Conclusion
The overall goal of RLS treatment is symptom management during times of inactivity rather than a total elimination of symptoms. If augmentation develops, treatment strategies are available.

Augmentation prevention strategies are important to reduce risk and include:

- Educate healthcare providers to avoid prescribing dopamine medications in the first place, with rare exception.
- Take the lowest effective dose of a dopaminergic drug. Do not exceed maximum FDA-approved dosages for RLS, and do not increase a previously stable dose of a dopamine agent.
- Avoid carbidopa/levodopa for daily RLS treatment due to rapid augmentation.
- Keep serum ferritin levels above 75-100 mcg/L and transferrin saturation above 20%.

RLS patients who take dopaminergic medications should be alert to signs and symptoms of augmentation and be advised to contact their healthcare providers immediately if symptoms develop. Patients should not make any changes to their treatment without first consulting their providers.

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The RLS Foundation is dedicated to improving the lives of the men, women, and children who live with this often devastating disease. Our mission is to increase awareness, improve treatments and, through research, find a cure for restless legs syndrome.

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Augmentation: Diagnosis and Treatment

Many individuals who have restless legs syndrome (RLS) experience a downward spiral of symptoms as a side effect of dopaminergic medications. This side effect, called augmentation, is the most common and least understood treatment issue encountered. With appropriate management by a healthcare provider, augmentation can be addressed to alleviate symptoms and allow patients to return to their normal daily activities.

What is augmentation?
Augmentation is defined as a worsening of RLS symptoms that occurs after starting a dopaminergic medication to treat RLS. The medication is effective when it is first started, but over time symptoms worsen with continued use. The worsening or change of symptoms needs to be considered in relation to what symptoms were like before starting treatment. Are symptoms getting worse since starting treatment? If the answer is yes, then the treatment may actually be worsening the disease; this is called augmentation.

Symptoms of augmentation include:

- Earlier onset of symptoms in the evening or afternoon
- Increase in symptom intensity
- Symptom spread to other body parts (trunk, arms or face)
- Shorter period of rest or inactivity before symptoms begin
- Loss of effectiveness of the medication dose that previously managed symptoms well
- Paradoxical response in which taking the medication may initially trigger symptoms

Do all RLS medications cause augmentation?
Augmentation is typically a side effect of medications that are designed to increase dopamine in the brain – for example, levodopa – or that mimic dopamine activity – for example, ropinirole, pramipexole and rotigotine, which are approved by the FDA for treating RLS.

The cause of augmentation is unknown, but it is thought that dopamine-related medications may overstimulate the brain and cause a change in dopamine receptors or dopamine levels, leading to an overall decrease in activity in the natural dopamine system. This decrease in natural dopamine function results in an increased need for dopamine-related medications (to replace the underactive dopamine system) and thus an increased dependency on the drug. Studies have shown that all dopamine medications used to treat RLS can cause augmentation. It is unclear which individuals will develop augmentation and how long it will take to develop. Research has shown that the longer a person stays on a dopamine agonist and the higher the dose of the medication, the more likely the medication will augment symptoms.

What are predisposing factors for augmentation?
Three factors have been shown to increase the risk of developing augmentation: dopaminergic medication dosages that exceed FDA maximums, carbidopa/levodopa taken daily for RLS treatment, and low body iron stores as measured by a serum

Augmentation is a side effect of dopaminergic therapy.

Augmentation prevention strategies:
1) Educate healthcare providers to avoid prescribing dopamine medications.
2) Take the lowest effective dose of a dopaminergic drug.
3) Do not exceed maximum FDA-approved dosages for RLS.
4) Avoid carbidopa/levodopa for daily RLS treatment due to rapid augmentation.
5) Keep serum ferritin levels above 100 mcg/L and transferrin saturation > 20%.

RLS
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ferritin test or percent transferrin saturation (iron/total iron binding capacity). Individuals with serum ferritin levels below the recommended 100 mcg/L[1,2] or 20% transferrin saturation treatment level are more likely to experience augmentation.

How quickly does augmentation develop?
Augmentation can occur at any time while a patient is taking a dopaminergic medication but typically does not occur until six months after beginning therapy. An estimated 5%–10% of those taking dopaminergic medications experience new onset of augmentation each year. After five years of taking dopaminergic medications 25%–50% of individuals may augment.

