ALBERTA MEDICAL ASSOCIATION
alberta college of pharmacists

DUE Quarterly

DRUG USE IN THE ELDERLY

April 2010 PROMOTING MORE EFFECTIVE MEDICATION USE BY SENIORS

Restless legs syndrome: An approach to diagnosis, medical workup, drug selection and drug dosing

The prevalence of restless legs syndrome (RLS) is estimated to be 5–15% in the general population, 15-20% of uremic patients and up to 30% of rheumatoid arthritis patients.[1,2]

In a Canadian-based population survey, prevalence of symptoms consistent with RLS was:

- 10-15%; it increased linearly with age and was reported more frequently in eastern provinces than Ontario and western provinces[3]
- 10.2% in patients older than 60 years, and reported more frequently by women[3] likely due to increased prevalence of secondary causes of RLS with age[4,5]

Pathophysiology

This sensorimotor neurological disorder results from impairment of dopamine transport in the substantia nigra, due to low intracellular iron.[6]

- Symptoms improve substantially with iron replacement for patients with low-iron stores (low serum ferritin) and with dopaminergic medications for patients with idiopathic RLS, all of which support understanding the pathophysiology.

Diagnosis

The diagnosis is:

- Made clinically.
- Very important, especially in the elderly, to determine whether it is idiopathic RLS or RLS due to a secondary cause.
- Made by four essential diagnostic criteria[9] the patient will describe:
  - Irresistible urge to move the legs
  - Urge to move that worsens at rest
  - Urge to move that improves with movement
  - Urge to move that is worse or only occurs in the evening and night

> The diagnosis is very important, especially in the elderly, to determine whether it is idiopathic RLS or RLS due to a secondary cause.

Clinical patterns[8]

- **Intermittent RLS –** Symptoms may present intermittently and are disturbing enough to the patient to require episodic treatment (e.g., when flying or sitting in a theatre). However, depending upon severity and impact of the intermittent symptoms on quality of life, daily dosing may be more appropriate.
- **Daily RLS –** Symptoms may present daily and are disturbing enough to require daily treatment.
- **Refractory RLS –** Symptoms are daily in spite of treatment with a dopamine agonist, suggestive of one or more of the following:
  - Inadequate response to treatment
  - Intolerable adverse effects
  - Augmentation (see the section "Adverse effects" on page 4)

Supportive clinical features[9]

Supportive clinical features follow, which help the clinician when symptoms are vague but clinical suspicion is high and a trial of treatment is worthwhile.

NEXT ISSUE

- Immunization of seniors

DUE Quarterly offers expert opinions — not ACP-AMA guidelines or evaluations of drug use.

- Positive family history of RLS
- Response to treatment with dopaminergic agents

Presence of periodic limb movements in sleep

- Brief abrupt lower-leg movements during sleep that wake the patient or disturb the bed partner
- Involuntary limb movements during periods of quiet wakefulness

Associated features[9]

Natural clinical course – The history of symptom onset is generally:

- More gradual and less severe if the patient is younger than 50 years
- Abrupt and more severe in those older than 50

Sleep disturbance is the most common reason to seek medical assistance.

- Difficulty initiating and maintaining sleep with RLS symptoms constitutes a moderate-to-severe degree of RLS

Secondary causes

Although the prevalence of RLS increases with age and is thought to be due to secondary causes, only one research paper has looked specifically at secondary causes of RLS in the elderly.

- The final conclusion was that "secondary causes of RLS become more common and a positive family history less common with increased age."[10]

RLS symptoms can be reproduced in many other disease states common with increasing age.

