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A review of current treatment strategies for restless legs syndrome (Willis–Ekbom disease)

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ABSTRACT

Restless legs syndrome (RLS), recently renamed Willis–Ekbom disease (WED), is a common movement disorder. It is characterised by the need to move mainly the legs due to uncomfortable, sometimes painful sensations in the legs, which have a diurnal variation and a release with movement. Management is complex. First, centres should establish the severity of RLS using a simple 10-item RLS severity rating scale (IRLS). They should also exclude secondary causes, in particular ensuring normal iron levels. Mild cases can be managed by lifestyle changes, but patients with a IRLS score above 15 usually require pharmacological treatment. Dopaminergic therapies remain the mainstay of medical therapies, with recent evidence suggesting opioids may be particularly effective. This article focuses on the different treatment strategies in RLS, their associated complications and ways to manage them.

KEYWORDS: Restless legs syndrome, RLS, therapy, medical treatment, side effects

Introduction

Restless legs syndrome (RLS), also known as Willis–Ekbom disease (WED), is a common neurological disorder characterised by an uncontrollable urge to move certain parts of the body, particularly the lower limbs. This is usually accompanied or caused by unpleasant sensations in the legs.[1] Symptoms of RLS appear or worsen during periods of inactivity or rest and improve with activity. The estimated prevalence of RLS ranges between 5% and 15%, but figures vary widely depending upon the population surveyed and the severity of symptoms required for inclusion.[2,3] RLS can be categorised as primary (idiopathic) or secondary. Secondary RLS occurs as a result of certain conditions, such as iron deficiency, pregnancy, end-stage renal disease, diabetes, rheumatoid arthritis and, occasionally, peripheral neuropathies.

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Diagnosis

The diagnosis of RLS is based primarily on the patient's clinical history and on a neurological examination to exclude peripheral neuropathy. The International RLS Study Group (IRLSSG) essential diagnostic criteria for RLS were revised in 2012 and can be used in clinical practice. They include:[4]

1. an urge to move the legs usually accompanied or caused by uncomfortable sensations in the legs
2. worsening of symptoms during times of rest or inactivity
3. partial or total relief of symptoms by movement
4. the symptoms only occur or are worse in the evening or night
5. the occurrence of the above features are not solely accounted for as symptoms primary to another medical or behavioural condition (such as myalgia, venous stasis, leg oedema, arthritis, leg cramps, positional discomfort or habitual foot tapping).

More recently, a single standard question for rapid screening for RLS has been validated.[5] The question, developed by the IRLSSG on the basis of standard diagnostic criteria, is: 'When you try to relax in the evening or sleep at night, do you ever have unpleasant, restless feelings in your legs that can be relieved by walking or movement?'. As this single question had 100% sensitivity and 96.8% specificity for the diagnosis of RLS, it can be used to screen large patient groups effectively. Nevertheless, the final diagnosis should always be confirmed by matching the patient's history and symptoms with the IRLSSG diagnostic criteria, accompanied by the exclusion of secondary conditions.

Treatment

The IRLSSG rating scale (IRLS) for determining the severity of RLS consists of 10 questions, each being scored into one of five severity categories (from 0 to 4), with the maximum total score being 40.[6] The severity of RLS symptoms is scored as mild (1–10), moderate (11–20), severe (21–30) and very severe (31–40). The patient's score can be used to decide whether pharmacological treatment would be beneficial.

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Non-pharmacological treatment

The majority of RLS cases are mild and can be managed by lifestyle changes or non-pharmacological treatment. Lifestyle factors known to precipitate RLS symptoms are high caffeine intake[7] (avoid any intake of caffeine before bedtime), excessive alcohol consumption[8] (avoid any intake of alcohol before bedtime), severe stress, shift work and intense physical activity near bedtime. Furthermore, sleep hygiene is important and may help patients with RLS. It is important, therefore, for patients with RLS to consider the following as part of their bedtime routine:

- a quiet, comfortable and cool sleeping environment
- appropriate nightwear (such as silk pyjama or dressing gown)
- regular sleep pattern (go to bed and wake up at regular hours, avoid daytime naps)
- associate bed with sleep (for instance, avoid watching TV from bed).

