What is Augmentation?

The following information has been compiled from data gathered by the Restless Legs Syndrome (RLS) Foundation and reviewed by members of the RLS Foundation's Scientific and Medical Advisory Board. This document is offered for informational purposes only. It is very important to share any augmentation concerns with your healthcare provider.

Many individuals who have restless legs syndrome (RLS) can attest to experiencing a downward spiral of symptoms as a side effect of some RLS medications. This effect, called augmentation, is one of the most common and least understood problems encountered in the treatment of RLS.

What is augmentation?
Augmentation is defined as a worsening of RLS symptoms that occurs after starting a medication to treat RLS. The medication is effective when it is first started, but over time symptoms worsen with continued use of the medication. The worsening or change of symptoms needs to be seen in relation to what symptoms were like before starting treatment. If you can answer "yes" to the question: Are my symptoms getting worse since starting this treatment? – then, your treatment may actually be worsening your disease; you may have augmentation. Augmentation is commonly experienced as an increasingly earlier onset of symptoms. Other signs of augmentation include: increased intensity of symptoms, a shorter period of rest or inactivity before symptoms start, and involvement of other parts of the body. Finally, the dose of drug that was previously helping with your symptoms may no longer be effective.

Do all RLS medications cause augmentation?
Augmentation is typically a side effect of medications that have the effect of increasing dopamine (for example, levodopa) in the brain or that mimic dopamine activity (for example, FDA approved drugs for treating RLS: ropinirole, pramipexole and rotigotine). 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 natural dopamine activity. This decrease in brain dopamine activity results in an increasing need for more dopamine-related medications (to replace the effects of dopamine), and thus an increasing dependency on the drug. Studies have shown that all dopamine medications used in treating RLS may cause augmentation. Less clear is which individuals will develop augmentation and how long it will take to develop if they do augment. Studies have shown that the longer a person stays on a dopamine agonist, the more likely the medication will augment symptoms.

What are predisposing factors for augmentation?
Higher dosage of dopaminergic medications and low body iron stores (as measured by a ferritin test) are two factors that have been known to increase the chance of augmentation. Studies have shown that individuals with serum ferritin levels below a "mid-normal" level (about 75-100 mcg/L) are more likely to experience augmentation. However, two studies of intravenous iron therapy have now been published[1,2] and support a change in the ferritin treatment-goal to at least greater than 100 mcg/L in RLS patients.

How quickly does augmentation develop?
Augmentation generally does not occur until six months after beginning a course of dopaminergic treatment. It is estimated that the rate of new onset augmentation is roughly 5-10% per year of those taking dopaminergic medication.

How do healthcare providers know whether you have augmentation or purely a worsening of RLS symptoms?
Your healthcare provider should conduct a careful medical history and physical exam to rule out other possible causes of worsening symptoms. The diagnosis of augmentation requires that you 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 your symptoms. RLS symptoms can vary in severity from day to day as well as over time, so just a couple of days of worsening symptoms are not sufficient to diagnose augmentation.

What other conditions are confused with augmentation?
Other factors that can temporarily worsen RLS symptoms must be ruled out by you and your healthcare provider before the diagnosis of augmentation is confirmed.

- Using medications such as sedating antihistamines (diphenhydramine) or anti-nausea medications can worsen RLS symptoms. Examples include many cold remedies and sleep aids such as Benadryl or Tylenol PM. Non-sedating antihistamines include RLS safe alternatives such as Allegra, Claritin, Clarinex and Zyrtec (usually).
- The addition of, or an increase in, antidepressants (exceptions include bupropion and trazodone) or antidopaminergic medications can worsen RLS symptoms.
- Caffeine, alcohol and nicotine should be reduced or discontinued as all can aggravate RLS symptoms.
- A serum iron panel test, which includes serum iron, ferritin, total iron binding capacity (TIBC) and percent iron saturation, should be conducted. A test of your hemoglobin level or complete blood count (CBC) is not an adequate or sensitive measure of your iron status. If your 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, or chronic sleep loss) that diminish the quality or quantity of your sleep can markedly worsen RLS symptoms.

