Ontario Renal Network

Restless Legs Syndrome

Adapted with permission from the BC Renal Agency's Pharmacy & Formulary Symptom Management Resources – Restless Legs Syndrome, developed by the agency's Pharmacy & Formulary Committee, and the Kidney Supportive Care Research Group (KSCRG), University of Alberta / Northern Alberta Renal Program. To review original source materials, see www.bcrenalagency.ca and www.ualberta.ca/~kscrg.

Ontario

Restless Legs Syndrome (RLS) Algorithm in Hemodialysis Patients

Assessment

Timing (especially at night or during dialysis), alleviating and exacerbating factors (e.g., movement, after dialysis, drugs), quality of discomfort (e.g., pain, pulling, itching, need to move, pins and needles, cramping etc.), and effect on sleep or other symptoms (e.g., anxiety and depression).

Consider Etiology

- Rule out mimic disorders
  - Movement disorders: akathisia, ADHD
  - Restlessness secondary to anxiety, depression, psychotic disorders
  - Local leg pathology (e.g., peripheral neuropathy, myelopathy, peripheral venous congestion, pruritus, cramps)
  - Positional discomfort
- Rule out drug-induced RLS
  - Dopamine antagonists (e.g., haloperidol, olanzapine, risperidone, metoclopramide, promethazine)
  - Antidepressants: Mirtazapine (up to 28%) or SSRI or SNRIs (<5%) (e.g., citalopram, escitalopram, fluoxetine, paroxetine, sertraline, duloxetine, venlafaxine)
  - Stimulants: alcohol, caffeine, nicotine
  - Others: TCAs, carbamazepine, lithium
- Assess risk/contributing factors
  - Iron deficiency
  - Sleep deprivation
  - Positive family history
  - Rheumatoid arthritis or Sjogren's
  - Pregnancy

Non-Pharmacologic Measures

- Discontinue or reduce offending drug, if feasible
- Correct iron deficiency – may prevent initial augmentation with dopaminergic therapy
- Encourage good sleep hygiene
- Stretching, massage, or exercise (including intradialytic exercise)
- Hot/cold water or towel
- Distracting attention (e.g., with puzzles)
- Limit caffeine/alcohol
- Smoking cessation

Refer to the Ontario Renal Network Restless Legs Syndrome Patient Self-Management Guide for more information.

Pharmacologic Options

(If RLS symptoms occur during HD, give medication prior to HD)

AVOID opioids and quinine

- **For intermittent RLS**, levodopa/carbidopa (Sinemet)***** 100/25 mg tablet – ½ tablet PO HS†, titrate Q3-7 days to effect up to 200/50 mg PO HS†. If patient awakens in middle of the night with RLS, use CR formulation (levodopa doses ≥200 mg may increase risk of augmentation – see dopamine agonists below for definition).
- **For daily RLS**, dopamine agonists
  - Compared to levodopa, has decreased risk of augmentation (i.e., paradoxical increase in RLS symptoms caused by medication) but increased incidence of hypotension and nausea. If augmentation occurs, consider reducing dose, splitting dose, or trying rotigotine. Caution with rotigotine re: narcolepsy (driving is not recommended).
  - Ropinirole***** 0.25 mg PO 2 hours prior to HS†; increase by 0.25 mg PO Q7 days to effect up to a maximum of 4 mg/day
  - Pramipexole***** 0.125 mg PO 2 hours prior to HS†; may increase by 0.125 mg PO Q7 days to effect up to a maximum of 0.75 mg/day
- If ineffective with dopaminergic agent or RLS with painful neuropathy:
  - Gabapentin***** 100 mg PO HS†; titrate by 100 mg Q7 days to a maximum of 300 mg PO HS†
  - Pregabalin***** 25 mg PO HS†; titrate by 25 mg Q7 days to a maximum of 75 mg PO HS†

INADEQUATE CONTROL

- Benzodiazepines
  - Preferably avoid secondary to potential for dependency, questionable efficacy and adverse effects due to clonazepam's long half-life. If severe insomnia, refer to Insomnia Treatment Algorithm. Use with caution in the elderly.
  - Clonazepam***** 0.5 mg PO HS†, titrate by 0.5 mg Q7 days to a maximum of 2 mg PO HS
- Clonidine***** 0.05 mg PO HS if patient is not hypotensive or bradycardic