As RLS usually affects the first part of the sleep cycle at night, patients may be advised to alter their sleep pattern by going to bed late and waking up late.

During an attack, patients may benefit from:

- a hot or cold massage, rubbing or massaging the affected limbs[9]
- bathing in hot or cold water
- physical activities such as walking, stretching and exercise
- relaxation exercises (eg biofeedback or yoga)
- distracting the mind by mental exercises (for example, reading an interesting book during the onset of symptoms).

Many other unproven therapies have been described on the basis of individual experience, such as the use of capsaicin cream or magnesium and halcyon bracelets, but these cannot be recommended at this time.

Treating secondary causes

It is important to distinguish between primary and secondary RLS. Primary RLS tends to run a chronic course and symptoms worsen with time, especially in patients with early onset. By contrast, in secondary RLS symptoms may remit once the secondary cause (eg iron deficiency or end-stage renal disease) is treated. Iron deficiency is an important factor even in primary RLS; therefore, iron parameters (specifically serum ferritin levels) should be measured. Those with low or borderline levels require oral iron treatment for 1 to 2 months with a repeat measurement of serum ferritin levels to avoid iron overload.[10] Box 1 summarises blood tests necessary to exclude secondary causes of RLS.

Patients with severe RLS and insomnia may require sleep studies such as polysomnography[11] or immobilisation tests,[12,13] but in practice these are rarely performed in the UK.

Avoiding medication that exacerbate restless legs syndrome

Several drugs are known to worsen RLS symptoms and, if possible, these should be avoided. Medications that are known to induce or exacerbate RLS symptoms include: antihistamines, dopamine antagonists, anti-nausea medications, anxiolytics, antidepressants (such as mirtazapine, escitalopram, fluoxetine and mianserin), neuroleptics (such as olanzapine), beta-blockers, anticonvulsants, L-thyroxine and lithium.[14] In clinical practice, it is useful to enquire about medication intake and taper down the doses of any antihistamines or dopamine antagonists that are being used.

Box 1. Recommended blood tests to rule out secondary restless legs syndrome.

Iron studies (specifically serum ferritin level is essential)
Full blood count (to exclude anaemia)
Serum vitamin B_{12} and folic acid
Serum glucose and HbA1C
Urea and electrolytes
Serum creatinine
Albumin levels (optional)
Thyroid function tests (optional)

Pharmacological treatment

An estimated 10–15% of RLS patients have symptoms severe enough to require medical management of RLS.[15] Treatment is only required when the symptoms are clinically significant. All possible treatment options only address the symptoms and are not preventive. Furthermore, as RLS is a chronic disorder, it is likely that once the patient starts medication, they will continue to use it for the rest of their lives. Therefore, RLS should be treated in order to alleviate sensory and motor symptoms, to improve sleep and quality of life and to prevent cardiovascular complications. The dosage should be kept as low as possible.

Currently, dopaminergic agents are used as first-line treatment for moderate to severe RLS. Randomised placebo controlled studies have established the efficacy of dopamine agonists (DA) in RLS for both improvement of symptoms and reduction in periodic leg movements during sleep and awakening.[16] The European Federation of Neurological Societies has recommended non-ergot DAs, such as ropinirole and pramipexole as tablets or rotigotine as patches. In the UK, DAs are the only licensed treatment for RLS. The different DAs and their recommended doses are summarised in Table 1. The doses are considerably smaller than those used for patients with Parkinson's disease. DAs should be administered as a single evening dose and are effective for the short- and long-term treatment of idiopathic RLS. If the patient shows intolerance to one agent, then another DA should be tried. Oral therapies such as pramipexole and ropinirole are both effective, but their use depends on tolerability and efficacy. Rotigotine patches have the advantage of being efficacious during both the day and night, and many clinicians prescribe the patch once oral therapies have failed. DAs alleviate symptoms in up to 70% of patients.

