RESTLESS LEG SYNDROME

• Algorithm for Hemodialysis Patients
• Supplemental Summary
• Medication Monographs

TABLE OF CONTENTS

Restless Leg Syndrome (RLS) Treatment Algorithm in Hemodialysis Patients .................. 1

Restless Leg Syndrome (RLS) Treatment Algorithm for Hemodialysis Patients:
Supplemental Evidence for Treatment Options ................................................................. 2

Medications for Restless Leg Syndrome
Levodopa/Carbidopa (Sinemet®) ................................................................. 4
Pramipexole (Mirapex®) ............................................................................. 5
Ropinirole (Requip®) .................................................................................. 6
Clonazepam (Rivotril®) ........................................................................... 7
Clonidine (Catapres®) ............................................................................... 8
Gabapentin (Neurontin®) ................................................................. 9
Pregabalin (Lyrica®) .............................................................................. 10
Restless Leg Syndrome (RLS) Algorithm in Hemodialysis Patients

**Assessment**
- Rule out mimic disorders
- Rule out drug-induced RLS
- Assess risk/contributing factors
  - Iron deficiency
  - Sleep deprivation
  - Positive family history
  - Rheumatoid arthritis or Sjogren's
  - Pregnancy

**Medication Options**

**AVOID opioids and quinine**
*If RLS symptoms occur during HD, give medication prior to HD*
- 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 the middle of the night with RLS, use CR formulation (levodopa doses ≥200 mg may increase risk of augmentation).
- For daily RLS, dopamine agonists
  - Compared to levodopa, decreased risk of augmentation but increased incidence of hypotension and nausea. Caution re: sleep attack (driving is not recommended).
  - Ropinirole 0.25 mg PO 2 hours prior to HS*; increase by 0.25 mg PO Q7days to effect up to a maximum of 4 mg/day [PREFERRED]
  - Pramipexole 0.125 mg PO 2 hours prior to HS*; may increase by 0.125 mg PO Q7days 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 Q7days to a maximum of 300 mg PO HS*
  - Pregabalin 25 mg PO HS*; titrate by 25 mg Q7days to a maximum of 75 mg PO HS*

**Drug-induced RLS**
- Dopamine antagonists:
  - Antipsychotics: pimozide, haloperidol, olanzapine, risperidone
  - Metoclopramide, promethazine
- Antidepressants:
  - Mirtazapine (up to 28%)
  - SSRI (<5%), e.g. citalopram, escitalopram, fluoxetine, paroxetine, sertraline
  - SNRI’s (<5%), e.g. duloxetine, venlafaxine
- Stimulants: alcohol, caffeine, nicotine
- Others: TCA’s, carbamazepine, lithium

**Initial Recommendation**
- Discontinue or reduce offending drug, if feasible
- Correct iron deficiency – may prevent initial augmentation with dopaminergic therapy
- Encourage good sleep hygiene [see insomnia flowchart] Click here for link

**Mimic Conditions**
- Movement disorders: akathisia, ADHD
- Restlessness secondary to anxiety, depression, psychotic disorders
- Local leg pathology, e.g. peripheral neuropathy, myelopathy, peripheral venous congestion
- Positional discomfort

**Refractory Symptoms**
- 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.
  - Clonazepam 0.5 mg PO HS*, titrate by 0.5 mg Q7days to a maximum of 2 mg PO HS
  - Clonidine 0.05 mg PO HS if patient is not hypotensive

**Symptom Management Resources: Restless Leg Syndrome**
Purple: Covered by BCPRA
Blue: Covered by Pharmacare
Black: No coverage

UPDATED NOVEMBER 2012
Restless Leg Syndrome (RLS) Treatment Algorithm for Hemodialysis Patients
Supplemental Evidence for Treatment Options

RLS should only be treated if patients have severe and bothersome symptoms which impair their sleep or quality of life. In terms of non-pharmacological strategies, correct iron deficiency, if applicable, as iron is a cofactor in dopamine production. Consider a trial of abstinence from alcohol, caffeine and nicotine. Rule out any offending medication(s) that may be contributing and reducing the dose or discontinuing, if feasible. Refer to the list of offending medications in algorithm. Consider a trial of mental alerting activities, such as video games or crossword puzzles, to reduce symptoms at times of boredom.

In terms of pharmacotherapies, available literature in hemodialysis patients is limited. Most studies are of small sample size, from single centre, have significant drop-outs and short follow-up. Recommendations are largely extrapolated from the general population and based on expert opinions.

