East Lancashire Health Economy
Medicines Management Board

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The Management of Restless Legs Syndrome in Adults in Primary Care

Victoria Birchall /Susan McKernan
Midlands and Lancashire CSU

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VERSION CONTROL

Version Number	Date	Amendments made
1.0	December 2015	Version 1. Approved

Contents

1. INTRODUCTION

Restless Legs Syndrome (RLS), also known as Willis-Ekborn disease, is a common sensory motor neurological disorder which causes a characteristic, overwhelming and irresistible urge to move the limbs, usually the legs but can also additionally affect the arms – in addition to uncomfortable, abnormal sensations which appear without any sensory stimulation.[1] RLS is often associated with sleep disturbance as symptoms are typically worse in the evenings.

RLS can be classified as either primary (idiopathic) RLS or secondary RLS, whereby the symptoms are secondary to an underlying condition (most commonly pregnancy, iron deficiency, or stage 5 chronic kidney disease), or the use of certain drugs (for example, some antidepressants, some antipsychotics, and lithium).[3] Idiopathic restless legs syndrome (RLS) affects between 1.9–4.6% of adults in northern Europe. It is twice as prevalent in women as in men.[3]

The Ekborn Syndrome Association offers support and more information for people affected by restless legs syndrome, and can be accessed via http://www.rls-uk.org/

2. PURPOSE AND SUMMARY

The purpose of these guidelines is to provide a quick reference guide for use in primary care summarising information on the diagnosis and management of RLS in primary care.

3. SCOPE

This guidance covers the management of RLS in primary care and gives information about when to refer to secondary care.

4. GUIDANCE

4.1 Diagnosis[7]

The International Restless Legs Syndrome Study Group has identified five criteria for diagnosing RLS.

Diagnosis can be made if **all** of the following are met:

- 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
- 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
- the urge to move the legs and any accompanying unpleasant sensations are partially or totally **relieved by movement**, such as walking or stretching, or at least as long as the activity continues
- 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
- the occurrence of the above features are **not solely accounted for as symptoms primary to another medical or a behavioural condition** (e.g. myalgia, venous stasis, leg oedema, arthritis, leg cramps, positional discomfort, habitual foot tapping).

*NB. Sometimes the arms or other parts of the body are involved in addition to the legs.[7]

Differential Diagnoses[1]

- Nocturnal leg cramps
- Akathisia, often drug induced
- Neuropathy, including alcohol related neuropathies
- Peripheral Vascular disease, including varicose veins and DVT
- Painful legs and moving toes
- Radiculopathy
- Attention deficit hyperactivity disorder in children
- Erythromelalgia, fibromyalgia, neuropathic pain in MS
- Anxiety/ generalised anxiety disorder
- Osteoarthritis
- Intermittent claudication
- Rapid eye movement (REM) sleep behaviour disorder

4.2 Aetiology[2]

In the majority of cases, there is no obvious cause of RLS. Recent literature links RLS to dopaminergic dysfunction, reduced iron in the central nervous system, genetic linkages, or alteration in neurotransmitters such as hypocretins, endorphins levels and immune dysfunction, and inflammatory mechanisms.

Secondary RLS can occur as a complication of a clinical condition, or as a result of a health-related factor. There are three major reversible secondary causes linked to depleted iron stores:[3]

- Pregnancy (usually occurs in the third trimester and resolves a few weeks post-partum, drug treatment is not recommended during pregnancy or breast feeding)
- Iron deficiency
- End-stage renal failure

Other secondary causes include[3]:

- Vitamin B12/ folate deficiency
- Peripheral neuropathy
- Parkinson's disease
- Rheumatoid arthritis
- Spinocerebellar ataxia
- Medication e.g. antiepileptics, antidepressants
- Certain substances e.g. caffeine, alcohol, tobacco