Rebound, which may be confused with augmentation, is the 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 the use of shorter-acting medications such as the short-acting form of carbidopa/levodopa (Sinemet), rather than longer-acting dopamine agonists such as pramipexole (Mirapex) or ropinirole (Requip). Rebound may disturb sleep at the end of the night and may require medication adjustment.

What to do if augmentation develops

If you suspect augmentation, do not discontinue the use of your dopamine medication on your own. Visit your healthcare provider and share your concerns about your worsening RLS symptoms. There is no specific lab test for augmentation, so your physician will need to take a careful history of the progress of your RLS symptoms, as well as review a list of all of your medications, including over-the-counter therapies. After ruling out other possible causes of the worsening of your symptoms, your provider will need to confirm that augmentation is the most likely cause. If your symptoms are significant and your quality of life is diminished, your doctor may suggest you reduce the dosage of the problematic dopaminergic medication or stop taking it. In this case, you may find it very difficult to reduce or eliminate the drug; there are several ways to do so, and your doctor will discuss the best approach for you.

The most common approach involves adding a different class of drug, and once adequate levels of the new drug are achieved, slowly (e.g., over weeks to months) reducing the dose of the dopamine drug (levodopa, ropinirole or pramipexole). One possibility is to substitute an alpha-2-delta ligand such as pregabalin (Lyrica), gabapentin (Neurontin) or gabapentin enacarbil (Horizant, FDA approved for treating RLS). While this approach may be effective, these drugs may be insufficient to control RLS symptoms in the absence of the dopaminergic agents.

An alternate plan involves replacing the dopamine drugs with an opioid, such as methadone or oxycodone. When taken in adequate doses (up to 20–40 mg/day initially if needed) opioids can help the transition from dopamine drugs. You may experience side effects (for example, nausea, constipation or sleepiness), but most people typically do well, and after a few weeks may need only small doses (5–15 mg/day). If necessary, other drugs such as Horizant or Lyrica may then be added to reduce or possibly eliminate the opioids.

A third way to manage augmentation if on a short-acting dopamine agonist is to change to a long-acting dopamine agonist. 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 has been found in one study to have fewer problems with augmentation. That study, however, did not use rotigotine to substitute for pre-existing augmentation as a result of shorter-acting dopamine agonist. So there is no data on whether changing to a long-acting dopamine agonist will reduce the risk of developing further problems with augmentation. If augmentation does develop, then some RLS experts have found that getting patients off the long-acting agents when they are used to treat pre-existing augmentation, is substantially harder.

A final approach is to slowly reduce the dose of the dopamine drug, then take a drug-free holiday of 10 days before reassessing further treatment requirements. Experts suggest that you not reduce ropinirole more than 0.5 mg every three days, or pramipexole more than 0.25 mg every three days. Once you stop the dopamine medication, during the first four days your RLS symptoms will be very severe, and you will likely get almost no sleep. Improvement in symptoms will usually happen by day five or six. During time off the drug, you should maximize non-drug treatments, such as good sleep habits and moderate exercise. Be very cautious about using sedating medications during the first four to five days of the drug-free withdrawal period.

If you are like many patients (especially those with severe augmentation who take high doses of dopamine drugs), you may find it too difficult to eliminate your dopamine medication due to the marked worsening of RLS symptoms on withdrawal. However, if you are able to stop the dopamine drug, as with all of the above approaches which eliminate these agents, reinstating a dopaminergic medication at a later time will often lead to rapid reappearance of augmentation.

To learn more about augmentation and how you can address it, talk with your healthcare provider.

[1] Cho YW, Allen RP, Earley CJ. Clinical efficacy of ferric carboxymaltose treatment in patients with restless legs syndrome. *Sleep Med.* 2016. 25:16-23.
[2] Allen RP, Adler CH, Duc W, Butcher A, Bregman DB, Earley CJ. Clinical efficacy and safety of IV ferric carboxymaltose (FCM) treatment of RLS: A multi-centred, placebo-controlled preliminary clinical trial. *Sleep Med.* 2011. 12:906–913.

RLS
RESTLESS LEGS SYNDROME FOUNDATION

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.

3006 Bee Caves Road | Suite D206 | Austin, Texas 78746 | 512.366.9109
www.rls.org | rlsfoundation.blogspot.com | Discussion Board: bb.rls.org