Restless Legs Syndrome Foundation
Legislative Agenda
115th Congress, 2nd Session

About The Foundation

The Restless Legs Syndrome Foundation is a nonprofit §501(c)(3) organization dedicated to improving the lives of men, women, and children living with this often-devastating neurological condition. The Foundation works to increase awareness, improve treatments, and support research to find a cure. From a few volunteers meeting in a member's home in 1992, the Foundation has grown steadily; it now has members in every state, local support groups, and a track record that includes over $1.6 million provided to support fundamental research.

About Restless Legs Syndrome

Restless legs syndrome (RLS) is essentially an irregular biological drive, like hunger or thirst, that forces affected individuals to keep moving, thus reducing their ability to rest. Patients with this disease experience a deep, viscerally-irritating sensation in the legs that continues to increase until they are literally forced to move their legs or get up and walk (and the sensation abates so long as the individual keeps moving). RLS is best characterized as a neurological sensory-motor disorder with symptoms that are triggered from within the brain itself. It is estimated that up to 5 to 7 percent of the U.S. population may have RLS, of which half will have moderate to severe forms of the disease. RLS impacts men, women, and children, though it is 3 to 4 times more common in women and twice as common in older Americans.

Due to the inability to sleep and work, RLS can cause disability, depression, and suicidal ideation (as well as increased risk for co-morbid conditions such as heart attack, stroke, and Alzheimer's). There is no cure, and the current standards of care features several medications, which do not provide life-long coverage. One of the established effective treatment options for this disease is low-dose opioid medications. These are commonly used when other drug classes have failed. RLS-expert experience indicates that the dose of opioids used to manage RLS tends to be significantly lower than is used to treat chronic pain and to work effectively without addiction or drug tolerance issues for many years.

Legislative and Policy Priorities

- The needs of RLS patients who depend on regular use of low-dose opioids to manage their disease must be taken into account in crafting legislation, policy, and regulations aimed at drug abuse that arises from large doses used (or misused) in the treatment of chronic pain. Any emerging proposals or rules must provide safe harbor for the low dosage effective in treating RLS, and we encourage an official update to the U.S Pharmacopeia to formally recognize and protect this specific form of utilization moving forward.
- The National Institutes of Health (NIH) currently coordinates a modest, but meaningful $6 million research portfolio in RLS through the National Institute of Neurological Disorders and Stroke and related Institutes and Centers. Please support a $2 billion funding increase for NIH to bring total NIH funding up to $39.3 billion and to facilitate continued growth in the RLS portfolio.
- Please support the Congressionally Directed Medical Research Program at the Department of Defense (DoD) and oppose any effort to eliminate or restrict important ongoing research activities. Further, please continue to include "sleep disorders" as a category eligible for study through the DoD's Peer-Reviewed Medical Research as Congress completes the FY 2019 Defense Appropriations Bill.

Many federal, state, and private health coverage policies affecting the practice of pain management require that patients:

1) Are tried on other recognized chronic-pain management treatment before starting opioids.
2) Secure an opioid prescription through certified pain management professionals.
3) Have their medications reduced over time (or provided in minimal quantities).
4) Generally, limit access to opioids.

While valid for chronic pain treatment, these policies are not appropriate for evaluating the use of opioids to treat RLS. RLS is not related to chronic pain. RLS is a neurological disease impacting sleep and should be managed by a neurologist or sleep disorders specialist. Moderate to severe RLS is almost always a life-long disease. When low-dose opioids are indicated to treat RLS, the condition specifically requires that opioid medications are not reduced over time. Please work with your colleagues in Congress to ensure that RLS patients retain access to physician-directed care and treatment.

Restless Legs Syndrome Foundation
The Opioid Crisis and Patient Access to Effective Therapy
Statement of Principles

About The Foundation

The Restless Legs Syndrome Foundation is a nonprofit §501(c)(3) organization dedicated to improving the lives of men, women, and children living with this often-devastating neurological condition. The Foundation works to increase awareness, improve treatments, and support research to find a cure. From a few volunteers meeting in a member's home in 1992, the Foundation has grown steadily; it now has members in every state, local support groups, and a track-record that includes over $1.6 million provided to support fundamental research.

Restless Legs Syndrome and Opioid-Based Therapy

Restless legs syndrome (RLS) causes unpleasant or uncomfortable sensations in the legs together with an uncontrollable urge to move them. The National Institute of Neurological Disorders and Stroke housed within the National Institutes of Health describes RLS as a neurological sensory-motor disorder whose symptoms are produced within the brain. It is estimated that up to 5 to 7.5 percent of Americans may have RLS.

RLS can significantly disrupt sleep, thus dramatically impacting work and quality of life. Equally important, the profound sleep loss may put these individuals at risk for developing heart attacks, strokes and even Alzheimer's disease. There is currently no cure for this disease and any symptomatic relief achieved with medications is not guaranteed to work forever. Therefore, all potential treatment options that are known to be effective treatments for RLS, need to be available to the individual. Opioid medications are a recognized, effective treatment for managing RLS when alternative first-line medications do not work or become ineffective. Clinical studies and the experience of RLS-experts indicate that the average total-daily dose of opioids used to manage RLS is significantly lower than doses prescribed to treat chronic pain. Research has also demonstrated that utilization of these therapies to manage RLS does not show clinical indications of addiction or drug tolerance.

