REVIEW

Pharmacotherapy Options in Restless Legs Syndrome

Michael P. Perkins, Christopher J. Lettieri and Aaron B. Holley

Pulmonary, Critical Care and Sleep Medicine, Walter Reed Army Medical Center, Washington DC, USA.
Corresponding author email: michael.p.perkins@us.army.mil

Abstract: Restless legs syndrome (RLS) is a common sleep disorder, clinically diagnosed in the presence of a unique symptom complex which adversely impacts a patient's quality of life. There is an urge to move the legs which develops during or is worsened by rest, is alleviated with movement, and is more severe in the evenings. RLS can be idiopathic or exist in association with several conditions including pregnancy, iron deficiency, advanced renal disease, and the use of certain medications. There is likely a genetic predisposition to the development of RLS. The physiologic mechanisms behind RLS are not fully understood but likely include derangements in the dopamine and iron regulatory systems. Several pharmacotherapeutic options, within the dopaminergic, antiepileptic, opioid, and sedative-hypnotic drug classes, have proven beneficial in the treatment of RLS. There is little evidence to suggest superiority of any specific agent and treatment is individualized based on symptoms and modified according to drug efficacy and tolerance. With the correct agent, or combination of agents, patients generally respond well with favorable long term treatment success.

Keywords: restless legs syndrome, pharmacologic therapy, drug therapy, dopamine, dopaminergic, sleep disorder

This article is available from http://www.la-press.com.

Introduction

In 1685, Sir Thomas Willis provided the first known description of Restless Legs Syndrome (RLS) in a chapter entitled "Instructions for Curing the Witching Evil," in the book *London Practice of Physick*. He described a disorder in which when patients "betake themselves to sleep, presently in the arms and legs, leaping and contractions of the tendons, and so great a restlessness and tossing of their members ensue, that the diseased are no more able to sleep, than if they were in a place of the greatest torture."[1] This syndrome was again referenced by several physicians throughout the nineteenth and early twentieth century and was then extensively described by Professor Karl-Axel Ekbom. In Professor Ekbom's quintessential work, spanning over forty years from the late 1930s to 1970, he established the nomenclature "Restless Legs Syndrome" and provided a comprehensive description of the disorder, extensive insight into its etiology and genetic predisposition, and some of the first reports of successful RLS pharmacotherapy.[1]

Restless legs syndrome is a common, often under-recognized sensorimotor sleep disorder characterized primarily by motor restlessness. RLS is a clinical diagnosis made using four key subjective criteria that are supported by objective features (Table 1).[2] Subjective criteria include an unpleasant sensation in the extremities resulting in an urge to move. This sensation is often improved or resolved with movement, is exclusively present or aggravated by rest or inactivity, and is generally present or worse in the evening or night. The urge to move may be severe, and many patients are unable to sit still. Symptoms most often affect the legs, but other body parts may be involved. Although RLS may follow an insidious course with onset at a younger age, prognosis and severity are highly variable. Some patients experience only mild, intermittent symptoms with periods of complete remission. For others, the symptoms are severe, frequent, and progressive. Symptom severity may be classified using the International Restless Legs Scale (IRLS), which has proven to be a reliable, valid, and responsive tool.[3,4] The IRLS contains ten items which assess the sensory and motor symptoms of RLS and their impact on quality of life and mood.[4] Most recent pharmacotherapy trials for RLS have included only patients with moderate to severe RLS, defined as an IRLS score of greater than or equal to 15.

Periodic limb movements (PLMs) during sleep are common in patients with RLS and occur in approximately 80% of individuals.[5] Their presence supports the diagnosis and they have been used as a target or endpoint in therapeutic trials. However, they are not required for the clinical diagnosis of RLS and are largely non-specific. The presence of PLMs while awake (PLMW) is more sensitive and specific for RLS.[5] The number of PLMs per hour, or PLM index (PLMI) while asleep, seems to correlate with RLS disease severity.[6]

RLS symptoms have a well documented impact on quality of life. Up to 90% of patients will experience some degree of sleep disturbance, resulting in frequent daytime somnolence. Anxiety, depression, and social withdrawal are also common. As such, treatment is indicated based not only on the frequency and severity of symptoms, but also on the effect the symptoms have on the patients overall quality of life.

Table 1. Diagnostic criteria for RLS.

Essential clinical criteria*
- Urge to move the legs, usually with an uncomfortable sensation in the legs**
- The urge to move the legs brought on or worsened by rest
- The urge to move the legs is alleviated or improved with movement
- The urge to move develops or is worsened at night

Associated clinical features
- Periodic limb movement
- Theraputic response to levodopa or dopamine receptor agonist
- The urge to move the legs produces a sleep disturbance
- Family history of RLS

*All four criteria required for diagnosis.
**Occasionally other body parts are involved.