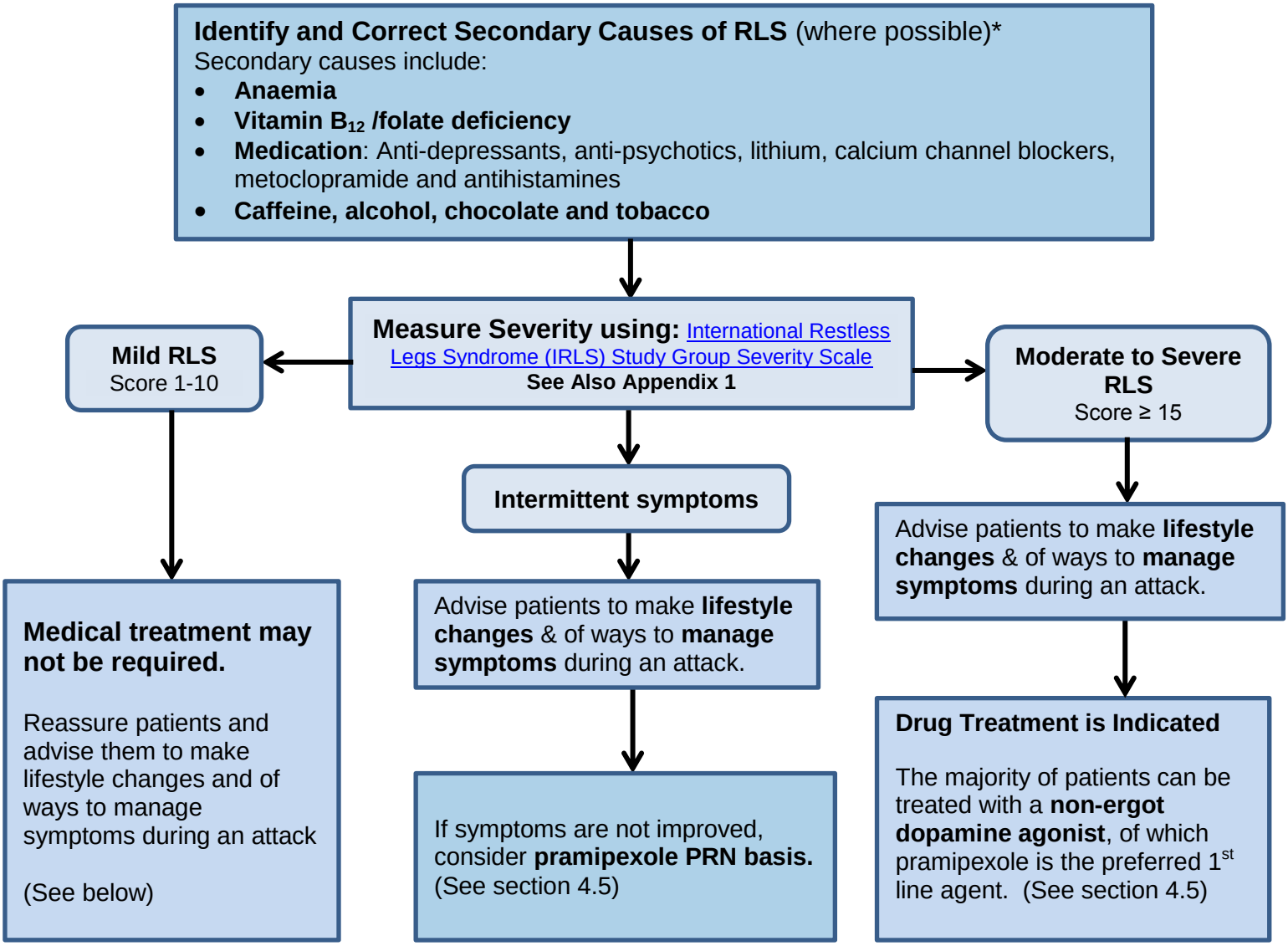
4.3 Investigations[3]

If RLS is suspected a physical examination and blood tests are required.

Blood tests include:

- Full blood count
- Serum ferritin
- Serum vitamin B12/ folate
- Serum glucose
- Urea and electrolytes
- Thyroid function tests

Figure 1: Restless Legs Syndrome -Treatment Algorithm



Lifestyle Advice

All patients with RLS should be advised to make lifestyle changes such as:

- Reducing or avoiding alcohol and chocolate
- Smoking cessation
- Moderate regular exercise
- Good sleep hygiene
- Weight loss
- Stress reduction

Appropriate management of co-morbidities such as anxiety and insomnia may reduce the RLS symptoms

Symptom Management

During an attack, there may be benefit in the following:

- Walking and stretching the affected limbs
- Applying heat e.g. via heat pads or bathing in a hot bath
- Relaxation exercise e.g. yoga
- Distracting the mind
- Massaging the affected limbs

Referral

Most cases of RLS can be managed by primary care.
Referral may be considered for the following patient presentations:

- Intolerable side effects with treatment
- Response to treatment becomes inadequate over time despite dose increased dose or maximal treatment, cesses to be effective
- Treatment exacerbates symptoms, or causes them to appear earlier in the day i.e. augmentation

4.5 Prescribing Information

4.5.1 Non-ergot dopamine agonists (Pramipexole, ropinirole, rotigotine)
These are the preferred agents for the treatment of RLS for the majority of patients because they have the greatest evidence base, are licensed for use in RLS and are not prone to abuse**.**

Table 1. Prescribing Information: Non-Ergot Dopamine agonists

<table>
<tr><th>Medication[9]
(RLS licensing status)</th><th>Dosing Information[9] See SPC for more details</th><th>Additional Information[9]</th></tr>
<tr><td>Pramipexole tablets
(symptomatic treatment of moderate to severe idiopathic RLS in adults)

The product licence relates to a baseline score ≥ 15 on the IRLS Study Group Severity Scale.</td><td>Initial dose: 0.088 mg of base (0.125 mg of salt) taken once daily 2-3 hours before bedtime.

Titration: Dose may be increased every 4-7 days to a maximum of 0.54 mg of base (0.75 mg of salt) per day, according to symptoms, only if required, as below.

<table>
<tr><th>Titration Step</th><th>Dose (mg of base) Once Daily in the evening</th><th>Dose (mg of salt)

Once Daily in the Evening</th></tr>
<tr><td>1</td><td>0.088</td><td>0.125</td></tr>
<tr><td>2*</td><td>0.18</td><td>0.25</td></tr>
<tr><td>3*</td><td>0.35</td><td>0.50</td></tr>
<tr><td>4*</td><td>0.54</td><td>0.75</td></tr>
<tr><td colspan="3">* if needed</td></tr>
</table>

If there is more than a few days interruption of treatment, re-initiate by dose titration as above</td><td>This is the preferred 1st line treatment because:
• There is evidence of effectiveness in a wider range of patients (IRLS score ≥ 15)
• Many patients respond to 0.125mg doses, allowing faster titration compared to ropinirole
• It can be used on a ‘when required’ basis for patients with intermittent symptoms

The response should be evaluated after 3 months and the need for continuation considered.</td></tr>
<tr><td>Ropinirole tablets
(symptomatic treatment of moderate to severe idiopathic RLS in adults)

Product licence relates to baseline score ≥ 24 on the IRLS Study Group Severity Scale.</td><td>Initial dose: 0.25 mg once daily up to 3hrs before bedtime for 2 days.

Titration: If this dose is well tolerated it should be increased to 0.5 mg once daily for the remainder of week 1. The daily dose should then be increased by 0.5mg each week, to a maximum of 4mg daily until optimal therapeutic response is achieved.

If there is more than a few days interruption of treatment, re-initiate by dose titration as above</td><td>This is suggested as a second line treatment in patients who have not responded to or are intolerant to treatment with pramipexole.

The response should be evaluated after 3 months and the need for continuation considered.</td></tr>
<tr><td>Rotigotine patches
(symptomatic treatment of moderate to severe idiopathic RLS in adults)

Product licence relates to baseline score ≥ 15 on the IRLS Study Group Severity Scale.</td><td>Initial dose: rotigotine patch 1 mg/24 hours.

Titration: increase if needed by 1 mg/24 hours after one week. Maximum recommended dose: 3 mg/24 hours.

If it is necessary to discontinue rotigotine, this should be done gradually to reduce the risk of neuroleptic malignant syndrome. The daily dose should be reduced in steps of 1 mg/24 h with a dose reduction preferably every other day, until complete withdrawal is achieved.</td><td>Because of the longer duration of action rotigotine may be useful for patients with significant daytime symptoms, but use should be restricted to those patients who have not responded to treatment with alternative dopamine agonists and lifestyle changes as it costs significantly more compared to alternatives.

