Current Treatments for Restless Leg Syndrome

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Program Overview:

To provide participants with an understanding of current treatments for restless leg syndrome.

OBJECTIVES:

After completing this program, participants will be able to:

- Describe the symptoms of RLS
- Outline the factors involved in a differential diagnosis of RLS
- Review non-pharmacologic and behavioral treatments for mild RLS symptoms
- Differentiate between treatments for secondary RLS and those for primary RLS
- List first-line medications for moderate to severe symptoms
- Understand augmentation and rebound effects with certain medications
- List medications that are appropriate for mild or intermittent RLS symptoms
Overview

Restless legs syndrome or restless leg syndrome (RLS) is a common neurological movement disorder that affects about 10% of adults (approximately 12 million Americans). The disorder is described as a strong or uncontrollable urge to move the legs, sometimes suddenly, in an effort to stop unpleasant sensations that occur at night or at times of rest. The sensations are described in terms such as crawling, pins and needles, tingling, prickly, painful, or worming. Movement sometimes alleviates the symptoms but they tend to recur. The sensations may rarely occur on the arms, as well, and often there is a family history of RLS. While not life-threatening, RLS can make life an agony for the people who live with it.

RLS symptoms have been associated with a variety of risk factors including increased age, chronic kidney disease, diabetes, iron deficiency, Parkinson’s disease, peripheral neuropathy and pregnancy. Given the current increasing rates of at least four of these risk factors in the US population (median age, obesity, lack of exercise, diabetes), we can safely predict that RLS prevalence will increase dramatically in the coming years.

Approximately one third of patients with RLS experience symptoms prior to the age of 18, with a genetic predisposition occurring more frequently in those who experience early symptoms. The prevalence of RLS increases with age and is more common in females.

RLS may be considered a primary condition, or it may occur secondary to iron deficiency, renal failure, rheumatoid arthritis, diabetes, Parkinson’s disease, pregnancy, or with the use of certain medications. Diagnosis is clinical and includes an urge to move the legs accompanied by uncomfortable sensations (paresthesias), urges that occur while at rest, improvement of symptoms with physical activity, and symptoms that worsen in the evening or at night. RLS typically causes sleep disturbances and is often associated with depression and anxiety, all of which can have a negative effect on quality of life.

Pathophysiology

The exact cause of RLS is not known but is clearly associated with disruptions of dopaminergic function in the brain. Iron deficiency is considered an important contributory factor in RLS as iron is a cofactor in dopamine production. The enzyme tyrosine hydroxylase is essential in the production of dopamine from tyrosine and uses iron as a cofactor. A shortage of iron would naturally inhibit this critical conversion.

Although the relationship between iron and dopamine function within the central nervous system is not well understood, abnormalities in dopamine pathways often result in the involuntary movements found in Parkinson’s disease, a condition related to RLS.

Symptoms

Patients have a difficult time characterizing the sensations associated with RLS and speak of crawling, aching, throbbing or other indescribable feelings in their legs, or they may say they simply have a need to move.

Most people with RLS have mild or intermittent symptoms; only about 30 percent of people with RLS in a recent study experienced moderate to severe symptoms. Clinical trials tend to classify symptoms as severe when they are experienced 15 days or more per month.

Periodic limb movements of sleep (PLM or PLMS) are repetitive movements, mostly of the legs, that occur every 20-40 seconds. They are often present in RLS patients and can cause significant sleep disturbances and wakefulness. Approximately 85 percent of individuals with
RLS experience PLM, but relatively few people with PLM also have RLS.\textsuperscript{10} Treatments that effectively reduce RLS symptoms typically also reduce PLM episodes.

RLS can have a serious impact on quality of life\textsuperscript{9} and is associated with anxiety or depression.\textsuperscript{11} Insomnia and its consequences are common, and patients report problems both with falling and staying asleep. Many people with RLS have trouble performing well at work as a result of poor concentration and impaired memory, and even report difficulty with their relationships due to sleep deprivation. Sitting for long periods during flights can also trigger symptoms, so travel can become difficult.

Many people experiencing RLS symptoms do not seek medical help because they believe their symptoms will not be taken seriously or that they are untreatable. Adding to the confusion are some doctors who attribute RLS symptoms to stress, nervousness, aging or some other condition.\textsuperscript{8}

The international restless legs study group (RLSG) has produced a severity scale\textsuperscript{12}, which can be helpful in assessing patients’ symptoms and their impact on daily life. This validated, ten-question patient survey can be used both to quantify the severity of RLS and the patient’s response to therapy.