---

**EVIDENCE**

**Levodopa**

In a randomized, double-blind, placebo-controlled, crossover trial of 5 hemodialysis patients with uremic RLS, levodopa/carbidopa 100/25 mg 1 hour before HS was compared to placebo x 1 week with 1-week washout. There was no consistent subjective improvement in sleep quality, sleep latency, the number of awakenings or RLS symptoms. The mean percentage of periodic limb movement (PLM) while asleep was 15.1 ± 4.9% with placebo and decreased to 8.6 ± 4.0% with levodopa/carbidopa (p=0.014). The mean PLM index while asleep was 101.0 ± 29.1 with placebo and was significantly decreased to 61.0 ± 28.3 with levodopa/carbidopa (p=0.006).

In another randomized, double-blind, placebo-controlled, crossover trial of 11 HD patients, levodopa/benserazide 100/25 mg to 200/50 mg 1 hour before HS compared to placebo x 2 weeks without washout was shown to improve few nocturnal awakenings, sleep quality, general condition and quality of life and to decrease severity of RLS, respectively. No severe adverse effects reported.

Wetter et al showed that levodopa was more effective than placebo in reducing PLM index and improving sleep quality in a randomized, double-blind, placebo-controlled, crossover trial of 11 uremic patients with RLS.

**Pramipexole**

In an open label of 10 hemodialysis patients with RLS with 8 month follow-up, pramipexole showed an improvement in the International Restless Leg Study Group (IRLSSG) severity scale and PLM index during sleep and while awake. Pramipexole was prescribed at an initial dose of 0.125 mg, 2 hours before sleep, with an optional upward titration according to response and tolerance to a maximum daily dose of 0.75 mg, with one dose taken at least 2 hours before dialysis. Nine patients showed a response within the first week with a mean dose of 0.25 mg per day. Domperidone was prescribed to control side effects. The mean score in the severity scale fell from 25.8 ± 5.75 (in the severe range) in the pretreatment evaluation to 7.7 ± 8.36 after treatment (p<0.005). Sleep latency, total hours of sleep, number of awakenings, and sleep efficiency showed no significant change.

**Ropinirole**

In an open label, prospective, randomized, controlled crossover trial of 10 hemodialysis patients, ropinirole was shown to be superior to levodopa SR in reducing 6-item IRLS score, 16.6±2.8 to 4.4±3.8 vs. 16.7±3.2 to 11.1±4, respectively (p=0.0001) and increasing sleep time. Four patients reported a complete reversion of RLS symptoms. Ropinirole dose was 0.25 mg PO daily, doubling Q5days for the first 2 weeks until symptom relief, then up to a maximum of 2 mg/day (mean dose was 1.45 mg/day). Levodopa SR dose was 100/25 mg PO daily, then doubling after 2 weeks until symptom relief (mean levodopa dose 190 mg/day). Vomiting reported in one levodopa patient resulted in study discontinuation.

**Gabapentin**

In an open label controlled trial of 15 hemodialysis patients, gabapentin 200 mg PO post-HD x 4 weeks was significantly more effective than levodopa 125 mg PO daily. The median RLS score decreased from baseline of 17 to 10 and 3 after treatment with levodopa and gabapentin, respectively. In SF-36 assessment, gabapentin improved general
health, body pain and social function (P<0.001) while levodopa significantly improved body pain only (p<0.002). Gabapentin was significantly superior to levodopa for sleep quality, sleep latency (p<0.001) and sleep disturbance (p<0.000).

In a randomized double-blind, controlled, crossover trial\(^7\) of 13 patients, gabapentin 300 mg PO 3 times weekly at the end of HD x 6 week was more effective than placebo. IRLSSG rating score decreased from a mean of 5.8 ± 2.3 with placebo to 3.0 ± 2.2 with gabapentin (p<0.01). Eleven of 13 patients responded to gabapentin but not to placebo, one responded to placebo but not gabapentin while one responded to neither drug. Lethargy was reported.

**Clonidine**

In a randomized, double-blind, placebo-controlled, parallel study\(^8\), clonidine 0.075 mg PO BID was compared to placebo x 3 days in 20 patients. Complete relief of symptoms was noted in 8/10 pts, marked alleviation in 1/10 patients and unchanged symptoms in 1/10 patients treated with clonidine, compared with placebo (p<0.001).

