Medications and RLS: Patient Guide

This document is offered for informational purposes only; no goods, products or services are endorsed by the RLS Foundation. This is not a complete list of medications that may be available. It is very important to talk with your healthcare provider about potential side effects and drug interactions before making any change to your medication treatment plan.

Overview
There are many non-drug therapies that can help relieve symptoms of RLS for some people. However, for individuals experiencing frequent or severe symptoms, medications may be an important part of their treatment strategy in addition to non-drug therapies. If you need to take medication, your healthcare provider will work with you through careful trials to find a medication and dosage that works best to manage your symptoms. At this time, the US Food and Drug Administration (FDA) has approved four drugs for treating RLS:

- ropinirole (Requip)
- gabapentin enacarbil (Horizant)
- pramipexole (Mirapex)
- rotigotine (Neupro)

The approved doses are included in parentheses for these medications. In addition, several medications that are FDA approved for treatment of other medical conditions have undergone clinical studies with RLS patients and may provide symptom relief, such as gabapentin (Neurontin) and pregabalin (Lyrica).

Alpha-2-Delta Drugs
Alpha-2-delta drugs are one of the two classes of medications considered as effective first-line treatments. These medications are thought to relieve discomfort by changing the excitability of nerves that carry RLS sensations or pain. Side effects of alpha-2-delta drugs can include sleepiness, weight gain, edema, dizziness, depression, and problems with thinking. These symptoms can be prevented or reduced by slowly increasing the medication dose. Among this class of drugs are medicines that are and are not FDA approved. Regardless of approval of FDA, the alpha-2-delta ligands are effective in the treatment of RLS.

- gabapentin enacarbil (Horizant): (300 mg & 600 mg)
- FDA approved for treating RLS
- Extended-release formula
- Taken once daily, generally before dinner

Dopaminergic Agents
Dopamine agonists are a second class of medications often prescribed as first-line therapy for RLS and are also used to treat Parkinson’s disease. Dopamine agonists are medications that mimic dopamine activity in the brain. One potential side effect of dopamine agonists is augmentation, which may be serious and difficult to treat in some cases (see “Augmentation”). Side effects of dopamine agonists include nausea, daytime sleepiness, orthostatic hypotension (a temporary lowering of blood pressure when standing up from a lying or seated position), and compulsive behaviors such as increased interest in gambling, shopping, or sexual behavior.

- ropinirole (Requip): (0.25–4.0 mg)
  - FDA approved for treating RLS
  - ropinirole extended release (Requip XL) is not FDA approved for treating RLS
- pramipexole (Mirapex): (0.125–0.5 mg)
  - FDA approved for treating RLS
- pramipexole dihydrochloride extended release (Mirapex ER) is not FDA approved for treating RLS
- rotigotine (Neupro Patch): (1–3 mg)
  - FDA approved for treating RLS
- 24-hour patch applied at the same time each day directly to a new clean, dry place on the skin

Augmentation
Augmentation is a complication of dopaminergic agents in which RLS symptoms worsen over time (usually over months to years) after an initial improvement with the drug. With augmentation, symptoms develop earlier in the day, occur after shorter periods of rest/inactivity, spread from the legs to the arms and other body parts, or increase in intensity and the current medication dose prescribed no longer manages RLS symptoms. In this case, increasing the medication may improve symptoms temporarily, but over time (weeks to years), the symptoms will worsen again. Augmentation can occur with any of the dopamine agonists or Sinemet and sometimes with the painkiller tramadol.

Preventing Augmentation
Development of augmentation is more common with higher doses of the medication (however augmentation can occur at even the lowest doses), longer duration of dopaminergic usage and low iron stores. Therefore, avoiding dopamine agonists and carbidopa/levodopa products and/or using the lowest effective dose is the most effective way to prevent augmentation. Other methods that may prevent the development of augmentation include: using intermittent (non-daily) treatment, using longer-acting dopamine agonists, and intermittently reducing the dose of the dopamine agonist or taking a drug holiday. However, if another drug, such as an opioid, is not substituted, there may be a marked worsening from reducing or stopping a dopamine agonist.

Treating Augmentation
For mild augmentation consider keeping the same dopamine agonist but dividing the same dose into an earlier and a later dose, or completely...
Benzodiazepines: the only therapy for RLS, as they can lead to side effects without sedatives. sedatives are effective for improving sleep quality, but are usually not recommended as the only therapy for RLS, as they can lead to side effects without improving the RLS symptoms themselves.