Patient Counselling: Apply at ~same time each day, replace after 24hrs on a different site.</td></tr>
</table>

Non-Ergot Dopamine Agonist Patient Counselling Points

- Treatment can in some patients, exacerbate symptoms, or cause them to appear earlier in the day (augmentation)
- Some patients see a rebound in symptoms on cessation of treatment
- Treatment can cause sudden hypersomnia – patients should also be warned of this overwhelming sensation of sleepiness occurring with little or no warning, and the need to exercise caution when driving or operating machinery
- Dopamine agonists are also rarely associated with impulse control disorders such as pathological gambling

4.5.2 Alpha-2 delta ligands (Gabapentin and Pregabalin)

- Alpha-2 delta ligands may be of benefit in a restricted patient group. i.e. Patients with severe sleep disturbance (disproportionate to other RLS symptoms), co-morbid insomnia or anxiety, RLS related or co-morbid pain, or with a history of ICD. [3]
- However, in the first instance, it is recommended that these co-morbidities are investigated and managed.
- Because of the side effect profile, where possible use should be avoided in patients who are obese, have co-morbid depression, are at increased risk of falls, who have cognitive impairment or where there is likely a risk of abuse. (A non-ergot dopamine agonist should be used in preference)
- **Alpha-2 delta ligands are not licensed for use in restless legs syndrome** i.e. use is off-label. As such, prescribers should follow relevant guidance around this taking responsibility for the decision and being satisfied that use best serves the patients individual needs. The patient should provide informed consent, which should be documented. (For more information see the General Medical Council's 'Good practice in prescribing and managing medicines and devices')[10]
- **Gabapentin is recommended as the 1st line alpha-2 delta ligand**
  Initial dose: 300mg 1–2 hours before bedtime (or anticipated onset of symptoms).
  Titration: increase by 300mg after 3–7 days if needed.
  Maximum recommended dose for RLS is 2700mg (doses above 1500mg should be given in divided doses).[3]
- **Pregabalin** may be considered where gabapentin is ineffective or not tolerated
  Initial dose: 25 mg 1–2 hours before bedtime (or anticipated onset of symptoms).
  Titration: increase by 25 mg after 3–7 days if needed.
  Maximum recommended dose for RLS is 300 mg.[3]

4.5.3. Use of weak opioids is NOT recommended

Although weak opioids such as tramadol and codeine are recommended as a second-line treatment option by the EURLSSG taskforce (consensus opinion group),[8] evidence-based European guidelines from 2012 state there is insufficient evidence to make a recommendation regarding these medicines.[5] For this reason and in view of the potential risks of tolerance and abuse associated with opioids, they are not recommended for use in the treatment of restless legs syndrome within the Lancashire health economy.

4.5.4 Targinact (Oxycodone hydrochloride/naloxone hydrochloride) is not recommended for treatment of restless legs syndrome.

Please see LMMG new medicines review for more details. Efficacy and safety data in support of Targinact® was not sufficient to allay concerns regarding;

- Safety issues and side effects associated with long term use of opioids
- The controlled drug status and potential for opioid abuse
- A lack of evidence for use beyond 1 year and uncertainty around the mechanism of action and potential for tolerance to develop when used to treat restless legs syndrome.

5. 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(2):101-119.
2. Nagandla, K. and De, S. (2013) Restless legs syndrome: pathophysiology and modern management. Postgraduate Medical Journal 89(1053), 402-410
3. National Institute for Health and Care Excellence Clinical Knowledge Summaries Restless Legs Syndromes March 2015 accessed on 14/10/15 at http://cks.nice.org.uk/restless-legs-syndrome#!topicsummary
4. Garcia-Borreguero D, Kohnen R, Silber M et al. The long-term treatment of restless legs syndrome/Willis Ekborn disease: evidence-based guidelines and clinical consensus best practice guidance: a report from the International Restless Legs Syndrome Study Group. Sleep Medicine 2013 14; 675-684.
5. Garcia-Borreguero D, Ferini-Strambi L, Kohnen R et al. European Guidelines on Management of RLS: report of a joint task force by the European Federation of Neurological Societies, the European Neurological Society and the European Sleep Research Society European Journal of Neurology 2012, 19; 1385-1396.
6. Restless Legs Syndrome: Diagnosis and Treatment in Primary Care 2008. Restless Legs Syndrome Foundation.
7. 2012 Revised International Restless Legs Syndrome Study Group Diagnostic Criteria for RLS accessed at http://irlssg.org/diagnostic-criteria/ on 22/10/15
8. Garcia-Borreguero D, Stillman P, Benes H et al. European Restless Legs Syndrome Study Group (EURLSSG) Algorithm for the diagnosis and treatment of restless legs syndrome in primary care *BMC Neurology* 2011 11:28
9. The electronic medicines compendium accessed at http://www.medicines.org.uk/emc on 9/11/15
10. The General Medical Council. Good Practice Guidance in prescribing and managing medical devices http://www.gmc-uk.org/Prescribing_guidance.pdf_59055247.pdf