The most common secondary causes include:

- Low iron stores (low ferritin, less than 50ug/L)
- Chronic renal failure/uremia
- Peripheral neuropathy of any cause
- Arthritis and fibromyalgia
- Medications such as sedating antihistamines, most antidepressants (primarily TCAs and selective serotonin uptake inhibitors), antipsychotics, dopamine-blocking antiemetics (e.g., metoclopramide) and lithium

Medical work-up

The medical work-up includes the following:

- Rule out other primary sleep disorders
  - Clinical assessment – Visit the Toward Optimized Practice website (www.topalbertadoctors.org) for insomnia guidelines
  - Refer to a sleep specialist or sleep centre where appropriate
  - Refer to a movement disorders clinic where appropriate
- Blood work includes:
  - Work-up for anemia and low iron stores
    - Complete blood count and ferritin
  - Work-up for peripheral neuropathy
    - Vitamin B12 and folate
    - Nerve conduction studies
    - Electromyography
  - Work-up for renal failure and uremia
    - Creatinine
    - Blood urea nitrogen
    - Electrolytes
- Ensure adequate control of glucose in diabetics

Treatment

The following rules should apply when treating the elderly for RLS, given concerns regarding polypharmacy and that RLS is treated long term with agents having substantial adverse effects:

- Take the time to make an accurate clinical diagnosis.
- Rule out potential secondary causes of RLS.
- Treat secondary causes of RLS first and reassess the symptoms.
- Use a team approach (including pharmacist, family, other allied health care workers) to ensure:
  - Adequate monitoring of symptom relief
  - Appropriate dose (amount) and timing of the dose(s)
  - Presence of adverse effects or drug interactions

The most common mistake with the treatment of RLS is to prescribe a bedtime dose of the medication and not reassess the symptoms to adjust the dose accordingly.

Dosing – general rules

- See "Practically speaking ... "on page 3.
- Use the lowest dose that controls symptoms.
- Medications should be taken prior to the onset of symptoms within the window of onset of action to prevent onset of symptoms.
  - If symptoms are present in the evening and at sleep onset, split the dose and administer accordingly to prevent onset of symptoms.
- The goal of treatment is control of symptoms and improved sleep quality and daytime function.
- **Do not** leave dosing in the hands of the patient without reassessment.

Drug selection – general rules (expert opinion)

- **Dopaminergics**
  - Pramipexole – A longer half-life agent. Works well with symptoms that persist through the evening, to sleep onset and through the night.
  - Ropinirole – A shorter half-life agent. Works well for short-lived and intermittent symptoms.
  - Carbidopa/levodopa – Wide range of dosing options for complex patients via regular and controlled-release preparations. But adverse effects risks, such as augmentation and GI upset, tend to be higher.
  - First-line options – Dopamine agonists

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Practically speaking . . .

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Therapeutic options

Clinically significant symptoms of intermittent daily restless legs syndrome (RLS) frequent and troublesome enough for daily treatment

Lifestyle factors and non-pharmacological options: For all patients with RLS symptoms. Good-quality evidence is lacking, however.

- Limit caffeine, tobacco and alcohol intake. (See "Non-drug therapy," on page 4, for more details.)

First-line options – Dopamine agonists (See page 2 for more details.)

Drug	Dosing and titration	Officially indicated	Comments	Approx. cost /30 days	AHW* status
Ropinirole (Requip, generics)	- 0.25 mg once daily 1-3 hours before bedtime - Titrate to 0.5 mg on day 3 and to 1 mg on day 8; increase by 0.5 mg every week if needed, to a maximum of 4 mg/day	- FDA: Moderate to severe primary RLS	- Not studied in patients with severe renal impairment (CrCl < 30 mL/min); no dosage adjustment required for moderate renal impairment - Titrate with caution in hepatically impaired patients - Most patients benefit from 2 mg/day or less	$30 (2 mg/day)	Regular benefit
Pramipexole (Mirapex, generics)	- 0.125 mg taken once daily 2-3 hours before bedtime - Dose may be increased every 4-7 days to 0.50 mg/day if needed; no evidence 0.75 mg/day provides additional benefit	- Canadian and FDA: Moderate to severe idiopathic RLS	- Duration between titration steps should be increased to 14 days in patients with renal impairment (CrCl 20-60 mL/min) - Dose reduction in patients with hepatic impairment is not considered necessary - Mean effective dose ~ 0.375 mg/day	$32 (0.5 mg/day)	Regular benefit 0.5 mg tablet strength not a benefit