**Differential Diagnosis**\textsuperscript{1, 13}

The diagnosis of Restless Legs Syndrome is based on clinical criteria. In 2003, the International Restless Legs Syndrome Study Group developed four criteria\textsuperscript{13}, all of which must be met before the diagnosis is made:

1. An urge to move the leg, usually accompanied or caused by uncomfortable and unpleasant sensations in the legs
2. The urge to move or unpleasant sensations beginning or worsening during periods of rest or inactivity, such as lying or sitting
3. The urge to move or unpleasant sensations partially or totally relieved by movement, such as walking or stretching, for at least as long as the activity continues
4. The urge to move or unpleasant sensations worse in the evening or night than during the day or only occurring in the evening or night

Diagnosis begins with a focused history and physical examination followed by a laboratory analysis, which may identify conditions with similar symptoms or the underlying cause of the RLS. The history will include frequency and severity of symptoms, previous treatments for RLS, current medications, family history of RLS, and use of caffeine, alcohol or tobacco. While not necessary for the diagnosis, laboratory tests that include a basic metabolic panel and ferritin level can help eliminate secondary causes.

The differential diagnosis of RLS includes nocturnal leg cramps, claudication, peripheral neuropathy and akathisia (See Table 1).

<table>
<thead>
<tr>
<th>Condition</th>
<th>Distinguishing Features</th>
</tr>
</thead>
<tbody>
<tr>
<td>Akathisia:</td>
<td>An internal desire to move, most commonly associated with the use of neuroleptic medicine; desire to move not necessarily associated with discomfort in the legs; symptoms are not worse at night</td>
</tr>
<tr>
<td>Nocturnal leg cramps</td>
<td>Sudden involuntary muscle contractions; palpable tightening of the leg muscles</td>
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<td>---------------------</td>
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<tr>
<td>Peripheral neuropathy</td>
<td>Etiologies include trauma, nerve compression, diabetes, nutritional disorders, infections, others; generally causes sensory disturbance; may or may not be more noticeable at night; not typically relieved by activity</td>
</tr>
<tr>
<td>Peripheral vascular disease</td>
<td>Primarily a consequence of atherosclerosis; cramping-type pains that are exacerbated by activity and improve with rest; symptoms not worse at night</td>
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</table>

The existence of PLMS as a symptom supports the diagnosis of RLS. Children and adults can be diagnosed using the same four criteria, although children will voice descriptions of leg discomfort using age-appropriate words connoting “pain.” In young children, it might be helpful to ask them to use numbers or pictures to describe and locate the pain. In addition, children with the condition may also have sleep disturbances, a biologic parent or sibling with RLS, or a polysomnographic-documenting PLMS index of 5 or more per hour of sleep.\(^\text{13}\)

### Treatments for RLS

**Secondary RLS\(^\text{1}\)**
RLS may be secondary to other conditions, and symptoms may resolve as the underlying condition is treated:

- In iron deficiency (with or without anemia), RLS symptoms may be relieved with supplemental iron although it is not beneficial in individuals with ferritin levels above 50 ng per ml.\(^\text{1}\)
- RLS is common during pregnancy (especially during the third trimester) but symptoms typically resolve after delivery.
- In chronic kidney disease, patients who undergo a kidney transplant may see their RLS symptoms resolve.

**Behavioral Changes /Non-pharmacologic Therapies\(^\text{1}\)**
For patients with mild or intermittent symptoms, lifestyle modifications may eliminate or reduce symptoms to a tolerable level, although few studies on the efficacy of such changes are available. A few small studies have shown that RLS symptoms improved with an aerobic and strength training program and with supplemental iron in patients who are iron deficient. Activities that stimulate mental function may provide some relief; gentle stretching, massage and warm baths may also lessen or alleviate symptoms. Good sleep hygiene, including fixed bedtime and awakening times, getting the proper amount of sleep, and avoiding daytime naps, as well as the elimination of substances that might exacerbate symptoms (antidepressant medications, caffeine, nicotine, and alcohol) are typically recommended to patients before a trial of medications is started.