Could this just be a worsening of RLS symptoms?
Healthcare providers should conduct a careful medical history and physical exam to rule out other possible causes of worsening symptoms. The diagnosis of augmentation requires that the patient previously demonstrated at least some positive response to the prescribed dopaminergic medication, that other possible causes for a worsening of symptoms have been ruled out, and that there has been a consistent change in symptoms. RLS symptoms can vary in severity from day to day, as well as over time. A few days of symptom worsening is not sufficient for a diagnosis of augmentation.

What conditions are confused with augmentation?
Factors that can temporarily worsen RLS symptoms must be ruled out by the patient and their healthcare provider before confirmation of an augmentation diagnosis. These include:

- Use of medications such as sedating antihistamines (diphenhydramine, doxylamine) or antinausea medications. Examples are cold remedies and sleep aids such as Benadryl, Unisom, or Tylenol PM. Nonsedating antihistamines such as Allegra, Claritin, Clarinex and Zyrtec (usually) are less likely to worsen RLS symptoms.
- Addition of or increased use of antidepressants (exceptions include bupropion and trazodone) or antidopaminergic medications (haloperidol, risperidone, aripiprazole).
- Use of caffeine, alcohol or nicotine, which can aggravate RLS symptoms.
- Low iron stores. A morning, overnight fasting, serum iron panel test that includes serum iron, ferritin, total iron binding capacity (TIBC) and percent iron saturation should be conducted. A test of hemoglobin level or complete blood count (CBC) is not an adequate or sensitive measure of iron status. If an iron panel suggests abnormally low or even low normal iron stores, then iron treatment should be considered.
- Problems with sleep (for example sleep apnea, irregular sleep schedule, chronic sleep loss, or insomnia disorder) that diminish the quality or quantity of sleep. Sleep issues can markedly worsen RLS symptoms.
- Rebound, which may be confused with augmentation. Rebound is a flare-up of RLS symptoms as a medication dose is wearing off. "End-of-dose rebound" typically occurs in the early morning. This contrasts with augmentation, where symptoms occur earlier in the evening or afternoon. Rebound in RLS appears to occur most often with shorter-acting medications such as the short-acting form of carbidopa/levodopa (Sinemet), rather than longer-acting dopamine agonists such as pramipexole ER (Mirapex ER) or ropinirole XL (Requip XL). Rebound may disturb sleep at the end of the night and may require medication adjustment.

Augmentation indications
It can be challenging to distinguish between augmentation and a worsening of RLS due to natural disease progression. Healthcare providers must be alert to these indications of augmentation:

- Patient request for dose increase of a dopaminergic medication prescribed for RLS that previously was effective.
- Reported breakthrough of RLS symptoms with an accompanying increase in symptom intensity and involvement of other body parts.
- 24-hour occurrence of symptoms.
- Patient request for medication doses earlier in the day. (Symptoms previously appeared solely in evening or nighttime but now manifest earlier in the day.)

What if augmentation develops?
If augmentation is suspected, the patient should not discontinue the use of dopamine medication but should immediately consult a healthcare provider. There is no specific lab test for augmentation, so the provider will need to take a careful history of the RLS symptom progression and review current medications, including over-the-counter therapies. After ruling out other possible causes of the worsening of symptoms, the provider will need to confirm that augmentation is the most likely cause. If symptoms are significant and quality of life is diminished, the healthcare provider may suggest reducing the dosage of the problematic dopaminergic medication or, over time, discontinuing it. Withdrawal may be very difficult and should not be attempted without medical supervision. A healthcare provider will help determine the best approach for reducing medication.

How is augmentation addressed?
The first approach to addressing augmentation involves administration schedule readjustment (split-dosing) or increasing the dose of the current dopaminergic drug – not to exceed FDA maximums. FDA-approved drugs for treating RLS are ropinirole (Requip), pramipexole (Mirapex), rotigotine (Neupro) and gabapentin enacarbil (Horizant).