Levodopa is used occasionally as the first-line treatment for intermittent RLS symptoms (less than three times a week) in Germany, Austria and Switzerland. It is mainly used as a rescue medication and so is taken when symptoms occur or when they are anticipated. Levodopa therapy is associated with a high rate of side effects, such as augmentation (an overall increase in RLS symptom severity) (60–80%),[17] and is not recommended as first-line treatment in the UK. Levodopa can also be used as a clinical 'challenge test' for the diagnosis of RLS.[18]

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Table 1. Pharmacological treatment of restless legs syndrome with recommended dose, time to full therapeutic effect, half-life and possible side effects. The side effects are described on the basis of published profiles and some relevant case reports. Use of second line drugs can be undertaken after informed discussion and choice. Adapted with permission from Garcia-Borreguero *et al* (2013)[13] and Garcia-Borreguero *et al* (2011).[19]

Medication	Minimal starting dose/maximal recommended dose	Time to full effect of the therapeutic dose	Half-life	Side effects
Levodopa	50 mg/200 mg	At first dose	1.5–2 hours	High rates of augmentation and loss of efficacy with rebound phenomena.
Ropinirole	0.25 mg/4 mg	4–10 days	6 hours	Augmentation, impulse control disorder, nausea, low blood pressure, dizziness, headache, nasal congestion, sleepiness in susceptible patients.
Pramipexole	0.125 mg/0.54 mg	At first dose	8–12 hours	Augmentation, impulse control disorder, nausea, low blood pressure, dizziness, headache, nasal congestion, sleepiness in susceptible patients.
Rotigotine	1 mg/3 mg	1 week	5–7 hours	Skin irritation, low risk of augmentation, nausea, low blood pressure, dizziness, headache, nasal congestion, sleepiness in susceptible patients. Risk of ICD may be lower.
Pregabalin	25 mg/300 mg	3–6 days	10 hours	Sleepiness, dizziness, headache, fluid retention.
Clonazepam	0.50 mg/2.0 mg	First dose: effect mainly on sleep	30–40 hours	High risk of sleepiness, dizziness, morning drug hangover.
Gabapentin	300 mg/2,700 mg	3–6 days	5–7 hours	Sleepiness, dizziness, fluid retention.
Tramadol	25 mg/100 mg	N/A	5–8 hours	Dizziness, sleepiness, constipation, dry mouth
Oxycodone	2.5 mg/25 mg	N/A	2–4 hours	Dizziness, fatigue, constipation, nausea

Second-line off-label treatment options for daily RLS symptoms are α2δ ligands (such as gabapentin or pregabalin) and opioids (such as oxycodone, propoxyphene, tramadol, tilidine or codeine). These are particularly useful for patients with painful RLS symptoms, coexisting neuropathy or pain elsewhere.[19] A recent study found that prolonged-release oxycodone-naloxone caused an 8-point reduction in the mean IRLS sum score compared to placebo. This represents one of the most effective treatment responses ever seen in RLS, and so the use of this combined medication in severe RLS is likely to be adopted.[20]

Table 1 summarises the different medications used for the treatment of RLS, their recommended minimum start dose, maximum dose and main important side effects.

Follow up

RLS patients should be followed up regularly to monitor treatment efficacy, as the disease tends to worsen over time. The European Restless Legs Study Group (EURLSSG) recommends that even in the absence of complications, patients need to see their physician every 6–12 months. A symptom diary completed over 7–14 days prior to the consultation could provide the physician with details about the severity of symptoms and the effect of treatment.

If a patient complains of worsening of RLS symptoms while being on treatment, the physician should check whether the patient is compliant, if they are taking any additional medication that may exacerbate symptoms or whether they have become more sedentary as this can cause symptoms to appear earlier during the day. It is important to check iron parameters during follow-up consultations as iron deficiency is implicated in the onset as well as the severity of RLS.[10]

Treatment complications

Early morning rebound

Early morning rebound is the reappearance of RLS symptoms in the early morning as the effects of medication are wearing off. Symptoms tend to be worse than expected if no medication was taken but they disappear several hours later. Early morning rebound occurs more frequently with short half-life medication such as levodopa.[21] It is important to exclude concurrent conditions, such as depression or sleep apnoea, before modifying the current treatment. To manage this complication, the dose of the currently prescribed drug can be increased, the time of administration can be changed or another dopaminergic agent with a longer half-life can be prescribed.[22]

Tolerance and loss of efficacy

Tolerance consists of a decrease in the response to a drug over time, requiring an increase in dose to achieve the original amelioration of symptoms. This is to be differentiated from the natural worsening of RLS symptoms, which would also require higher drug doses. Unlike rebound or augmentation, symptoms are not worse than before treatment initiation. It is not completely known whether tolerance inevitably precedes and leads to augmentation.