**STUDY REFERENCES**


**GENERAL REFERENCES**


# Medications for Restless Leg Syndrome

## DOPAMINERGIC AGENTS

### Levodopa/Carbidopa (Sinemet®)

<table>
<thead>
<tr>
<th>Mechanism of Action</th>
<th>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.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pharmacokinetics</td>
<td>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 hrs for controlled release tablets. Half-life 1.5 hrs (levodopa) and more prolonged with controlled release formulation.</td>
</tr>
<tr>
<td>Adverse Effects</td>
<td>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. &lt;3 times per week).</td>
</tr>
<tr>
<td>Dosing Guidelines (Normal Renal Function)</td>
<td>Immediate release 100 mg/25 mg tablet - 1/2 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 Q3-7days to effect up to a maximum levodopa dose of 200 mg per day.</td>
</tr>
</tbody>
</table>

### Renal Dosing Guidelines GFR (mL/min)

<table>
<thead>
<tr>
<th>Renal Dosing Guidelines GFR (mL/min)</th>
<th>&gt;50 (mL/min)</th>
<th>10 to 50 (mL/min)</th>
<th>&lt;10 (mL/min)</th>
</tr>
</thead>
<tbody>
<tr>
<td>100%</td>
<td>100%</td>
<td>100%</td>
<td></td>
</tr>
</tbody>
</table>

### Supplemental Dose After

<table>
<thead>
<tr>
<th>IHD</th>
<th>PD</th>
</tr>
</thead>
<tbody>
<tr>
<td>Yes</td>
<td>Unlikely</td>
</tr>
</tbody>
</table>

### Pharmacare Coverage

| Yes |

### Cost (30-day supply) without dispensing fee

| 100/25 mg PO HS - immediate release tablets $23.10; CR tablets $24 |

---

*Return to Table of Contents*
## Pramipexole (Mirapex®)

### Mechanism of Action
Non-ergot dopamine agonist: stimulates dopamine activity in stratum and substantia nigra.

### Pharmacokinetics
- 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.

### Adverse Effects
Dose related: headache (16%), insomnia (9% to 13%), abnormal dreams (1-8%), lightheadedness, somnolence (6%), hallucinations (rare); hypotension (rare); 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.

### Dosing Guidelines (Normal Renal Function)
0.125 mg PO 2 hours prior to HS; increase dose by 0.125 mg every 3-7 days up to a maximum of 1.5 mg per day. Most patients require <0.5 mg per day.

### Renal Dosing Guidelines GFR (mL/min)

<table>
<thead>
<tr>
<th>GFR (mL/min)</th>
<th>&gt;50 (mL/min)</th>
<th>10 to 50 (mL/min)</th>
<th>&lt;10 (mL/min)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>100%</td>
<td>100% (but slow titration to q7 days)</td>
<td>0.75 mg per day</td>
</tr>
</tbody>
</table>

### Supplemental Dose After
- IHD: None
- PD: Unlikely

### Pharmacare Coverage
No

### Cost (30-day supply) without dispensing fee
0.5 mg PO HS $33.90
# Medications for Restless Leg Syndrome

## DOPAMINERGIC AGENTS

### Ropinirole (Requip®)

#### Mechanism of Action
Non-ergot dopamine agonist: stimulates dopamine activity in stratum and substantia nigra.

#### Pharmacokinetics
- 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.

#### Adverse Effects
Dose related: Headache (16%), insomnia (9% to 13%), abnormal dreams (1-8%), lightheadedness, somnolence (6%), hallucinations (rare); hypotension (rare); 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.

#### Dosing Guidelines (Normal Renal Function)
- 0.25 mg PO 2 hours prior to HS; increase by 0.125 mg q3-7days up to a maximum of 4 mg per day. Most patients require ≤2 mg per day.

<table>
<thead>
<tr>
<th>Renal Dosing Guidelines GFR (mL/min)</th>
<th>&gt;50 (mL/min)</th>
<th>10 to 50 (mL/min)</th>
<th>&lt;10 (mL/min)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>100%</td>
<td>100%</td>
<td>100%</td>
</tr>
</tbody>
</table>

#### Supplemental Dose After
- IHD: None
- PD: Unlikely

#### Pharmacare Coverage
No

#### Cost (30-day supply) without dispensing fee
- 2 mg PO HS $14.10

---

**Return to Table of Contents**
# Medications for Restless Leg Syndrome

## Clonazepam (Rivotril®)

<table>
<thead>
<tr>
<th>Mechanism of Action</th>
<th>Binds to benzodiazepine receptors on the postsynaptic GABA; enhanced inhibitory effect of GABA on neuronal excitability by increased neuronal membrane permeability to chloride ions.</th>
</tr>
</thead>
</table>
| 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 behavior (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   |
| Pharmacare Coverage | Yes       |
| Cost (30-day supply) without dispensing fee | 0.5 mg PO HS $2.40 |