† **If RLS symptoms occur during HD, give medication prior to HD**

* **covered by ODB**

Medications for Restless Legs Syndrome

Dopaminergic Agents

<table>
<tr><th colspan="4">Levodopa/Carbidopa (Sinemet®)</th></tr>
<tr><td>Mechanism of Action</td><td colspan="3">Levodopa is a dopamine precursor; carbidopa inhibits the peripheral breakdown of levodopa by inhibiting its decarboxylation, and thereby increases available levodopa at the blood brain barrier.</td></tr>
<tr><td>Pharmacokinetics</td><td colspan="3">• Bioavailability of levodopa is 70–75% for controlled release formulation compared to immediate release tablets
• Should not be taken with high protein food for maximal absorption
• Extensively metabolized – levodopa metabolites (active and inactive) and 50% carbidopa are renally excreted
• Time to peak 30 minutes for immediate release and 2 hours for controlled release tablet. Half-life 1.5 hrs (levodopa) and more prolonged with controlled release formulation.</td></tr>
<tr><td>Adverse Effects</td><td colspan="3">• Agitation, confusion, dizziness, sedation, orthostatic hypotension, dyspepsia, nausea; morning rebound (recurrence of RLS in early morning) 20-35%; augmentation (worsening of RLS symptoms, including earlier onset of symptoms, increased intensity or spread of symptoms to the arms) 80%
• The risk of augmentation increases with levodopa dose ≥ 200 mg per day and may be lower with intermittent use (e.g., <3 times per week)</td></tr>
<tr><td>Dosing Guidelines (Normal Renal Function)</td><td colspan="3">• Immediate release 100 mg/25 mg tablet – ½ tablet PO HS or at start of HD; if patient is awakened with restless leg in middle of the night, try CR formulation
• Titrate by levodopa 50–100mg Q3–7 days to effect up to a maximum levodopa dose of 200 mg per day</td></tr>
<tr><td rowspan="2">Renal Dosing Guidelines GFR (mL/min)</td><td>>50 (mL/min)</td><td>10 to 50 (mL/min)</td><td><10 (mL/min)</td></tr>
<tr><td>100%</td><td>100%</td><td>100%</td></tr>
<tr><td rowspan="2">Supplemental Dose After</td><td colspan="2">IHD</td><td>PD</td></tr>
<tr><td colspan="2">Yes</td><td>Unlikely</td></tr>
<tr><td>Drug Coverage</td><td colspan="3">• Immediate release: Yes – covered by ODB
• CR formulation: No – not covered by ODB</td></tr>
<tr><td>Estimated Cost (30-day supply) without dispensing fee
(Prices as of October 2018)</td><td colspan="3">100/25 PO QHS – immediate release tablets – $8.70; CR tablets – $28.90</td></tr>
</table>