Due to the devastating nature of RLS, if patients were to lose access to these therapies, they would also lose the ability to effectively manage their disease.

Key Issues for Policymakers:

- About one in thirty three Americans have a chronic un-abating, moderate-to-severe form of RLS that, if left untreated, will cause unthinkable devastation in their lives.
- This disease is a neurologically-based sleep disorder, and therefore, management should not fall under the exclusive purview of Pain-management specialists when opioids are part of treatment. The underlying neuropathology in RLS is quite different from that associated with chronic pain. Therefore, long-term outcomes for opioid use in RLS should not be extrapolated from their use in chronic pain.
- The total daily dose of opiates commonly used to treat RLS is often lower than that used in managing chronic pain, which dramatically reduces the risk of tolerance and dependency.
- RLS patients and their physicians need assurance that regulations designed to curb abuse of opiates do not inadvertently penalize patients suffering from a serious disease who have exhausted other treatments. Regulations that seek to limit refills, require frequent doctors' visits and co-payments, or erect other barriers can have a devastating effect on RLS patients with no countervailing public health or safety benefit.
- Any legislation, policy, or regulation must take into account the specific needs of RLS patients and not paint them with the same broad brush as other communities utilizing (and often struggling with) opioid-based treatments.

RESTLESS LEGS SYNDROME FOUNDATION

March 27, 2018

The Honorable Greg Walden
Chairman
House Energy and Commerce Committee
2185 Rayburn House Office Building
Washington, DC 20515

The Honorable Frank Pallone
Ranking Member
House Energy and Commerce Committee
237 Cannon House Office Building
Washington, DC 20515

The Honorable Michael Burgess
Chairman
Health Subcommittee
2336 Rayburn House Office Building
Washington, DC 20515

The Honorable Gene Green
Ranking Member
Subcommittee on Health
2470 Rayburn House Office Building
Washington, DC 20515

Dear Chairmen Walden and Burgess and Ranking Members Pallone and Green:

Thank you for your leadership on combating the opioid crisis. While you debate the Committee's response to this epidemic, the Restless Legs Syndrome (RLS) Foundation asks that you protect the needs of patient communities who depend on appropriate access to low total daily dose opioid therapies to manage their debilitating condition.

The Restless Legs Syndrome Foundation is a nonprofit §501(c)(3) organization dedicated to improving the lives of men, women, and children living with this often-devastating neurological condition. The Foundation works to increase awareness, improve treatments, and support research to find a cure.

Many in our community utilize low total daily dose opioid medications to treat the underlying neuropathology issues associated with this condition. RLS is not a chronic pain condition, and studies have shown that appropriate access to these therapies allows patients to live productive lives without an increased risk of developing opioid use disorder. For your review, we have included one such study recently conducted by the Mayo Clinic, as well as our Foundation's statement of principles.

Thank you again for your leadership on this issue. If we can be of any assistance as you to continue to deliberate, please contact the Foundation's Washington Representatives, Dale P. Dirks and Peter Herzog, at herzog@hmcw.org or (202) 544-7499.

Sincerely,

Karla M Dzienkowski

Karla Dzienkowski
Executive Director

RESTLESS LEGS SYNDROME FOUNDATION

February 21, 2018

The Honorable Thad Cochran
Chairman
Committee on Appropriations
Subcommittee on Defense
U.S. Senate
Washington, D.C. 20510

The Honorable Richard Durbin
Ranking Member
Committee on Appropriations
Subcommittee on Defense
U.S. Senate
Washington, D.C. 20510

The Honorable Kay Granger
Chairman
Committee on Appropriations
Subcommittee on Defense
U.S. House of Representatives
Washington, D.C. 20515

The Honorable Pete Visclosky
Ranking Member
Committee on Appropriations
Subcommittee on Defense
U.S. House of Representatives
Washington, D.C. 20515

Dear Chairmen Cochran and Granger, and Ranking Members Durbin and Visclosky:

Thank you for your leadership of the Defense Appropriations Subcommittees and your commitment to critical medical research activities. I write you today on behalf of constituents suffering from Restless Legs Syndrome (RLS) across the country to express our gratitude for ensuring that "sleep disorders" will remain eligible for study through the Department of Defense Peer Reviewed Medical Research Project in FY 2018, and ask that as you finalize FY18 appropriations you continue to list sleep disorders as conditions eligible for study. As you and your colleagues begin work on appropriations for FY 2019, please continue to support the inclusion of "sleep disorders" as a condition eligible for study through the PRMRP.

Insufficient sleep (due to sleep disruption and frank sleep deprivation) as well as circadian misalignment (i.e., being awake when the brain wants to sleep, for example, from jet lag and night missions) is rampant in the military and has significant negative impacts on force readiness. Congress has historically included sleep disorders in the list of eligible conditions for research under this program and researchers compete successfully each year.

On behalf of the RLS and sleep disorders community, thank you again for your continued support and for your consideration of this request.

Sincerely,

Karla M Dzienkowski

Karla Dzienkowski
Executive Director

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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 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 shown 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 from the short-acting dopamine agonists 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.

The RLS Foundation does not endorse or sponsor any goods, products or services. This publication has been reviewed and approved by our Scientific and Medical Advisory Board. Laypeople are warned against making any changes in their treatment based on this information without consulting their healthcare provider.

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. The organization's goals are to increase awareness, improve treatments and, through research, find a cure for restless legs syndrome.

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