**Treatment Goals and Medications Used in RLS\(^\text{1, 14}\)**
Some medications have been shown to intensify symptoms of RLS and, when they are discontinued, symptoms may improve. Medications that may worsen symptoms include lithium, antihistamines, caffeine, dopamine agonists including neuroleptics and antiemetic’s, selective serotonin reuptake inhibitors, and tricyclic antidepressants. In one study, selective serotonin reuptake inhibitors were shown to increase PLMS while bupropion (Wellbutrin) decreased leg movements. This information may be helpful in the selection of antidepressants for RLS patients.

A cure is possible only for secondary RLS when and if the underlying cause can be discovered and eliminated as a trigger. The goal of medication therapy, then, is to alleviate RLS symptoms. Since medication therapy for RLS is typically long-term and is sometimes accompanied by significant side effects, it should only be initiated when benefits outweigh the risks and non-pharmacologic therapies have been tried. Even then, some patients may require intermittent treatment or medications to be taken only on an as-needed basis. Timing of the medication may also be important since symptoms occur mainly at night.

Several classes of medications have been shown to improve RLS symptoms in randomized, controlled trials. They include dopamine agonists, carbidopa/levodopa, gabapentin, opioids, and benzodiazepines. In some cases, more than one class of medication may be used concomitantly to relieve symptoms.

**Dopamine agonists**

Dopamine agonists increase the level of dopamine in the brain and may provide relief for patients with more severe, daily symptoms of RLS. They are currently the most common medication used to treat RLS and make up approximately 90% of prescriptions. The group includes non-ergotamine dopamine agonists, pramipexole and ropinirole, and ergotamine-based dopamine receptor agonist, pergolide, all of which have been effective in reducing symptoms in randomized, controlled studies when compared to a placebo. Adverse effects of dopamine agonists include nausea, orthostasis, and daytime drowsiness; augmentation may occur with daily dosing. Although they have not been reported in RLS patients using dopamine agonists (only in Parkinson’s patients), impulse control symptoms such as gambling, excess spending and eating, and increased sexual desire may occur.

**Non-ergot-derived dopamine agonists**

Non-ergot dopamine agonists are considered the drugs of choice for moderate to severe daily RLS because of their safety profile and FDA-indicated status.

**Ropinirole** (Requip®, Requip XL®)

**Overview**

In May 2005, ropinirole (Requip) was the first drug to receive FDA approval for the treatment of RLS. Requip is an orally administered nonergot-based dopamine agonist that has been shown to improve symptoms of primary RLS in several double-blind, placebo-controlled, randomized trials.

**Mechanism of action**

The mechanism of action for Requip in RLS is unknown but evidence suggests involvement with the primary dopaminergic system. It exhibits specificity and affinity for D2 and D3 dopamine receptor subtypes, with more affinity for the D3.

**Pharmacokinetics/pharmacodynamics**

After oral administration, ropinirole is absorbed rapidly and reaches peak concentration in 1-2 hours. Clinical studies have shown that over 88% of a radiolabeled dose is recovered in urine. Its absolute bioavailability is 55%, which indicates significant metabolism occurs.
before it reaches circulation. The bioavailability from a tablet compared to oral solution is 85%. Absorption of ropinirole is not affected by food but its $T_{\max}$ is increased by 2.5 hours and its peak serum concentration is decreased by approximately 25% when taken with a high fat meal. The elimination half-life of ropinirole is approximately 6 hours. Ropinirole is metabolized through hydroxylation and N-despropylation to N-despropyl and hydroxy metabolites, which are rapidly glucuronidated. Less than 10% of the drug is eliminated in the urine in its unchanged form. The predominant metabolite in urine (40%) is N-despropyl ropinirole followed by the carboxylic acid metabolite (10%) and the glucuronide of the hydroxy metabolite (10%).

Dosages and Formulations
Requip is available as tablets in the following strengths: 0.25 mg, 0.5 mg, 1 mg, 2 mg, 3 mg, 4 mg, and 5 mg.

Requip XL is an extended-release form of Requip that is available in 2 mg, 4 mg, 6 mg, 8 mg and 12 mg tablets. It has not been studied in RLS patients but lower starting doses and more gradual titration is recommended in RLS than in Parkinson’s patients.

Requip therapy is typically started at a low dose and gradually titrated upward, as tolerability allows, achieving the optimum effect. It is not necessary to adjust the initial dose based on gender, weight, or age. In patients over the age of 65, oral clearance of ropinirole is reduced by 15% when compared to younger patients. Since the dosage of ropinirole is adjusted upward based on individual patient response, no adjustment of dose is necessary for older patients.