6. ACKNOWLEDGEMENTS

Thank you to East Lancashire Health Economy for their guidance which provided the basis for these guidelines.

This guidance does not override the individual responsibility of health professionals to make decisions in exercising their clinical judgement in the circumstances of the individual patient, in consultation with the patient and/or guardian or carer. For full prescribing information please refer to the BNF and SPC ensuring correct indication is consulted.

Leads for this guidance: Midlands and Lancashire CSU	
Version	Version 1 (Available online at http://www.lancsmmg.nhs.uk/ , click on 'Guidelines')
Ratified by	Lancashire Medicines Management Group
Guidance effective from	December 2015
Date of next review	Novemeber 2018. As required- minimum 3 yearly

Appendix 1. Restless Legs Syndrome Rating Scale

<table>
<tr><td colspan="2">Have the patient rate his/her symptoms for the following ten questions.
The patient and not the examiner should make the ratings, but the examiner should be available to clarify any misunderstandings the patient may have about the questions.
The examiner should mark the patient's answers on the form.</td></tr>
<tr><td>In the past week…

(1) Overall, how would you rate the RLS discomfort in your legs or arms?
(4) Very severe
(3) Severe
(2) Moderate
(1) Mild
(0) None</td><td>In the past week…

(6) How severe was your RLS as a whole?
(4) Very severe
(3) Severe
(2) Moderate
(1) Mild
(0) None</td></tr>
<tr><td>In the past week…

(2) Overall, how would you rate the need to move around because of your RLS symptoms?
(4) Very severe
(3) Severe
(2) Moderate
(1) Mild
(0) None</td><td>In the past week…

(7) How often did you get RLS symptoms?
(4) Very often (6 to 7 days in 1 week)
(3) Often (4 to 5 days in 1 week)
(2) Sometimes (2 to 3 days in 1 week)
(1) Occasionally (1 day in 1 week)
(0) Never</td></tr>
<tr><td>In the past week…

(3) Overall, how much relief of your RLS arm or leg discomfort did you get from moving around?
(4) No relief _
(3) Mild relief
(2) Moderate relief
(1) Either complete or almost complete relief
(0) No RLS symptoms to be relieved</td><td>In the past week…

(8) When you had RLS symptoms, how severe were they on average?
(4) Very severe (8 hrs or more per 24 hr)
(3) Severe (3 to 8 hrs per 24 hr)
(2) Moderate (1 to 3 hrs per 24 hr
(1) Mild (less than 1 hr per 24 hr)
(0) None</td></tr>
<tr><td>In the past week…

(5) How severe was your tiredness or sleepiness during the day due to your RLS symptoms?
(4) Very severe
(3) Severe
(2) Moderate
(1) Mild
(0) None</td><td>In the past week…

(10) How severe was your mood disturbance due to your RLS symptoms - for example; angry, depressed, sad, anxious or irritable?
(4) Very severe
(3) Severe
(2) Moderate
(1) Mild
(0) None</td></tr>
<tr><td colspan="2">Sum of scores=</td></tr>
<tr><td colspan="2">Scoring criteria are: Mild (score 1-10); Moderate (score 11-20); Severe (score 21-30); Very severe (score 31-40)</td></tr>
<tr><td colspan="2">Answers for this IRLS are scored from 4 for the first (top) answer (usually ‘very severe’) to 0 for the last answer (usually none). All items are scored.
The sum of the item scores serves as the scale score.
The International Restless Legs Syndrome Study Group holds the copyright for this scale.</td></tr>
</table>