Split-dosing involves taking half of the prescribed dose earlier in the day and the other half at the usual administration time. If symptoms do not resolve, a common approach is to add a new class of drug, and once adequate levels of the new drug are achieved, to slowly (over weeks to months) reduce the dose of the dopamine drug. One possibility is to add an alpha-2-delta ligand such as pregabalin, gabapentin or gabapentin enacarbil (Horizant). While this approach may be effective, these drugs may be insufficient to control RLS symptoms in the absence of the dopaminergic agents.

A second way to manage augmentation from short-acting dopamine agonists is to change to a long-acting dopamine agonist, but this approach has fallen out of favor among RLS specialists. Although only the rotigotine (Neupro) patch is FDA approved for treating RLS, long-acting forms of pramipexole (Mirapex ER) and ropinirole (Requip XL) are available. Rotigotine was found in one study to have fewer problems with augmentation. That study, however, did not use rotigotine to substitute for preexisting augmentation that resulted from shorter-acting dopamine agonist. There is no data on whether changing to a long-acting dopamine agonist will reduce the risk of developing further problems with augmentation, whether rotigotine masks augmentation because of the 24-hour medication delivery system, or whether rotigotine truly reduces the risk of augmentation. If augmentation does develop, then some RLS experts have found that tapering off the long-acting agents when they are used to treat preexisting augmentation is substantially harder. Although symptoms may improve, the underlying change in the dopamine system of the brain is not likely to have changed, and with time the augmentation will return.

An alternate plan to alpha-2 delta ligand medications involves adding an opioid – such as buprenorphine, suboxone, methadone or oxycodone – to the dopamine agonists and then tapering off the dopamine agonists. When taken in adequate doses, opioids can help the transition from dopamine drugs. Common side effects are nausea, constipation, dizziness and sleepiness, but most people do well. After recovering from the dopamine agonist withdrawal process, patients may need decreasing doses of opioids over time. If necessary, other drugs such as gabapentin enacarbil or pregabalin may be added back to reduce or possibly eliminate the opioids.

During augmentation, aggressive iron supplementation is extremely important. Intravenous iron infusion – with a stronger formulation of iron of 1,000 mg including ferumoxytol (Feraheme), low molecular weight iron dextran (INFeD), ferric derisomaltose (Monoferric) or ferric carboxymaltose (Injectafer) – may be used to rapidly increase blood iron levels. Oral iron supplements can be used for ferritin < 75-100 mcg/L or transferrin saturation < 20%, but it may take weeks to months to improve levels, and most people with deteriorating symptoms due to augmentation will need a more rapid increase in iron levels. Iron infusions come with no serious or long-term risks, but obtaining access to infusion sites or providers with infusion authorization, along with lack of insurance coverage unless blood iron levels are in the anemia range, are significant barriers to this treatment.

The final step is to reduce slowly the dose of the dopamine drug – with or without a second treatment – followed by at least 12 drug-free nights before reassessing further treatment requirements. Experts suggest reducing ropinirole by no more than 0.5 mg every 3–7 days, or pramipexole by more than 0.125 mg every 3–7 days. During the first 4 days after stopping the dopamine medication, RLS symptoms may be very severe and the patient may have reduced sleep. Improvement in symptoms will usually happen by day 5 or 6. The degree of withdrawal symptoms and time to recovery between dosage decreases varies widely among individuals. Often, higher doses of the new treatment are needed to taper off the remaining dopamine agonist doses. During time off the drug, it is important to maximize nondrug strategies, such as good sleep habits, moderate exercise, treatment of obstructive sleep apnea, and other coping strategies. Be very cautious about using sedating medications during the first 4–5 days of the drug-free withdrawal period, particularly if there is loss of sleep already. The RLS Foundation's handout *Medication Withdrawal after Augmentation* offers more information on this approach.

Many patients (especially those with severe augmentation who take high doses of dopamine drugs) find it too difficult to eliminate a dopamine medication due to the marked worsening of RLS symptoms on withdrawal. However, if the dopamine drugs are eventually fully discontinued using any of the above approaches, reinstating a dopaminergic medication at a later time will often lead to rapid reappearance of augmentation. Once augmentation has occurred, all medications in the dopaminergic class are no longer an available option for treatment.