In general, RLS patients should be started on 0.25 mg of Requip once daily, 1-3 hours before bedtime. The dose may be titrated upward based on its effect on symptoms and how well it is tolerated. After 2 days, the dose is increased to 0.5 mg once daily and then to 1 mg once daily at the end of the first week. The dose may be increased by 0.5 mg daily each week until the 6th week when it can be increased to 4 mg once daily. At the 4 mg once daily dose, patients may discontinue Requip without a taper.

Contraindications
Requip is contraindicated for patients with known hypersensitivity (urticaria, angioedema, rash or pruritus) to ropinirole or any of its excipients.

Complicating factors and adverse effects
Patients should be warned about drowsiness and even falling asleep while engaged in activities of daily living while taking Requip. Syncope has been reported in approximately 1% of RLS patients taking ropinirole during clinical trials. Dopamine agonists appear to impair blood pressure regulation that can lead to postural hypotension, although the incidence was low in clinical trials with RLS patients. Postural hypotension may occur more frequently during the early period of therapy or with an increase in dose.

Patients with Parkinson’s disease have a higher risk of developing melanoma than the general population. Since it is not known whether the increased risk is due to Parkinson’s or the drugs used to treat the disease, all patients taking Requip should be advised to monitor for melanomas regularly.

Augmentation of symptoms (earlier onset of symptoms daily, increased symptoms or spread of symptoms to the arms) has occurred in RLS patients taking dopaminergic medications but has not been studied specifically for patients taking Requip. Ropinirole may be excreted in breast milk and has been shown to have adverse effects on embryo-fetal development.
**Pramipexole** (Mirapex®, Mirapex ER®) 21, 22

**Overview**

Pramipexole is a non-ergot dopamine agonist used primarily in the treatment of Parkinson’s disease that was approved by the FDA for treatment of moderate-to-severe primary RLS in 2006. Mirapex ER, an extended release form of pramipexole approved by the FDA for use in Parkinson's patients in February 2010, is not indicated for the treatment of restless legs syndrome.

**Mechanisms of action**

Pramipexole binds to the D₂ and D₃ dopamine receptors in the brain but has no significant effect on other serotonergic receptor families. Its exact mechanism of action in RLS is not understood but it is believed to be related to its ability to stimulate dopamine receptors in the brain.

**Pharmacokinetics/pharmacodynamics**

Compared to ropinirole, pramipexole has a slower onset of action and a longer half-life. 18

It is absorbed rapidly and reaches peak concentrations in approximately 2 hours.

Pramipexole absorption is not affected by food although the $T_{\text{max}}$ is increased by about an hour when it is taken with a meal. The absolute bioavailability of pramipexole is greater than 90% and it is metabolized to a minimal extent — most of the pramipexole dose is eliminated in urine (90%) as unchanged drug. The elimination half-life is roughly 8 hours in healthy volunteers and 12 hours in elderly volunteers.

**Formulations and dosages**

Mirapex is available in 0.125 mg, 0.25 mg, 0.5 mg, 0.75 mg, 1 mg and 1.5 mg tablets. The recommended initial dose of Mirapex for RLS is 0.125 mg once daily 2-3 hours before bedtime. The dose may be increased gradually (every 4-7 days) to 0.5 mg. There is no evidence that increasing the dose beyond 0.5 mg provides any benefit to RLS patients. If patients need to discontinue use of the drug, the dose should be tapered gradually to avoid rebound and augmentation.

Because therapy with pramipexole is initiated at a low dose and titrated upward to reach the optimum therapeutic dose that is tolerable, no adjustment of the initial dose based on gender, weight, age or race is necessary. Patients with renal insufficiency may be unable to eliminate pramipexole efficiently and may require dose adjustment.

**Contraindications**

Mirapex is contraindicated in patients who have demonstrated hypersensitivity to pramipexole or any of the drug’s excipients.

**Complicating factors and adverse effects**

As with ropinirole, patients should be aware that they may experience extreme daytime drowsiness or even fall asleep during their daily activities. 22 Patients taking pramipexole may experience orthostatic hypotension, especially during the initial up-titration phase. RLS patients taking pramipexole may experience hallucinations or intense sexual urges or urges to gamble, although these are very rare. Pramipexole may be excreted in breast milk. Rebound may occur in RLS patients who are suddenly withdrawn from Mirapex. Augmentation may also occur and may increase with increasing length of exposure to the medication.

