



# Understanding RLS and Augmentation Frequently Asked Questions

## 1. What is augmentation?

Answer: Augmentation is the worsening of RLS symptoms that occurs after using medications to treat Restless Legs Syndrome (RLS) also known as Willis-Ekbom Disease. Dopamine drugs such as carbidopa/levodopa (Sinemet), pramipexole (Mirapex), ropinirole (Requip) and rotigotine (Neupro) are all medications that can contribute to the development of augmentation.

## 2. Do researchers know the cause of augmentation and is it preventable?

Answer: The underlying cause of augmentation is unknown but higher doses of prescribed dopaminergic medications and low-normal or deficient body iron stores are two factors thought to contribute to the development of augmentation. Using the lowest effective dose of dopamine medications and maintaining a “mid-normal” (at least 75-100 mcg/L) ferritin level may lessen the risk of augmentation.

## 3. How long does it take to develop augmentation?

Answer: If an RLS patient who is known to be stable on their current treatment therapy for at least six months requests more medication, then augmentation should be considered. It is possible to develop augmentation at any time while taking dopaminergic medications, even when taking medications at FDA approved doses for treatment of RLS. Additionally, if an individual experienced augmentation and then returned to a dopaminergic treatment the patient may augment much faster the second time when taking dopaminergic medications.

## 4. Why are dopamine medications still used in the treatment of RLS when there is a known risk of augmentation?

Answer: Dopamine medications used at or below FDA approved doses have provided excellent relief for RLS sufferers. All individuals with RLS using dopaminergic therapy must be aware of the early indications of augmentation.

## 5. Can rotigotine (Neupro patch) cause augmentation?

Answer: Rotigotine is a dopamine agonist and therefore can cause augmentation. Rotigotine may, however, result in less augmentation than other dopamine agonists. It is unclear whether rotigotine just masks the appearance of augmentation because of the constant 24-hour delivery of the medication or whether it truly reduces the risk of augmentation.

## 6. Do the extended release forms of Mirapex (pramipexole), Requip (ropinirole) have less augmentation potential?

Answer: The extended release forms of the dopamine agonists pramipexole EX and ropinirole XL have not been evaluated in controlled studies to make a determination of the risk of augmentation. As seen with rotigotine, when you provide dopamine agonist coverage around the clock, it may take years for underlying changes in the brain dopamine to finally break through and cause symptoms. Some RLS experts have noted that long-acting dopamine agonists are being used more frequently by healthcare providers as a strategy for treating the progressive worsening of the RLS symptoms (i.e., augmentation) that is a result of the short-acting dopamine agonist use. Although the 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. It is substantially more difficult to get patients off long-acting dopamine agonists than it is with the short-acting agents.

## 7. Is it possible to develop augmentation when taking Horizant (gabapentin enacarbil)?

Answer: Gabapentin enacarbil (Horizant) is the only FDA-approved medication in the class of drugs referred to as “alpha-2-delta ligands”. These medications do not directly affect the dopamine system. Gabapentin enacarbil is an extended-release medication used for treatment of moderate to severe RLS. Gabapentin (Neurontin) and pregabalin (Lyrica) are prescribed off label for the treatment of RLS symptoms. At this time, the clinical experience of RLS experts indicates alpha-2-delta ligand medications do not cause a significant degree of augmentation.

## 8. What tests are available for physicians to screen for the development of augmentation?

Answer: There are no diagnostic tests to aid physicians in the diagnosis of augmentation, although there are formal diagnostic criteria and a series of recommended clinical screening questions (below). Diagnosis is made by clinical history, accompanied by a thorough medical examination and evaluation of symptoms to rule out other possible causes for a worsening of RLS symptoms while taking a prescribed dopaminergic medicine that previously managed RLS symptoms. It is important to note, changes in symptoms must be consistent and not a fluctuation in daily RLS symptoms for a diagnosis of augmentation to be made.

The International Restless Legs Syndrome Study Group (IRLSSG) recommends four questions for physicians to screen for augmentation:<sup>1</sup>

1. Do RLS symptoms appear earlier in the day than when the drug was first started?
  2. Are higher doses of the drug now needed to control the RLS symptoms compared to the original effective dose?
  3. Has the intensity of symptoms worsened since starting the medication?
  4. Have symptoms spread to other body parts (e.g., arms)
1. since starting the medication?

## 9. Do opioids cause augmentation? Is tramadol considered a dopamine drug?

Answer: Tramadol is the only opioid that has been reported to cause augmentation. Tramadol is a mixed opioid with dopaminergic properties. None of the other opioids have been reported to cause augmentation.

## 10. How difficult is it for a doctor to distinguish between the development of augmentation and the worsening of RLS due to the natural progression of the disease?

Answer: This distinction can be challenging. A doctor should watch for one or more of these indications of augmentation:

1. Patient request for a dose increase of a dopaminergic medication to control RLS symptoms
  2. Reported breakthrough of RLS symptoms accompanied
1. by an increase in symptom intensity
  3. Symptoms occurring 24 hours a day - both morning and afternoon
  4. Requesting medication doses earlier in the day

## 11. How can I stop augmentation from occurring?

Answer: Avoidance of dopamine agonists and levodopa for the treatment of RLS will prevent augmentation. However, these medications can be useful in the treatment of RLS. If these medications are needed, taking the lowest possible effective dose and keeping ferritin level above 75-100 mcg/L are the best preventive measures. It is important to remember that the goal of therapy is to “treat to be comfortable” during times of immobility rather than the necessity of eliminating all RLS symptoms.

<sup>1</sup>2015 Summary for the prevention and treatment of RLS/WED Augmentation a combined task force of the IRLSSG, EURLSSG and the RLS Foundation. <http://irlssg.org/summary/> Accessed November 30, 2015

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