Return to Table of Contents
## Clonidine (Catapres®)

<table>
<thead>
<tr>
<th>Mechanism of Action</th>
<th>Central alpha-2 adrenoreceptor agonist.</th>
</tr>
</thead>
</table>
| Pharmacokinetics    | Normal half-life 12 to 16 hours  
50% hepatic metabolism  
58% excreted unchanged. |
| Adverse Effects     | Sedation, hypotension, dry mouth; abrupt discontinuation may lead to rebound hypertension. |
| Dosing Guidelines   | Start with low dose - 0.05 mg PO HS |

<table>
<thead>
<tr>
<th>Renal Dosing Guidelines (GFR (mL/min))</th>
<th>&gt;50 (mL/min)</th>
<th>10 to 50 (mL/min)</th>
<th>&lt;10 (mL/min)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>q12h</td>
<td>q12 to 24h</td>
<td>q24h</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Supplemental Dose After</th>
<th>IHD</th>
<th>PD</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dose after HD</td>
<td></td>
<td>q24h</td>
</tr>
</tbody>
</table>

| Pharmacare Coverage | Yes |

| Cost (30-day supply) without dispensing fee | 0.1 mg PO HS $4.50 |

---

**Return to Table of Contents**
# Gabapentin (Neurontin®)

## Mechanism of Action
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.

## Pharmacokinetics
Saturable oral bioavailability (900 mg-60%; 1200 mg-47%; 2400 mg-34%) Limited hepatic metabolism, 70-80% excreted unchanged in the urine Normal half-life 5-6.5 hours.

## Adverse Effects
Sedation, confusion, incoordination, peripheral edema.

## Dosing Guidelines (Normal Renal Function)
Start with 100 mg PO HS, then 100 mg TID, titrate gradually to effect and as tolerated to a max of 3600 mg per day (in 4 divided doses).

## Renal Dosing Guidelines GFR (mL/min)

<table>
<thead>
<tr>
<th>GFR (mL/min)</th>
<th>400 mg PO TID</th>
<th>300 mg PO q12-24h</th>
<th>usual max of 300 mg per day</th>
</tr>
</thead>
<tbody>
<tr>
<td>&gt;50 (mL/min)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>10 to 50 (mL/min)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;10 (mL/min)</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

## Supplemental Dose After IHD PD

<table>
<thead>
<tr>
<th>IHD</th>
<th>PD</th>
</tr>
</thead>
<tbody>
<tr>
<td>100 mg or dose after HD</td>
<td>300 mg q2days</td>
</tr>
</tbody>
</table>

## Pharmacare Coverage
Yes

## Cost (30-day supply) without dispensing fee
300 mg PO daily - $11.40
### Medications for Restless Leg Syndrome

#### Pregabalin (Lyrica®)

<table>
<thead>
<tr>
<th>Mechanism of Action</th>
<th>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</th>
</tr>
</thead>
</table>
| Pharmacokinetics    | Oral bioavailability 90%  
Limited hepatic metabolism, 90% excreted unchanged in the urine  
Normal half-life 5-6.5 hours. |
| Adverse Effects      | Sedation, confusion, incoordination, peripheral edema. |
| Dosing Guidelines (Normal Renal Function) | Start with 25 mg PO HS, titrate to effect and as tolerated to a max of 300 mg PO BID. |

#### Renal Dosing Guidelines GFR (mL/min)

<table>
<thead>
<tr>
<th>Renal Dosing Guidelines GFR (mL/min)</th>
<th>&gt;50 (mL/min)</th>
<th>10 to 50 (mL/min)</th>
<th>&lt;10 (mL/min)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>100%</td>
<td>25-150 mg/day</td>
<td>25-75 mg/day</td>
</tr>
</tbody>
</table>

#### Supplemental Dose After

<table>
<thead>
<tr>
<th>IHD</th>
<th>PD</th>
</tr>
</thead>
<tbody>
<tr>
<td>25 mg or dose after HD</td>
<td>No data</td>
</tr>
</tbody>
</table>

#### Pharmacare Coverage

| No                        |

#### Cost (30-day supply) without dispensing fee

| 50 mg PO HS - $52.50      |