<table>
<tr><th colspan="4">Rotigotine</th></tr>
<tr><td>Mechanism of Action</td><td colspan="3">Rotigotine is a non-ergot dopamine agonist. The precise mechanism of rotigotine is unknown but it believed to stimulate D2-receptors in the substantia nigra leading to dopaminergic transmission to motor areas in the basal ganglia.</td></tr>
<tr><td>Pharmacokinetics</td><td colspan="3">Metabolism by conjugation and N-dealkylation by multiple CYP isoenzymes, sulfotransferases, half-life after patch removal 5-7 hours, excretion in urine (71% as inactive conjugates or metabolites) and feces (23%)</td></tr>
<tr><td>Adverse Effects</td><td colspan="3">• Hypotension, orthostatic hypotension edema, drowsiness, dizziness, sleep disorder (disturbance in initiating or maintaining sleep), hallucination, insomnia, nausea, vomiting, application site reaction, dyskinesia (all >10%), impulse control disorder <1%
• Sudden onset of sleep (1-2%)</td></tr>
<tr><td>Dosing Guidelines (Normal Renal Function)</td><td colspan="3">• Initial: apply 1 mg/24 hours patch once daily; may increase by 1 mg/24 hours weekly, based on clinical response and tolerability; maximum 3mg/24 hours. Apply patch to clean, dry, hairless area of intact healthy skin on the abdomen, thigh, hip, flank, shoulder, or upper arm at approximately the same time daily. Do not apply to same application site more than once every 14 days.
• Discontinuation of Treatment: Decrease by 1mg every 24 hours or every other day until withdrawal complete</td></tr>
<tr><td rowspan="2">Renal Dosing Guidelines GFR (mL/min)</td><td>>50 (mL/min)</td><td>10 to 50 (mL/min)</td><td><10 (mL/min)</td></tr>
<tr><td>100%</td><td>100%</td><td>100%</td></tr>
<tr><td rowspan="2">Supplemental Dose After</td><td colspan="2">IHD</td><td>PD</td></tr>
<tr><td colspan="2">No</td><td>No</td></tr>
<tr><td>Drug Coverage</td><td colspan="3">No – not covered by ODB</td></tr>
<tr><td>Estimated Cost (30-day supply) without dispensing fee
(Prices as of October 2018)</td><td colspan="3">1 mg patch/24 hr x 30 days – $125.25</td></tr>
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<table>
<tr><th colspan="4">Pramipexole (Mirapex®)</th></tr>
<tr><td>Mechanism of Action</td><td colspan="3">Non-ergot dopamine agonist: stimulates dopamine activity in stratium and substantia nigra</td></tr>
<tr><td>Pharmacokinetics</td><td colspan="3">• Rapid and almost complete absorption
• Protein binding: 15%
• Metabolism: <10%
• Excreted unchanged: >90%
• Half-life: 8.5 hours, 12 hours (elderly)
• Time to peak: 2 hours</td></tr>
<tr><td>Adverse Effects</td><td colspan="3">• Dose related: headache (16%), insomnia (9% to 13%), abnormal dreams (1% to 8%), lightheadedness, somnolence (6%), hallucinations (rare); hypotension (rare); nausea (11% to 27%), constipation; compulsive behaviour (rare); sleep attack - falling asleep during activities without warning (rare but elderly male > 63 years of age are at higher risk)
• Augmentation may occur with prolonged use but is less common than levodopa</td></tr>
<tr><td>Dosing Guidelines (Normal Renal Function)</td><td colspan="3">• Dosing for restless legs: 0.125 mg PO 2 hours prior to HS; increase dose by 0.125 mg every 3-7 days up to a maximum of 0.75 mg per day
• Most patients require ≤0.5 mg per day</td></tr>
<tr><td rowspan="2">Renal Dosing Guidelines GFR (mL/min)</td><td>>50 (mL/min)</td><td>10 to 50 (mL/min)</td><td><10 (mL/min)</td></tr>
<tr><td>100%</td><td>100% but slow titration to Q14 days</td><td>100% but slow titration to Q14 days</td></tr>
<tr><td rowspan="2">Supplemental Dose After</td><td colspan="2">IHD</td><td>PD</td></tr>
<tr><td colspan="2">None</td><td>Unlikely</td></tr>
<tr><td>Drug Coverage</td><td colspan="3">Yes – covered by ODB</td></tr>
<tr><td>Estimated Cost (30-day supply) without dispensing fee
(Prices as of October 2018)</td><td colspan="3">0.125 mg PO QHS – $16.74</td></tr>
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<table>
<tr><th colspan="4">Ropinirole (Requip®)</th></tr>
<tr><td>Mechanism of Action</td><td colspan="3">Non-ergot dopamine agonist: stimulates dopamine activity in stratium and substantia nigra</td></tr>
<tr><td>Pharmacokinetics</td><td colspan="3">• Bioavailability: 45–55%
• First pass; protein binding 45–55%
• Extensive hepatic metabolism via cytochrome 1A2 to inactive metabolites
• Excreted unchanged <10% as unchanged drug
• Half-life: 6–8 hours
• Time to peak: 1–2 hours</td></tr>
<tr><td>Adverse Effects</td><td colspan="3">• Dose related: Headache (16%), insomnia (9% to 13%), abnormal dreams (1–8%), lightheadedness, somnolence (6%), hallucinations (rare); hypotension (< 25%); nausea (11–27%), constipation; compulsive behaviour (rare); sleep attack - falling asleep during activities without warning (rare but elderly male > 63 years of age are at higher risk)
• Augmentation may occur with prolonged use but is less common than levodopa</td></tr>
<tr><td>Dosing Guidelines (Normal Renal Function)</td><td colspan="3">• Dosing for restless legs: 0.25 mg PO 2 hours prior to HS; increase by 0.125 mg q3-7days up to a maximum of 3 mg per day
• Most patients require ≤2 mg per day</td></tr>
<tr><td rowspan="2">Renal Dosing Guidelines GFR (mL/min)</td><td>>50 (mL/min)</td><td>10 to 50 (mL/min)</td><td><10 (mL/min)</td></tr>
<tr><td>100%</td><td>100%</td><td>100%</td></tr>
<tr><td rowspan="2">Supplemental Dose After</td><td colspan="2">IHD</td><td>PD</td></tr>
<tr><td colspan="2">None</td><td>Unlikely</td></tr>
<tr><td>Drug Coverage</td><td colspan="3">Yes – covered by ODB</td></tr>
<tr><td>Estimated Cost (30-day supply) without dispensing fee
(Prices as of October 2018)</td><td colspan="3">0.25 mg PO QHS – $8.64</td></tr>
</table>