**Rotigotine** (Neupro)
Neupro, a short-acting dopamine agonist administered via a skin patch delivery system, was recalled by its manufacturer, Schwarz Pharma, in April 2008. Neupro was recalled because there were reports that rotigotine crystals were forming in the patches, which reduced their clinical performance.

**Ergotamine dopamine agonists**

Ergotamine dopamine agonists, including cabergoline (Dostinex) and pergolide (Permax) are effective in reducing RLS symptoms but are not FDA-indicated for RLS due to their poor safety profile. Pergolide was removed from the market by the manufacturer in 2007 after studies showed that it significantly increased rates of heart valve damage. Cabergoline remains on the market but is approved by the FDA only for treatment of prolactimonas.

**Carbidopa/levodopa** (Sinemet CR®, Sinemet®)

Overview
Levodopa, a dopamine precursor, is often combined with carbidopa, which blocks the peripheral breakdown of levodopa. Carbidopa/levodopa has been shown to be effective for RLS symptoms. The benefit of this combination is that it has a rapid onset of action that makes it especially useful in patients with intermittent RLS symptoms. The carbidopa/levodopa combination is mainly prescribed for Parkinson’s disease but has been used effectively to treat RLS symptoms. The few clinical trials with RLS patients have demonstrated its effectiveness at improving sleep duration and quality, quality of life, and severity of RLS symptoms and periodic limb movements during sleep when compared with placebo.

Not long ago, levodopa was proposed as the gold standard for RLS treatment due to its efficacy. However, long term use of levodopa is associated with a worsening of RLS symptoms, especially early morning rebound and augmentation. For this reason, it has fallen out of favor for daily, long-term use. It may still be useful in patients with intermittent symptoms or on an as-needed basis for occasional symptoms.

Mechanisms of action
Dopamine does not cross the blood-brain barrier; but levodopa, which is a dopamine precursor, does cross the blood-brain barrier and is presumed to be converted to dopamine in the brain.

Pharmacokinetics/pharmacodynamics
When levodopa is administered orally, it is rapidly decarboxylated to dopamine in the body so only a small portion of it is available to the central nervous system in its unchanged form. Carbidopa acts as an inhibitor of aromatic amino acid decarboxylation and thereby reduces the amount of levodopa required to produce the desired response by 75%, and increases plasma levels and half-life of levodopa. Carbidopa itself does not cross the blood-brain barrier and does not affect the metabolism of levodopa within the central nervous system. The incidence of nausea and vomiting is less with carbidopa/levodopa than with levodopa alone.

When Sinemet CR is administered with food, the availability of levodopa increases by about 50% and its peak concentration increases by about 25%. The half-life of levodopa may be prolonged after Sinemet CR because of continuous absorption. In elderly patients, one dose of Sinemet CR compared to one dose of Sinemet produces a longer mean time-to-peak concentration of levodopa (2 hours compared to 0.5 hours), and the average trough levels of levodopa at steady state were about 2 fold higher with CR than with standard Sinemet.
Formulations and dosages
Sinemet CR is supplied as sustained-release tablets in two strengths: a 25mg carbidopa/100 mg levodopa tablet, and a 50 mg carbidopa/200 mg levodopa tablet. Sinemet is available in 25 mg carbidopa/100 mg levodopa tablets, 25 mg carbidopa/250 mg levodopa tablets and 10 mg carbidopa/100 mg levodopa tablets.

The recommended dose of carbidopa/levodopa in RLS is Sinemet 25 mg/100 mg or Sinemet CR 25 mg/100 mg usually taken one hour before the onset of symptoms. If effective on the first night of use at the lowest dose, it may be used on an intermittent or as-needed basis. It may also be useful to administer the lowest dose as a therapeutic trial for patients in whom a diagnosis of RLS is in doubt.

Contraindications
Nonselective MAO inhibitors must be discontinued at least two weeks prior to starting therapy with Sinemet or Sinemet CR. Sinemet or Sinemet CR may be used concomitantly with an MAO inhibitor with selectivity for MAO type B, (selegiline HCL, for example). Sinemet and Sinemet CR are contraindicated in patients with narrow-angle glaucoma and with any known hypersensitivity to components of the drug. Sinemet and Sinemet CR should not be used in patients with suspicious skin lesions or a history of melanoma. Sinemet and Sinemet CR may be excreted in human breast milk.

