

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. With appropriate management by a healthcare provider, augmentation can be addressed to alleviate symptoms and allow individuals to return to their normal daily activities.

What is augmentation?

Augmentation is defined as a worsening of RLS symptoms after chronic use of dopaminergic medications. 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 – such as, levodopa – or that mimic dopamine activity – such as, 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.



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%.



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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
- Low body iron stores as measured by a serum ferritin test or percent transferrin saturation (iron/total iron binding capacity).

Serum ferritin, is a lab test that measures the amount of iron storage in the blood. Individuals with serum ferritin levels below the recommended 100 mcg/L or 20% transferrin saturation treatment level are more likely to experience augmentation.

How quickly does augmentation develop?

Augmentation can occur at any time while an individual 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 before confirmation of an augmentation diagnosis. These include:

- Use of medications such as sedating antihistamines (diphenhydramine, doxylamine) or anti-nausea medications. Examples are cold remedies and sleep aids such as Benadryl, Unisom, or Tylenol PM. Non-sedating 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 such as 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 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.
- Tramadol is a mixed opioid with dopaminergic properties that can cause augmentation. It is the only opioid with these properties, so it is important to monitor for any changes in RLS symptoms and alert your doctor to any worsening of symptoms.

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:

- Request for a 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.
- Request for medication doses earlier in the day. (Symptoms previously appeared solely in the evening or nighttime but now manifest earlier in the day.)

What if augmentation develops?

If an individual suspects augmentation, they should **not** discontinue the use of dopamine medication and should consult their healthcare provider immediately. 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. The healthcare provider will present available treatment options to help the individual choose the best approach for them in reducing the dopaminergic medication.

How is augmentation addressed?

Once augmentation starts, it will progress even if the dopamine agonist is not increased. Increasing the dose will only lead to more rapid and a more severe worsening of the RLS symptoms. Therefore, increasing the dose should never be considered an option to address augmentation. Ultimately, the dopamine agonist needs to be discontinued, with or without support from alternative medications such as opioids or alpha-2-delta agents like pregabalin, gabapentin or gabapentin enacarbil.

There are several approaches to transition individuals off of dopaminergic medications and methods will vary among RLS experts. The three common treatment approaches include: replacing the dopamine agonist with another drug, “cold turkey” method or the 12-day drug holiday.

The majority of RLS experts transition their patients off dopamine agonists by replacing them with another drug. The gabapentinoid class drugs (gabapentin, gabapentin enacarbil and pregabalin) may be successful for patients on very small doses of dopamine drugs with very mild augmentation symptoms, but they are not very potent and may not be effective in the augmented individual. Gabapentinoids may be more effective when the

individual has never taken a dopamine drug.

The majority of individuals will be successful and have the least discomfort transitioning from a dopamine agonist to a low dose opioid. Since the augmentation worsening of RLS by dopamine agonists tends to be permanent, the opioid drug will usually be needed indefinitely. Most opioids can be used but methadone is commonly used as it tends to be very effective, well tolerated and provides sustained relief of symptoms with less frequent dosing.

Alternately, many experts use buprenorphine. It is a partial opioid agonist that activates opioid receptors in the brain to provide long-term relief of RLS symptoms. It is less likely to cause side effects such as euphoria or respiratory depression due to its limited binding capacity to opioid receptors in the brain. Buprenorphine may be easier for patients to access since it is a Schedule III drug and allows for refills, compared to a Schedule II drug like methadone, which cannot include refills and pharmacists are increasingly reluctant to dispense.

During the transition, the opioid is started at a low dose and gradually increased as needed to control RLS symptoms while the dopamine drug is simultaneously weaned off. Some experts will taper the dopamine drugs over weeks or even months, which may be more tolerable and less stressful for some patients. Once the dopamine drugs are stopped, there will be a few weeks of marked worsening of the RLS symptoms requiring higher doses of the opioid. After a few weeks, the RLS symptoms typically improve, and the opioid dose can be reduced to a lower maintenance dose – a low-total-daily-dose of opioid medication.

The second approach is to have the patient go “cold turkey” by immediately stopping the dopamine drug completely. This treatment should be used only for lower doses of the drug (under 4–6 mg for ropinirole and 1–1.5 mg for pramipexole).

If an individual is on higher doses of the dopamine agonists, the drug can be tapered until a lower dose is reached and then the patient can stop the drug “cold turkey.” A low to moderate dose of the opioid is then added to relieve the marked worsening of the RLS symptoms. Patients with daytime RLS symptoms may need two or more opioid doses to control their RLS symptoms. If the RLS symptoms are not completely relieved with this low to medium dose, the patient can

add an additional dose of the opioid or take some or the full dose of the dopamine drug previously prescribed to control symptoms. It is often safer to take some or all of the dopamine drug when symptoms are not controlled rather than adding more of the opioid for acute relief as the dopamine drug is more reliable to relieve symptoms. And, if the opioid causes side effects, the symptoms would worsen with an increased dose. It is helpful to first see if the patient can tolerate the opioid by starting at a lower dose.

The next day, the patient should increase the opioid dose. This can be repeated over the next few days if needed until full control of RLS symptoms is achieved. It usually takes 1-4 days to determine the lowest opioid dose that controls the RLS. If the patient has significant adverse reactions to this treatment method (which if done properly should be a minority of patients), a slow taper of the dopamine drug can be instituted as described above. Most patients undergoing this “cold turkey” protocol find it to be a very quick and painless way to discontinue their dopamine drug.

The third approach follows the similar slow taper process as above. However, after the dopamine agonist is tapered off, the individual undergoes 12 drug-free nights (known as a drug holiday) before reassessing further treatment requirements. During the drug holiday, no other RLS medications are used. Individuals should never attempt a drug holiday without consulting a physician to carefully manage the withdrawal. For more information, please refer to the Foundations *Drug Holidays and RLS* handout.

Regardless of approach, withdrawal from a dopamine drug may be very difficult and should not be attempted without medical supervision. Working together with your healthcare provider, you can determine the best approach for augmentation management.

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. Individuals should not make any changes to their treatment without first consulting their providers.

This publication has been reviewed and approved by reviewers from the RLS Foundation Scientific and Medical Advisory Board.

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