Augmentation

Augmentation is a treatment-related side effect that is characterised by an overall increase in RLS symptom severity. It is the worst long-term complication of dopaminergic treatment

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Table 2. Max Planck Institute (MPI) diagnostic criteria for augmentation. Adapted with permission from Garcia-Borreguero *et al* (2007).[23]

Augmentation requires criteria A + B or A + C or A + B + C to be met

A) Basic criteria

- Increase in symptom severity experienced on 5 out of 7 days during the previous week.
- Increase in symptom severity is not accounted by any other factors (such as change in medication, lifestyle or natural progression of RLS).
- Positive response to prior treatment.

In addition, either B or C or both have to be met.

B) Persisting paradoxical response to treatment: RLS symptom severity increases some time after a dose increase and improves some time after a dose decrease.

C) Earlier onset of symptoms

- by at least 4 hours
- between 2 and 4 hours plus one of the following points i–iv compared to symptom status before treatment:
  - i shorter latency to symptoms when at rest
  - ii extension of symptoms to other body parts
  - iii greater intensity of symptoms (or increase in periodic limb movements could be measured by polysomnography or immobilisation test)
  - iv shorter duration of relief from treatment.

of RLS and leads to worse symptoms than were present before treatment had been started. The Max Planck Institute (MPI) diagnostic criteria for augmentation are listed in Table 2.

Augmentation occurs more frequently in patients who take daily doses higher than the following: 200 mg levodopa, 0.5 mg pramipexole, 2 mg ropinirole or 3 mg rotigotine. The rate of augmentation is greatest with levodopa and among the DAs, it is greatest with pramipexole and lowest with rotigotine with an incidence of approximately 2–3% per year.[24] Although the vast majority of augmentation cases are due to dopaminergic agents, a few cases have been reported with the use of tramadol.[14,24] No other medication has been found to cause augmentation. Predictors of augmentation have been identified as low plasma ferritin levels, previous episodes of augmentation, longer treatment duration and possibly a preceding tolerance to medication.[24,25]

Several approaches can be taken to prevent augmentation. The most effective preventative measure is to prescribe the lowest effective dose of dopaminergic medication. Ideally, a low dose of a long-acting dopaminergic agent (such as rotigotine) should be used; conversely, agents with high rates of augmentation (such as levodopa) should be avoided. Another measure is to divide the dopaminergic dose, administering the first dose earlier in the afternoon before symptom onset and the second dose after symptoms started. Divided dose of RLS medication has not, however, been approved yet. As low iron body stores may be responsible for the augmentation, iron parameters should be measured and an oral iron intake must be considered if serum ferritin is below 50 µg/l.

When the measures described above are unsuccessful and symptoms are so severe that they interfere with the patient's daily activities, a different DA may be prescribed. Augmentation is, however, likely to reoccur even when another dopaminergic agent is used. If changing dopaminergic agents does not improve symptoms, the dopaminergic dose should be further reduced while simultaneously initiating treatment with a non-dopaminergic agent (such as an α2δ ligand or an opiate), until the dopaminergic agent is discontinued altogether.[26]

Impulse control disorders

Impulse control disorders (ICD) are a well-known side effect of dopaminergic agents in patients with Parkinson's disease.[27] They have also recently been described in RLS, despite the lower doses of dopaminergic medication used by these patients. ICDs during RLS treatment are estimated to affect between 3% and 17% of patients and include obsessive-compulsive behaviour, hypersexuality, binge eating, pathologic gambling, punding and compulsive shopping.[28–30] The incidence of ICDs is dose-dependent and ceases when dopaminergic treatment is stopped. If ICDs occur during treatment with a dopaminergic agent, the medication should be either discontinued or progressively decreased until the side effect resolves, or until another non-dopaminergic drug can be substituted or added.