Benzodiazepine

Clonazepam (Rivotril®)			
Mechanism of Action	Binds to benzodiazepine receptors on the postsynaptic GABA; enhanced inhibitory effect of GABA on neuronal excitability by increased neuronal membrane permeability to chloride ions.		
Pharmacokinetics	• Well absorbed • Protein binding: 85% • Extensive hepatic metabolism via glucuronidation/sulfate conjugation • <2% excreted unchanged • Half-life :19–50 hours • Time to peak: 1–3 hours • Onset of action: 20–60 minutes		
Adverse Effects	Increased risk of falls/fractures, accidents, especially elderly, dependence, decreased cognition with long term use, dizziness, incoordination; complex sleep-related behaviour (e.g., sleep driving)		
Dosing Guidelines (Normal Renal Function)	0.5 mg PO HS, titrate gradually to effect every 7 days by 0.5 mg to a maximum of 2 mg per day		
Renal Dosing Guidelines GFR (mL/min)	**>50 (mL/min)**	**10 to 50 (mL/min)**	**<10 (mL/min)**
	100%	100%	100%
Supplemental Dose After	**IHD**	**PD**	
	None	Unlikely	
Drug Coverage	Yes – covered by ODB		
Estimated Cost (30-day supply) without dispensing fee (Prices as of October 2018)	0.5 mg PO QHS – $1.20		

Others

<table>
<tr><th colspan="4">Clonidine (Catapres®)</th></tr>
<tr><td>Mechanism of Action</td><td colspan="3">Central alpha-2 adrenoreceptor agonist</td></tr>
<tr><td>Pharmacokinetics</td><td colspan="3">• Normal half-life: 12 to 16 hours (up to 41 hours in renal failure)
• 50% hepatic metabolism
• 58% excreted unchanged</td></tr>
<tr><td>Adverse Effects</td><td colspan="3">Sedation, hypotension, dry mouth; abrupt discontinuation may lead to rebound hypertension</td></tr>
<tr><td>Dosing Guidelines (Normal Renal Function)</td><td colspan="3">Start with low dose – 0.05 mg PO HS</td></tr>
<tr><td rowspan="2">Renal Dosing Guidelines GFR (mL/min)</td><td>>50 (mL/min)</td><td>10 to 50 (mL/min)</td><td><10 (mL/min)</td></tr>
<tr><td>Q12 hours</td><td>Q12 to 24 hours</td><td>Q24 hours</td></tr>
<tr><td rowspan="2">Supplemental Dose After</td><td colspan="2">IHD</td><td>PD</td></tr>
<tr><td colspan="2">Dose after HD</td><td>Q24 hours</td></tr>
<tr><td>Drug Coverage</td><td colspan="3">Yes – 0.1 mg dose covered by ODB; 0.025 mg dose not covered by ODB</td></tr>
<tr><td>Estimated Cost (30-day supply) without dispensing fee
(Prices as of October 2018)</td><td colspan="3">0.05 mg PO QHS – $2.00 (for 0.1 mg dose)</td></tr>
</table>