Second-line options

Class	Drug	Dosing	Officially indicated	Comments	Approx. cost/30 days	AHW* status
Benzodiazepine	Clonazepam (Rivotril, generics) Temazepam (Restoril, generics)	- 0.25 to 2 mg at bedtime - 15 to 30 mg at bedtime	- Not approved for RLS	- Limited data on effectiveness; consider if significantly disturbed sleep - Of this class, **most experience in RLS has been with clonazepam** - Temazepam may be an option for RLS that awakens patient later in the night	$16 (1 mg hs) $15 (30 mg hs)	Regular benefit
Anticonvulsant	Gabapentin (Neurontin, generics)	- 100 to 300 mg initially per dose, once or twice daily in the late afternoon/ evening or before bedtime; trial data suggests a mean of 1,800 mg/day	- Not approved for RLS	- Of this class, **most experience in RLS has been with gabapentin**; other anticonvulsant options may include carbamazepine or pregabalin - Consider agent in co-morbid neuropathic pain, neurodegenerative disorders or fibromyalgia	$128 (1,800 mg/day)	Regular benefit
Opioid	Oxycodone (Generics oxycodone – immediate release; sustained release Oxycontin)	- 5-10 mg immediate release at bedtime - 10-20 mg sustained release at bedtime	- Not approved for RLS	- Limited studies of effectiveness - Of this class, **only oxycodone studied in placebo-controlled trials** - Reasonable choice in patients with co-morbid pain - Other opioid options may include propoxyphene, codeine or an opioid agonist, such as tramadol	$55 (20 mg/ day)	Regular benefit

*Alberta Health and Wellness

continued from page 2 ...

  - Begin with titrating doses adjusted to clinical response and tolerability. Common side-effects are generally mild and transient (nausea, orthostatic hypotension, daytime somnolence). The typical dose is much lower than for Parkinson's.
  - Cabergoline (Dostinex) is a therapeutic option (0.5 mg to 2 mg), requires special authorization and is expensive.
  - Pergolide (Permax) was withdrawn from the market (cardiac valves).

- **Benzodiazepines**
  - Clonazapam: A sedative is a reasonable option if a substantial component of insomnia and anxiety is associated with the dysthesia (RLS symptoms).
- **Anticonvulsants**
  - Gabapentin: This is a reasonable option with dominant symptoms of neuropathic-type pain, aching and discomfort, and standard therapy has failed.
- **Opioids**
  - Based on expert clinical opinion, consult with a sleep specialist or neurologist if a physician considers opioids for an elder.
  - The choice of neurologist versus sleep specialist depends on the clinician's opinion of whether the primary disturbance is sleep-related or neuropathy- and movement-related.

Adverse effects[9]

Augmentation: Symptoms worsen because of a specific therapeutic agent for RLS.

- Symptoms may start to appear two hours earlier and severity of symptoms may worsen.
- This generally occurs within six months of starting treatment.

Rebound: Symptoms develop in the early morning due to the "end-of-dose" effect associated with the half-life of the drug.

Medication treatments not recommended

- Quinine sulfate and tonic water (it is important to differentiate between RLS and cramps)
- Other (amantadine, bromocriptine, clonidine)

Non-drug therapy

- Non-drug therapies include avoidance of triggers (caffeine, alcohol and nicotine) and:
  - Manipulate muscles - ambulation, stretching, massage
  - Moderate exercise, e.g., aerobic and lower-body resistance training
  - Good sleep hygiene (sleep loss can worsen symptoms)
  - Mentally stimulating activities, e.g., games, puzzles
  - Cognitive therapy, focusing on coping strategies
  - Hot or cold baths
  - Acupuncture
  - Transcutaneous electric nerve stimulation
- Although there is limited evidence that non-drug therapies are efficacious (see "Practically speaking ... "), some are benign and may result in symptom improvement without proceeding to drug trials and exposing the patient to adverse effects.
- The most common non-drug therapy is calcium and magnesium prior to bed. Quinine and tonic, however, would **not** be recommended.

References are available upon request.

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We'd like your feedback . . .

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