Weight gain

Sleep loss has been shown to be related to weight gain and obesity.[31] Between 20% and 30% of patients with RLS eat during the night. It is important to differentiate weight gain, fluid retention (oedema) and binge eating. Weight gain is also a common side effect of α2δ ligands and appears to be dose-dependent. Water retention can also occur with dopaminergic agents.

Mood changes

Depression and anxiety are common comorbid conditions associated with RLS.[32] Patients with RLS, especially those who are taking α2δ ligands, are at greater risk of developing depression than healthy individuals. Furthermore, augmentation is a common trigger of anxiety. If depression

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occurs, the physician should avoid prescribing an antidepressant that is known to worsen RLS symptoms, such as a selective norepinephrine reuptake inhibitor (SNRI) or a selective serotonin reuptake inhibitor (SSRI). Suitable antidepressants include duloxetine, buproprion, lamictal, trazadone and desipramine. Cognitive behaviour therapy can also be of benefit.

Conclusions

RLS is a common condition and can have a great impact on quality of life, mainly because of disturbed night time sleep and daytime sleepiness. Treatment depends on the severity and frequency of symptoms, which can be determined by using the IRLSSG rating scale. Mild RLS may be managed with reassurance and lifestyle changes. Moderate to severe cases require pharmacological treatment. Secondary causes and exacerbating factors should be identified and treated. Patients with poorly managed RLS can suffer from severe morbidity and a poor quality of life associated with marked anxiety and, sometimes, depression. ■

Conflict of interest

Lisa Klingelhoefer, Ilaria Cova and Sheena Gupta declare that there are no competing interests concerning this article. Kallol Ray Chaudhuri is a founding member of RLS UK and declares that there are no competing interests concerning this article.

References

1 Allen RP, Picchietti D, Hening WA *et al.* Restless legs syndrome: diagnostic criteria, special considerations, and epidemiology. A report from the restless legs syndrome diagnosis and epidemiology workshop at the National Institutes of Health. *Sleep Med* 2003;4:101–19.

2 Nichols DA, Allen RP, Grauke JH *et al.* Restless legs syndrome symptoms in primary care: a prevalence study. *Arch Intern Med* 2003;163:2323–9.

3 Allen RP, Bharmal M, Calloway M. Prevalence and disease burden of primary restless legs syndrome: results of a general population survey in the United States. *Mov Disord* 2011;26:114–20.

4 International Restless Legs Syndrome Study Group. 2012 Revised IRLSSG Diagnostic Criteria for RLS. http://irlssg.org/diagnostic-criteria/ [Accessed 31 July 2014].

5 Ferri R, Lanuzza B, Cosentino FI *et al.* A single question for the rapid screening of restless legs syndrome in the neurological clinical practice. *Eur J Neurol* 2007;14:1016–21.

6 Walters AS, LeBrocq C, Dhar A *et al.* Validation of the International Restless Legs Syndrome Study Group rating scale for restless legs syndrome. *Sleep Med* 2003;4:121–32.

7 Lutz EG. Restless legs, anxiety and caffeinism. *J Clin Psychiatry* 1978;39:693–8.

8 Aldrich MS, Shipley JE. Alcohol use and periodic limb movements of sleep. *Alcohol Clin Exp Res* 1993;17:192–6.

9 Russell M. Massage therapy and restless legs syndrome. *J Bodywork Mov Ther* 2007;11:146–50.

10 Sun ER, Chen CA, Ho G, *et al.* Iron and the restless legs syndrome. *Sleep* 1998;21:371–7.

11 Michaud M, Paquet J, Lavigne G *et al.* Sleep laboratory diagnosis of restless legs syndrome. *Eur Neurol* 2002;48:108–13.

12 Montplaisir J, Boucher S, Nicolas A *et al.* Immobilization tests and periodic leg movements in sleep for the diagnosis of restless leg syndrome. *Mov Disord* 1998;13:324–9.

13 Garcia-Borreguero D, Kohnen R, Boothby L *et al.* Validation of the Multiple Suggested Immobilization Test: a test for the assessment of severity of restless legs syndrome (Willis-Ekbom Disease). *Sleep* 2013;36:1101–9.

