Lancashire & South Cumbria Medicines Management Group

The Management of Restless Legs Syndrome in Adults in Primary Care

Version 1.2 – November 2023

Introduction

VERSION CONTROL		
Version	**Date**	**Amendments made**
1.0	December 2015	New guideline.
1.1	February 2019	Updated prescribing information
1.2	November 2023	Minor clinical updates and reformat. Gabapentin and pregabalin prescribing information updated in line with NICE CKS RLS guidance

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Introduction

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. Over the age of 35 years, it is twice as prevalent in women as in men.[3]

RLS-UK is a charity which offers support and information for people affected by restless legs syndrome, and can be accessed via http://www.rls-uk.org/.

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.

Scope

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

Diagnosis and aetiology

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

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

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

RLS – treatment algorithm

Identify and Correct Secondary Causes of RLS (where possible)
Secondary causes include:
Iron deficiency anaemia or serum ferritin <50-75 micrograms/L
Vitamin B_{12} /folate deficiency
Pregnancy - reassure that symptoms are likely to resolve or improve soon after delivery — drug treatment is not recommended during pregnancy or breastfeeding
Medication e.g. Anti-depressants, anti-psychotics, lithium, calcium channel blockers, metoclopramide and antihistamines
Caffeine, alcohol, chocolate and tobacco

Measure Severity using International Restless Legs Syndrome (IRLS) Study Group Severity Scale
See Also Appendix 1

Mild RLS
Score 1-10

Intermittent symptoms

Moderate to Severe RLS
Score ≥ 15

Advise patients to make **lifestyle changes** & of ways to manage symptoms during an attack (see box below).

Medical treatment may not be required

Reassure patients. Advise them to make lifestyle changes and of ways to manage symptoms during an attack.

If symptoms have not improved, consider **pramipexole on PRN basis.**
(See '**Prescribing information'** for further information regarding pramipexole)

Drug Treatment is Indicated

The majority of patients can be treated with a **non-ergot dopamine agonist**, of which pramipexole is the preferred 1st line agent.
(**See 'Prescribing information'**)

Lifestyle Advice

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

Reducing or avoiding alcohol and caffeine
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

RLS – treatment algorithm

Referral[3]

Most cases of RLS can be managed by primary care.

Referral may be considered for the following patient presentations:

- Intolerable side effects with treatment
- An insufficient initial response despite an adequate dose and duration of treatment
- Response to treatment becomes inadequate over time despite an increased dose
- Maximal treatment ceases to be effective
- Augmentation

Augmentation[3]

Augmentation is a major complication of dopaminergic treatment for restless legs syndrome (RLS). It is a long-term consequence of treatment that may develop months or years after treatment is initiated.

Augmentation is characterized by worsening symptoms of RLS, in particular their earlier onset in the day, increased intensity, or spread to the arms or trunk. Rates of augmentation appear to be greater the higher the dose of any given drug, and the longer the duration of treatment.

Prescribing information

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**.**
Pramipexole should be considered first line.

For the most up to date information on each drug, including dose, dose titration, and safe drug withdrawal, please refer to the individual drug SPCs and the BNF.

Non-Ergot Dopamine Agonist Patient Counselling Points[3]

- 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
- Drug dosages should be kept to the minimum required to ease symptoms as the higher the dose, the greater the risk of augmentation. The daily dose should not exceed that recommended for RLS.[9]
- Patient's prescribed pramipexole or ropinirole should have their response to treatment evaluated after 3 months and the need for continuation considered.
- Consider rotigotine transdermal patch if the person has significant daytime symptoms as it has a long duration of action. 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. The need for treatment continuation should be reconsidered every 6 months.
- For people prescribed ropinirole they should be monitored regularly to assess for the possible development of mania as symptoms can occur with or without the symptoms of impulse control disorders.

Gabapentin and Pregabalin

Gabapentin and Pregabalin are classified as schedule 3 (CD No Reg POM) controlled drugs.
CD prescription writing requirements are a legal obligation and prescriptions will only be valid for 28 days after the appropriate date.

- Gabapentin and pregabalin **are not licensed** for use in RLS. As such, prescribers should follow relevant guidance and 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'.[8]
- Gabapentin and pregabalin may be preferred in restricted patient groups, including 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).
- Drug dosages should be kept to the minimum required to ease symptoms.

Gabapentin (off-label) is recommended 1st line
Please refer to the BNF for a summary of MHRA/CHM safety alerts relating to gabapentin.
Initial dose: 300mg (100mg initial dose if the patient is aged >65 years old) 1–2 hours before bedtime (or anticipated onset of symptoms).
Titration: 300 mg once daily on day one, twice daily on day two, and three times daily on day three, followed by further increases in 300 mg/day increments every 2–3 days to the maximum dose if required
Maximum recommended daily dose for RLS is 2700mg.[3]

Pregabalin (off-label) may be considered where gabapentin is ineffective or not tolerated.
Please refer to the BNF for a summary of MHRA/CHM safety alerts relating to pregabalin.
Initial dose: 75mg (50mg initial dose if aged >65 years-old).
Titration: divided doses are advised. The initial pregabalin dose can be doubled after 3–7 days, and then increased incrementally on a weekly basis to the maximum dose if required.
Maximum recommended daily dose for RLS is 450mg.[3]

Prescribing information

Use of 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),[7] 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.

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

LSCMMG RAG rating = BLACK (Do not prescribe)

Please see LSCMMG website for further detail.

References

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Appendix 1

Restless legs syndrome rating scale

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.

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

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

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

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

In the past week...

(6) How severe was your RLS as a whole?
- (4) Very severe
- (3) Severe
- (2) Moderate
- (1) Mild
- (0) None

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

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

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

Sum of scores=

Scoring criteria are: Mild (score 1-10); Moderate (score 11-20); Severe (score 21-30); Very severe (score 31-40)

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.