying augmentation are unknown but the phenomenon is thought to be due to a combination of receptor profile, post-synaptic receptor defects (or altered receptor regulation) and downregulation of the dopaminergic system.

Augmentation can also occur with the selective dopamine agonists. It has been reported less frequently with these agents than with levodopa but this may reflect the pattern of use of selective dopamine agonists in clinical studies, which have involved shorter durations of treatment than those normally associated with levodopa in clinical practice. The true incidence of augmentation with selective dopamine agonists is therefore unknown but it is likely to be lower than for levodopa because selective dopamine agonists have selective receptor profiles and are used at lower doses and for shorter periods than levodopa.

**Treatment scenarios**

There are no definitive criteria regarding which patients should be given pharmacological treatment, but the therapeutic principles for some typical scenarios are given below.

*Intermittent RLS*

A non-pharmacological approach should be tried first. If this proves ineffective, pharmacological treatment, preferably with dopamine agonists, can be considered. There are no evidence-based studies to provide any guide on whether treatment should be given on an intermittent basis or a continuous, long-term basis. Treatment must therefore be individualised.

*Daily RLS*

As with intermittent RLS, a non-pharmacological approach should be the first option. If there is no response, dopamine agonists or antiepileptics should be tried, with opioid agonists as a possible alternative choice. Treatment should be on a daily basis.

| Table 5: *Equipotent doses* | | |
|---|---|---|
| Drug | Daily dose | Price per daily dose (Danish kroner) |
| Levodopa + decarboxylase inhibitor | 200 - 800 mg | DKK 2.50 - 10.00 |
| Partial dopamine agonists | | |
| Ropinirole | 0.25 - 2 mg | DKK 2.09 - 11.40 |
| Pergolide | 0.25 - 0.75 mg | DKK 2.68 - 8.04 |
| Pramipexole (base) | 0.088 - 0.35 mg | DKK 4.42 - 13.86 |
| Bromocriptine | 7.5 mg | DKK 9.15 |
| Prices current as of May 2005 | | |

*Refractory RLS*

Refractory RLS is defined as RLS in which a) there is an inadequate initial response to treatment, b) the response to treatment has become inadequate with time or c) intolerable side-effects are experienced.

It is important in such cases to review the diagnosis of RLS. If the correct diagnosis has been made, four different approaches can be tried (this assumes that treatment is started with a dopamine agonist):

- Change to gabapentin
- Change to a different dopamine agonist
- Add a second agent such as gabapentin
- Change to an opioid

**Therapeutic approaches to RLS in pregnancy and childhood**

RLS in pregnant women is often associated with low ferritin and folate levels. Iron, folate and cyanocobalamin (vitamin $B_{12}$) supplements are therefore recommended but, otherwise, pregnant women are advised to abstain from pharmacological treatment for their RLS.

There is only weak evidence, if any, that pharmacological treatment has any therapeutic effect in children.

**Conclusion**

Any decision to treat RLS pharmacologically must be carefully weighed against the fact that a) the symptoms improve spontaneously after two to three months in many patients and b) side-effects commonly occur with drug treatment. Partial dopamine agonists have the best documented effect in RLS and are associated with the fewest side-effects. Levodopa is effective but there is a high risk of augmentation occurring. Antiepileptics can improve RLS symptoms but there is little evidence that low-potency opioids have any effect. There is no evidence that quinine, barbiturates or benzodiazepines have any sustained effect in RLS.

*Poul Jennum*
*Center for søvnforstyrrelser*
*Klinisk neurofysiologisk afdeling*
*Amtssygehuset i Glostrup*

*Centre for Sleep Disturbances*
*Department of Clinical Neurology*
*Glostrup County Hospital, Denmark*

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**Translator's note**

The fully referenced version of the original is available under http://www.irf.dk/dk/publikationer/rationel_farmakoterapi/maanedsblad/2005/restless_legs_syndrome.htm and a list of references is given under http://www.irf.dk/dk/publikationer/rationel_farmakoterapi/maanedsblad/2005/referencer_til_restless_legs_syndrome.htm.

In the first paragraph of the original, it is stated that RLS was first described in 1946. The date was in fact 1945.

David Parker
Translation Dept.
Boehringer Ingelheim GB