Complicating factors and adverse effects
Patients taking Sinemet CR may develop dyskinesias more frequently than those taking Sinemet, which may require a reduction in dose. Sinemet and Sinemet CR may cause such mental disturbances as suicidal thoughts and depression, which are thought to be due to the increase of dopamine in the brain. Other side effects include gastrointestinal upset, muscle weakness, somnolence and headache. Augmentation may occur in as many as 80% of patients with RLS receiving daily dosing.

Augmentation

Augmentation refers to a worsening of RLS symptoms due to medications, most often as:
- a shifting of the onset of symptoms to earlier in the day
- an increase in intensity of symptoms
- extension of symptoms to additional areas of the body
- a shorter rest period before symptoms begin
- a reduced period of relief with treatment
- worsening of leg movements while awake

Augmentation occurs more frequently with the use of levodopa than with dopamine agonists.

The management of augmentation in RLS is an important aspect of treatment. It may be difficult to determine whether augmentation is due to effects of a medication or to changes in a patient’s lifestyle. Furthermore, determining the point at which symptoms warrant a change in medication is not easy and is usually based on how symptoms affect a patient’s quality of life, changes in daily activities, treatment dose or timing of treatment, dosing of any concomitant medications, or any other related factors deemed disruptive by the patient.

Several factors may mimic augmentation and must be differentiated from true augmentation before medication is changed. Changes in a patient’s physical activity levels, addition of other medications that may worsen RLS symptoms, or iron deficiency should all be investigated. Since low ferritin levels (less than 50 μg/L) are associated with worsening RLS symptoms, a laboratory analysis of the patient’s serum ferritin would confirm or eliminate this factor.
Only after eliminating all augmentation mimics should a change in medication be undertaken. An initial approach involves testing the patient’s current dopaminergic medication by adding an additional dose or dividing the current dose. Another trial is to switch from a shorter-acting dopaminergic drug to a longer-acting one, from levodopa to a dopamine agonist, for example. If neither of these changes is effective, a change from a dopamine agonist to an opioid or antiepileptic medication may be effective.

Reducing the dose of a dopamine agonist will often reduce symptoms to pretreatment levels, although a worsening of symptoms may occur initially. To ameliorate this effect, the dopamine agonist may be combined with a second medication, such as an opioid. If all else fails, sometimes removing all drugs may show that the problem is more related to the natural worsening of RLS symptoms over time rather than true augmentation.

Nondopaminergic Medications
These medications are useful if there is a contraindication to the use of dopaminergic drugs, if they can treat a comorbid condition in addition to RLS, if dopaminergic drugs are not well tolerated or as an adjunctive medication in augmentation.

Antiepileptics

**Gabapentin (Neurontin)**

*Overview*
Gabapentin is an analgesic that also tends to prevent seizures, although the mechanism by which it does either is unknown. Gabapentin is a good first choice for patients who have RLS with neuropathic pain and a good second choice in patients for whom dopamine agonists are not effective. It can also be used in combination with dopamine agonists for refractory RLS symptoms. Gabapentin produces few side effects including dizziness, somnolence, weight gain, nausea and peripheral edema.

*Mechanism of action*
Gabapentin appears to have an effect on voltage-dependent calcium ion channels that interrupts the events leading to the experience of a neuropathic pain sensation. It appears to be effective for core symptoms as well as sleep-related symptoms of RLS. Although its mechanism of action in neuropathic pain and RLS is not known, limited studies have shown the efficacy of gabapentin for treating RLS symptoms.

*Pharmacokinetics/pharmacodynamics*
Gabapentin is not metabolized in the body and is excreted in the urine as an unchanged drug. Its bioavailability is not dose proportional — as the dose increases, its bioavailability decreases. Food has very little effect on the rate and extent of absorption of gabapentin. It has an elimination half-life of 5-7 hours.

*Formulations and dosages*
Neurontin is available in hard capsule form at 100 mg, 200 mg, and 400 mg doses, in film-coated tablets containing 600 mg and 800 mg of gabapentin, and as an oral solution containing 250 mg/5 mL of gabapentin. The dose of gabapentin recommended for use in RLS is 300-2700 mg with a maximum dose of 1200 mg per dose. In clinical trials for RLS, twice-a-day dosing has been effective with total dose ranging from 800 mg to 1800 mg per day split between one-third of the total dose at 12PM and two-thirds at 8PM. In clinical trials that compared ropinirole with gabapentin for RLS symptom relief, both test groups experienced significant improvement of symptoms but the gabapentin group experienced better sleep efficiency.
Contraindications
Neurontin is contraindicated in patients with demonstrated hypersensitivity to the drug or its ingredients.