14 Hoque R, Chesson AL Jr. Pharmacologically induced/exacerbated restless legs syndrome, periodic limb movements of sleep, and REM behavior disorder/REM sleep without atonia: literature review, qualitative scoring, and comparative analysis. *J Clin Sleep Med* 2010;6:79–83.

15 Hening W, Walters AS, Allen RP *et al.* Impact, diagnosis and treatment of restless legs syndrome (RLS) in a primary care population: the REST (RLS epidemiology, symptoms, and treatment) primary care study. *Sleep Med* 2004;5:237–46.

16 Garcia-Borreguero D, Kohnen R, Silber MH *et al.* The long-term treatment of restless legs syndrome/Willis–Ekbom disease: evidence-based guidelines and clinical consensus best practice guidance: a report from the International Restless Legs Syndrome Study Group. *Sleep Med* 2013;14:675–84.

17 Högl B, Garcia-Borreguero D, Kohnen R *et al.* Progressive development of augmentation during long-term treatment with levodopa in restless legs syndrome: results of a prospective multi-center study. *J Neurol* 2010;257:230–7.

18 Stiasny-Kolster K, Kohnen R, Moller JC *et al.* Validation of the 'L-DOPA test' for diagnosis of restless legs syndrome. *Mov Disord* 2006;21:1333–9.

19 Garcia-Borreguero D, Stillman P, Benes H *et al.* Algorithms for the diagnosis and treatment of restless legs syndrome in primary care. *BMC Neurol* 2011;11:28.

20 Trenkwalder C, Benes H, Grote L *et al.* Prolonged release oxycodone-naloxone for treatment of severe restless legs syndrome after failure of previous treatment: a double-blind, randomised, placebo-controlled trial with an open-label extension. *Lancet Neurol* 2013;12:1141–50.

21 Guilleminault C, Cetel M, Philip P. Dopaminergic treatment of restless legs and rebound phenomenon. *Neurology* 1993;43:445.

22 Garcia-Borreguero D, Odin P, Schwarz C. Restless legs syndrome: an overview of the current understanding and management. *Acta Neurol Scand* 2004;109:303–17.

23 Garcia-Borreguero D, Allen RP, Kohnen R *et al.* Diagnostic standards for dopaminergic augmentation of restless legs syndrome: report from a World Association of Sleep Medicine-International Restless Legs Syndrome Study Group consensus conference at the Max Planck Institute. *Sleep Med* 2007;8:520–30.

24 Garcia-Borreguero D, Williams AM. Dopaminergic augmentation of restless legs syndrome. *Sleep Med Rev* 2010;14:339–46.

25 Trenkwalder C, Hogl B, Benes H, Kohnen R. Augmentation in restless legs syndrome is associated with low ferritin. *Sleep Med* 2008;9:572–4.

26 Garcia-Borreguero D, Allen RP, Benes H *et al.* Augmentation as a treatment complication of restless legs syndrome: concept and management. *Mov Disord* 2007;22(Suppl 18):S476–84.

27 Antonini A, Cilia R. Behavioural adverse effects of dopaminergic treatments in Parkinson's disease: incidence, neurobiological basis, management and prevention. *Drug Saf* 2009;32:475–88.

28 Cornelius JR, Tippmann-Peikert M, Slocumb NL *et al.* Impulse control disorders with the use of dopaminergic agents in restless legs syndrome: a case-control study. *Sleep* 2010;33:81–7.

29 Schreglmann SR, Gantenbein AR, Eisele G, Baumann CR. Transdermal rotigotine causes impulse control disorders in patients with restless legs syndrome. *Parkinsonism Relat Disord* 2012;18:207–9.

30 Lipford MC, Silber MH. Long-term use of pramipexole in the management of restless legs syndrome. *Sleep Med* 2012;13:1280–5.

31 Chaput JP, Despres JP, Bouchard C, Tremblay A. The association between sleep duration and weight gain in adults: a 6-year prospective study from the Quebec Family Study. *Sleep* 2008;31:517–23.

32 Winkelmann J, Prager M, Lieb R *et al.* 'Anxietas tibiarum'. Depression and anxiety disorders in patients with restless legs syndrome. *J Neurol* 2005;252:67–71.

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