<table>
<tr><th colspan="4">Gabapentin (Neurontin®)</th></tr>
<tr><td>Mechanism of Action</td><td colspan="3">Selective, high affinity for voltage gated calcium channels in the brain and dorsal horn of the spinal cord. Reduces influx of calcium, thus inhibiting the release of excitatory neurotransmitters such as glutamate, noradrenaline, substance P and calcitonin gene related peptide.</td></tr>
<tr><td>Pharmacokinetics</td><td colspan="3">• Normal half-life: 5–6.5 hours
• Saturable oral bioavailability (900 mg – 60%; 1200 mg – 47%; 2400 mg – 34%)
• Limited hepatic metabolism, 70–80% excreted unchanged in the urine</td></tr>
<tr><td>Adverse Effects</td><td colspan="3">Sedation, confusion, incoordination, peripheral edema</td></tr>
<tr><td>Dosing Guidelines (Normal Renal Function)</td><td colspan="3">Start with 100 mg PO daily, then 100 mg TID, titrate gradually to effect and as tolerated to a max of 3600 mg per day (in 4 divided doses)</td></tr>
<tr><td rowspan="2">Renal Dosing Guidelines GFR (mL/min)</td><td>>50 (mL/min)</td><td>10 to 50 (mL/min)</td><td><10 (mL/min)</td></tr>
<tr><td>400 mg PO TID</td><td>300 mg PO Q12 to 24 hours</td><td>Usual max of 300 mg per day</td></tr>
<tr><td rowspan="2">Supplemental Dose After</td><td colspan="2">IHD</td><td>PD</td></tr>
<tr><td colspan="2">Yes for HD patients – 100 mg after dialysis
*consider additional dose post dialysis if usual dose given pre-dialysis</td><td>No evidence available</td></tr>
<tr><td>Drug Coverage</td><td colspan="3">Yes – covered by ODB</td></tr>
<tr><td>Estimated Cost (30-day supply) without dispensing fee
(Prices as of October 2018)</td><td colspan="3">100 mg PO QHS – $1.25</td></tr>
</table>

<table>
<tr><th colspan="4">Pregabalin (Lyrica®)</th></tr>
<tr><td>Mechanism of Action</td><td colspan="3">Selective, high affinity for voltage gated calcium channels in the brain and dorsal horn of the spinal cord. Reduces influx of calcium, thus inhibiting the release of excitatory neurotransmitters such as glutamate, noradrenaline, substance P and calcitonin gene related peptide.</td></tr>
<tr><td>Pharmacokinetics</td><td colspan="3">• Oral bioavailability: 90%
• Limited hepatic metabolism, 90% excreted unchanged in the urine
• Normal half-life: 5–6.5 hours</td></tr>
<tr><td>Adverse Effects</td><td colspan="3">Sedation, confusion, incoordination, peripheral edema</td></tr>
<tr><td>Dosing Guidelines (Normal Renal Function)</td><td colspan="3">• Start with 25 mg PO HS; titrate to effect and as tolerated to a max of 300 mg PO BID
• Start at minimum dose and titrate up as required</td></tr>
<tr><td rowspan="2">Renal Dosing Guidelines GFR (mL/min)</td><td>>50 (mL/min)</td><td>10 to 50 (mL/min)</td><td><10 (mL/min)</td></tr>
<tr><td>100%</td><td>• CrCl 30–60 ml/min: Maximum 300 mg/day, dosed BID or TID
• CrCl 15–30 ml/min: Maximum 150 mg day, dosed BID or once daily</td><td>25–75 mg/day, dosed once daily</td></tr>
<tr><td rowspan="2">Supplemental Dose After</td><td colspan="2">IHD</td><td>PD</td></tr>
<tr><td colspan="2">50% Pregabalin removed by HD. Ideally, give post HD. If dosing before HD, consider supplemental dose post HD.</td><td>No data</td></tr>
<tr><td>Drug Coverage</td><td colspan="3">Yes – covered by ODB</td></tr>
<tr><td>Estimated Cost (30-day supply) without dispensing fee
(Prices as of October 2018)</td><td colspan="3">25 mg PO QHS – $27.17</td></tr>
</table>

The Ontario Renal Network gratefully acknowledges the contributions of the many patients, caregivers, and providers that were involved in preparing this Symptom Management Resource. In addition, a special thank you to the BC Renal Agency and Dr. Sara Davison and the Kidney Supportive Care Research Group (KSCRG), University of Alberta / Northern Alberta Renal Program.

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1-855-460-2647, TTY 416-217-1815, publicaffairs@cancercare.on.ca Jun. 2019 ORN4060