Adverse effects and complicating factors
Patients taking antiepileptic drugs, including Neurontin, may experience an increase in suicidal thoughts and behavior and should be monitored for depression and related changes in mood or behavior. Gabapentin is secreted in breast milk.

**Pregabalin** (Lyrica CV) 18, 34, 35, 36, 37

Overview
Lyrica is FDA approved to treat diabetic nerve pain, pain after shingles, and fibromyalgia; but evidence has been accumulating from studies that pregabalin is also effective for treatment of RLS symptoms, and it improves sleep patterns for RLS patients.

In December 2011, Pfizer released results from a Phase 3 study of Lyrica (Pregabalin) for RLS. The randomized, double-blind, 12-month trial with 700 patients showed that RLS patients treated with Lyrica (300 mg/day) experienced a statistically significant improvement in symptom severity and a statistically significant reduction in the rate of augmentation compared with pramipexole (0.5 mg/day) over 12 months. Most common adverse events with Lyrica were dizziness, somnolence, headache, nausea, dry mouth, upper respiratory tract infection, and disturbance of attention. At present, Pfizer does not plan to seek regulatory approval for Lyrica’s use with restless legs syndrome.

Mechanism of action
Pregabalin’s mechanism of action is not fully understood but it appears to exert a similar action to gabapentin by binding to the alpha_2D receptors in the brain and disrupting calcium channel currents without blocking them.

Pharmacokinetics/pharmacodynamics
Pregabalin is absorbed well after oral administration with peak concentrations achieved within 1.5 hours. Its oral bioavailability is greater than 90% and is dose-independent. After single doses of 25-300 mg and multiple doses of 75-900 mg per day, maximum plasma concentrations increase linearly. With repeated doses, steady state is achieved within 24-48 hours. Pregabalin absorption is decreased by 25-30% when given with food and the time to maximum concentration is increased to 3 hours. However, taking Lyrica with food has no clinically relevant effect on total absorption. Pregabalin has been shown to cross the blood-brain barrier in rats although there are no data in humans.

Pregabalin undergoes very little metabolism and almost 90% is eliminated by renal excretion as unchanged drug, with an elimination half-life of approximately 6 hours. Pregabalin clearance may be impaired in the elderly and dosage reductions may be required. In those with renal impairment, dosage reduction is necessary.

Formulations and dosages
Lyrica is available in oral solution of 20 mg pregabalin per mL; prescriptions should be written in mg. It is also available in 25 mg, 50 mg, 75 mg, 100 mg, 200 mg, 225 mg and 300 mg capsules.

Lyrica may be taken with or without food. When the drug is discontinued, it should be tapered gradually over a 1 week period. No dose has been set for use in RLS but one clinical trial found efficacy between 300 and 450 mg daily before bed. Another determined
that symptoms as measured on the IRLS scale were improved at or above a 150 mg dose. At this level, sleep measures improved after 12 weeks of treatment.

Contraindications
Lyrica is contraindicated in patients with known hypersensitivity to the drug or its ingredients.

Adverse effects and complicating factors
Angioedema, sometimes life-threatening, has been reported in patients taking Lyrica, especially swelling of the face, mouth, and neck. Hypersensitivity reactions including skin redness, blisters, hives, rash, dyspnea, and wheezing have also been reported. Lyrica may increase the risk of suicidal thoughts and depression as well as dizziness, somnolence, and weight gain. Other rare adverse effects include blurred vision, elevations in creatine kinase, decreased platelet count, and prolongation of PR interval. It is not known if pregabalin is excreted in human milk nor has its safety in pediatric populations been studied. Lyrica should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

**Gabapentin enacarbil** (Horizant) 38

Overview
In April, 2011, the FDA approved a new drug for RLS, Horizant Extended Release Tablets, a once daily treatment for moderate to severe RLS. Horizant’s active ingredient is gabapentin enacarbil, which is metabolized to gabapentin in the body. Side effects include daytime drowsiness and dizziness.

Mechanism of action
Gabapentin enacarbil is a pro-drug of gabapentin. The precise mechanism of action in RLS is unknown but its high affinity for the α2δ subunit of voltage-activated calcium channels suggests a relationship with pain sensation.

