Restless Leg Syndrome (RLS) – Information for GPs

Background

Restless Legs Syndrome (RLS), also known as Willis-Ekbom disease, is a neurological disorder characterised by an irresistible urge to move in order to stop uncomfortable or odd sensations in certain parts of the body in particular the lower limbs. As it usually interferes with sleep, it is also considered a sleep disorder.

A single standard question for rapid screening of RLS has been validated by the IRLSSG (International Restless Legs Syndrome Study Group), which 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?'.

Types of RLS

There are two recognised forms of RLS:

1) Primary or idiopathic RLS

Primary RLS has no known cause but is often genetically linked. It usually begins slowly, can come and go, sometimes for months on end and is often progressive.

2) Secondary RLS

Often has a sudden onset and is usually associated with another medical condition or the use of certain drugs e.g. anti-depressants (SSRI's, SNRI's,TCA's), anti-histamines, anti-emetics. Three major secondary causes of RLS are:

- Pregnancy (usually 3rd trimester)
- Iron-deficiency anaemia- (Iron levels and Serum Ferritin mandatory for all patients with suspected RLS)
- End-stage renal disease

PLMD (Periodic Limb Movement Disorder) is a sleep disorder associated with repetitive movement of the limbs (most often legs). It usually occurs after sleep onset resulting in sleep disruption and daytime symptoms. 80% of patients with RLS have PMLD but it can also occur independently and may be related to iron deficiency. PLMD and RLS are managed identically.

Management

RLS can be managed by non-pharmacological approaches such as improving sleep hygiene or patient specific pharmacological interventions. Information on dosing, and general adverse effects of the treatment options used are detailed on pages 2 and 3. Not all treatments often used for the treatment of RLS are licensed specifically for this condition, however when considered as treatment for some of the specific symptoms of RLS, use could be considered to be within licence (e.g. opioids for managing pain associated with RLS)

The problem of disease augmentation

Augmentation is the most common but least understood problem associated with the treatment of RLS. Augmentation can be defined as a worsening of RLS symptoms that occur after initiation of treatment for RLS. The medication is effective when first started but over time with continued use of the medication symptoms may worsen. The worsening or change in symptoms must be seen in relation to what symptoms were like before starting treatment. The cause of augmentation is not known but believed to

be a side-effect of medications that have the effect of increasing dopamine in the brain or that mimic dopamine activity. Augmentation will usually not occur until six months after initiating a course of dopaminergic treatment.

Pharmacological treatments for RLS

Drug	Starting dose	MAX recommended dose	Time to full therapeutic effect	Half-life	Side-effects
Ropinirole	0.25 mg nocte	4mg nocte	4-10 days	6 hours	Nausea, low blood pressure, dizziness, headache, nasal congestion
Pramiprexole	0.088 mg nocte	0.54mg nocte	At first dose	8-12 hours	Nausea, hypotension, dizziness, headache, nasal congestion
Rotigotine patch**	1 mg nocte	3mg nocte	1 week	5-7 hours	Skin irritation, nausea, low blood pressure, dizziness, headache,
Gabapentin*	300 mg nocte	1200mg nocte	3-6 days	5-7 hours	Nausea, vomiting, headache, drowsiness, dizziness, confusion, weight gain
Pregabalin*	25 mg nocte	300mg nocte	3-6 days	10 hours	Drowsiness, dizziness, confusion, constipation, vomiting, oedema, weight gain
Clonazepam*	0.25 mg nocte	2mg nocte	At first dose	30-40 hours	Drowsiness, dizziness, morning drug hangover, GI disturbances, dry mouth
Zopiclone*	3.75 mg nocte	15mg nocte	At first dose	6 hours	Taste disturbance, nausea, vomiting, dizziness, dry mouth, headache, hallucination
Zolpidem*	5 mg nocte	10mg nocte	At first dose	2.5 hours	Diarrhoea, nausea, vomiting, dizziness, drowsiness, headache, hallucination
Codeine phosphate*	30 mg nocte	90mg nocte		3-4 hours	Fatigue, somnolence, constipation and nausea
Targinact (Oxycodone/ Naloxone)	5/2.5mg twice daily	20/10mg twice daily		Steady state concentration throughout the day when given twice daily	Fatigue, somnolence, constipation and nausea

*Does not have a specific product licence for the treatment of RLS
** Off label use; Rotigotine dose may be increased to 4mg daily in treatment resistant cases where an incomplete response observed- this option should be used before considering escalation to clonazepam or opioids

Pharmacological associated side effects of treatments for RLS

	Dopamine agonist- Short acting: (e.g. ropinirole, pramipexole)	**Dopamine agonist- Long acting** (e.g. rotigotine patch)	**α - 2 delta ligands** (e.g. gabapentin and pregabalin)	**Opiates** (e.g. codeine phosphate, and Targinact (oxycodone/naloxone)	**Clonazepam**
Augmentation	++	+	0	0	0
Loss of efficacy	++	N/A	+	+	N/A
Impulse control disorders	+	0/+	0	0	0
Excessive daytime sleepiness	+	+	++	+	+++
Mood	0	0	+	+	++
Weight gain (excluding fluid retention)	0	0	++	0	0
General Toxicity	+	++	+	++	+