Antidepressant Medication for RLS Patients
Depression and anxiety are significantly more common in RLS patients. Even though most antidepressant medications tend to worsen RLS, therapy should not be withheld for serious depression/anxiety problems, although RLS treatment may need to be increased.

Antidepressant drugs that tend to worsen RLS:
- Older tricyclic and combination antidepressants:
  - amoxapine (Ascendin), amitriptyline (Elavil), clodazepoxide and amitriptyline (Litbril), clomipramine (Anafranil), doxepin (Sinequan/Silenor), imipramine (Tofranil), perphenazine and amitriptyline (Etracon), perphenazine and amitriptyline (Triavil), trimipramine (Surmontil)
- Selective serotonin reuptake inhibitors (SSRIs):
  - citalopram (Celexa), escitalopram (Lexapro), fluvoxamine maleate (Luvox), fluoxetine (Prozac), paroxetine (Paxil), sertraline (Zoloft), vilazodone (Viibryd)
- Selective serotonin-norepinephrine reuptake inhibitors (SNRIs):
  - desvenlafaxine (Pristiq), duloxetine (Cymbalta), levomilnacipran (Fetzima), milnacipran (Savella), venlafaxine (Effexor)
- Atypical antidepressants:
  - mirtazapine (Remeron), vortioxetine (Trintellix)
- Atypical antipsychotic drugs (often used to treat depression and anxiety):
  - aripiprazole (Abilify), clozapine (Clozaril), olanzapine (Zyprexa), risperidone (Risperdal), quetiapine (Seroquel)

Antidepressant medications that do not worsen RLS:
- bupropion (Wellbutrin/Zyban) – may worsen anxiety and cause insomnia
- trazodone (Desyrel) – weak antidepressant but may help promote sleep desipramine (Norpramin) – an older secondary amine tricyclic antidepressant and based on clinical experience, may not worsen RLS protriptyline (Vivactil) – secondary amine tricyclic antidepressant nortriptyline (Pamelor) – secondary amine tricyclic antidepressant nefazodone (Serzone) – SNRI drug not used frequently as it may cause massive liver damage

Sedatives
Sedatives are effective for improving sleep quality, but are usually not effective for RLS. Generally, these medications are not recommended as the only therapy for RLS, as they can lead to side effects without improving the RLS symptoms themselves.

- Benzodiazepines:
  - temazepam (Restoril)
- Non-benzodiazepines:
  - eszopiclone (Lunesta), suvorexant (Belsomra), zaleplon (Sonata), zolpidem (Ambien)

Opioids
Opioids are used when RLS is moderate to severe and other treatment options (as noted above) are not tolerated or no longer effective. Side effects of opioids include constipation, nausea, changes in mood, and risk of abuse and non-medical diversion.

- morphine or its derivatives (oxycodone, hydrocodone, hydromorphone and oxymorphone) in immediate or extended-release formulations
- buprenorphine (Subutex or Suboxone) sublingual
- methadone
- tramadol (immediate and extended-release formulations)

What Can I Do?
- Working with your healthcare provider, you may need to undertake a series of medication trials to find one that effectively manages your symptoms.
- You may also consider asking your healthcare provider about exploring complementary and alternative medicine therapies as part of your treatment plan.
- Keep a symptom diary to track your symptoms, including the time of day they occur. It is also important to note if you missed or took any late medication doses. Share this information with your healthcare provider.
- Ask your healthcare provider to check your iron (ferritin) level (aiming for a ferritin level greater than 100 mcg/L), as low iron levels have been associated with worsening of RLS symptoms.
- Maintain good sleeping habits such as going to sleep and waking up at the same time daily.
- Avoid caffeine, which may increase RLS symptoms in some individuals.
- Get regular exercise and avoid alcohol, which is known to aggravate RLS symptoms.
- Work with your healthcare provider to find ways to improve or eliminate your symptoms by incorporating lifestyle changes, self-care and medications into your treatment plan.

It is important that you take your medication at the correct time in relationship to your RLS symptoms. If you have symptoms at night, your medication should generally be taken 1–3 hours before symptoms begin. There are some exceptions, so please discuss with your healthcare provider.

This publication has been reviewed and approved by the RLS Foundation Scientific and Medical Advisory Board. Literature distributed by the RLS Foundation, including this publication, is offered for information purposes only and should not be considered a substitute for the advice of a healthcare provider. The RLS Foundation does not endorse or sponsor any products or services. We invite you to become a member of the RLS Foundation member and receive our quarterly magazine, Night Walkers, as well as access to our library of handouts and brochures with the most current information available about RLS. Go to www.rls.org/become-a-member to help us find a cure!