Pharmacokinetics/pharmacodynamics
The T\text{max} of gabapentin after administration of 600 mg of Horizant was 5 hours in patients who fasted and 7.3 hours in patients who had not. With daily administration, steady state is reached in 2 days. Gabapentin enacarbil is metabolized in enterocytes and, to a lesser extent, in the liver to gabapentin. Gabapentin is not metabolized further to any appreciable degree and is excreted unchanged in the urine. Oral clearance from plasma after administration of Horizant with any amount or type of food ranged from 5-7 hours. Its elimination half-life is 5.1-6 hours and is unchanged by size of dose or multiple doses. Horizant and gabapentin are not interchangeable due their different pharmacokinetic characteristics.

Formulations and dosages
Horizant is available as extended-release tablets in 300 mg and 600 mg strengths. The recommended dose of Horizant for RLS is 600 mg once daily taken with food around 5 PM. The dose should be decreased for patients with renal impairment, and Horizant is not recommended in patients on dialysis.

Contraindications
There are no known contraindications.

Adverse effects and complicating factors
Horizant causes significant impairments to driving; patients should be cautioned to not drive until they gain experience with the drug. The impairment occurred within 2 hours and for up
to 14 hours after taking the drug and may be related to somnolence, which was experienced by up to 20% of patients taking 600 mg of Horizant per day in clinical trials. Somnolence persisted as a side effect of taking the drug in up to 30% of those reporting it. Other side effects included dizziness, an increase in depression and suicidal thoughts and behaviors, and hypersensitivity reactions including fever, rash, lymphadenopathy with organ involvement, and eosinophilia. It is not known whether gabapentin has any effect on pregnancy. Gabapentin is secreted in human milk, but it is not known if gabapentin derived from Horizant is secreted in human milk. The frequency of dosing may require adjustment for patients with renal impairment and for the elderly based on creatinine clearance.

**Low Potency Opioids**

Opioids were used in the past to treat RLS, but they are typically used today only when patients have not responded to other therapy. Opioids carry a major stigma, that of dependency, addiction, abuse, and difficulty with discontinuation, which is the main reason they have fallen out of use. In spite of these problems not being observed in many RLS patients who use the drugs, the issue must be carefully assessed on a patient by patient basis. Side effects of opioids include dizziness, somnolence, nausea, constipation, respiratory suppression, and urinary retention. They are still useful in patients with RLS for whom other medications have failed or where augmentation has developed. Opioids used occasionally in these patients include oxycodone, methadone, tramadol, and propoxyphene.

Limited studies have shown that opioids may improve symptoms of RLS. In a small (11 patients) study, oxycodone (roxicodone) treatment decreased RLS symptoms, decreased PLMS and improved alertness during the day. Another randomized, clinical trial showed that propoxyphene (Darvon) improved symptoms of RLS but was less effective than carbidopa/levodopa. A third study with 12 patients indicated that tramadol (Ultram) taken at night improved symptoms of RLS.

**Benzodiazepines**

Clonazepam was one of the first drugs used to treat RLS. It is still used as a second line medication, but it has not been studied extensively. It is useful in patients with intermittent RLS when insomnia is a significant problem and may be combined with dopamine agonists for refractory RLS.

Clonazepam is long-acting with a half-life of 30-40 hours and accumulates with daily dosing to cause daytime drowsiness, cognitive impairment, and impaired coordination over time especially in the elderly. The rationale for treating RLS, a disorder that is typically present for 8 hours a day or less, with clonazepam, a medication with a long half-life and accumulating side effects, is obscure. Existing studies provide conflicting results, at best.

**Research / Pipeline Medications**

Not much is known about the role of dopamine in RLS, but researchers suspect that symptoms result when transmission of dopamine signals is impaired. Another focal point of research is the interaction between iron levels and dopamine activity. It is currently known, for example, that serum ferritin level is predictive of the severity of RLS symptoms in older individuals.

In December 2011, Impax Labs Pharmaceutical Division began a phase 11b clinical trial of its drug candidate IPX159 in patients with moderate to severe restless leg syndrome. IPX159 is a new molecular entity in the US, although it has an established pharmacologic
and safety profile for non-RLS use outside the US. Results from this study are anticipated for mid-2013. IPX159 may represent a novel mechanism of action in RLS.

**Prognosis**

RLS can have a variable course and symptoms may even disappear for periods of time. For most people with RLS, however, symptoms return and tend to worsen with age. Treating underlying causes may reduce or eliminate symptoms of RLS, but multiple medications may be needed to provide long term relief. There is no “cure” for the condition at present.
Works Cited