Epidemiology

RLS is a commonly encountered condition in industrialized countries. In a large, multinational survey, 11.1% of patients presenting to their primary care provider reported symptoms of RLS and 2.4% reported a negative impact on life due to RLS symptoms.[7] The mean age of those with RLS was 56.9 years, the majority (68.1%) were women, and most reported an onset of symptoms prior to age 50. Most were undiagnosed despite reporting these symptoms to a physician. Other studies have shown similar findings, with a 5%–10% overall prevalence of RLS.[7–9] In the United States and Northern Europe, the prevalence of RLS appears to be considerably higher than in the Middle East and Asia, although epidemiologic data from these regions are sparse.[8] The prevalence of RLS increases with age, with some data suggesting peak prevalence in the seventh decade of life. The initial symptoms of RLS commonly begin in the second and third decades of life and follow a progressive course.[8] RLS is twice as likely to occur in women, and Caucasians are more commonly affected than African Americans.[9]

Etiology

RLS can be a primary disorder or a secondary disorder in association with several medical conditions. It is unclear if symptoms result as a consequence of these conditions or develop as a concomitant, co-morbid disease process. A higher than baseline prevalence of RLS has been well described with pregnancy (usually in the third trimester),[10,11] iron deficiency and end stage renal disease (ESRD).[11,12] Other potentially associated diseases include neuropathy, diabetes mellitus, and rheumatic disease, although these relationships are less clearly defined.[11] While adequate treatment of the underlying condition often improves the RLS symptoms, they are typically not eliminated, supporting the notion that RLS is not merely a secondary disorder. Certain medication classes, to include antidepressants, typical neuroleptics, and some anti-emetics can also cause or exacerbate RLS symptoms.[13]

Primary or idiopathic RLS is thought to result from a genetic predisposition. A family history is identified in 63%–92% of cases.[8] Recently, several RLS gene loci have been identified, which can follow either an autosomal dominant or recessive inheritance pattern.[9,14] Patients with a family history of RLS tend to develop symptoms earlier in life.[9]

Pathophysiology

The specific pathophysiologic mechanism responsible for the symptoms of RLS is unknown, but several studies implicate derangements in the dopaminergic, opiate, and iron regulation systems. Although results are mixed, some imaging studies report evidence of alterations in dopaminergic pre-synaptic and receptor binding systems in the CNS.[11] RLS symptoms and PLMs improve with dopaminergic agents and are exacerbated by centrally active dopamine receptor antagonists, further supporting this association.[11] Conversely, peripherally acting dopamine receptor antagonists do not affect RLS symptoms.[11] This is perhaps the strongest supportive evidence for altered function of dopamine pathways within the central nervous system (CNS). It is likely that there are no dopaminergic cells within the spinal cord. A11 cells exist within the midbrain and provide the spinal cord with its only dopaminergic axons. Because they provide the only link for CNS dopaminergic transmission to the periphery, these cells may play a role in the pathophysiology of RLS, but their exact role remains unknown.[15]

Iron deficiency has also been linked to RLS. Cerebral iron stores and CSF ferritin are often reduced in RLS patients and lower ferritin levels tend to be associated with more severe RLS symptoms.[16] Likewise, iron replacement therapy improves symptoms for some patients with RLS. There may be a common pathway between iron and dopamine regulation and function in RLS patients. Dopamine levels follow a well described circadian pattern which matches the circadian pattern of RLS symptoms. Animal data suggest that iron deprivation may lead to a marked accentuation of this pattern which could potentially contribute to nocturnal RLS symptoms. There are also data to suggest that iron deprivation decreases dopamine transporter function and may interfere with the rate limiting step for dopamine synthesis.[11]

Pharmacologic Management

Pharmacologic treatment should be considered for patients with persistent RLS symptoms despite non-pharmacologic measures and treatment of secondary causes. Dopaminergic agents, anti-epileptics, opiates, benzodiazepines, and sedative-hypnotic agents have all been used with some success (Table 2).[17]

Table 2. Drugs used to treat RLS.

Agent	Initial dose	Recomended maximal daily dose	Half-life in serum	Common side effects
Dopaminergic agents				
Levodopa (with carbidopaorbenserazide)	50 mg	200 mg, at bedtime	1.5–2 hr	Nausea or vomitting, orthostatic hypotension, hallucination, augmentation of symptoms, insomnia
Pramlpexole[*]	0.125 mg	l.5 mg, in 2 or 3 divided doses	8–10 hr (possibly longer with renal dysfunction)	Same as for levodopa, plus nasal congestion and fluid retention
Ropinirole[*]	0.25 mg	3.0 mg, in 2 or 3 divided doses	6–8 hr (possibly longer with hepatic dysfunction)	Same as for levodopa, plus nasal congestion and fluid retention
Sedative-hypnotic agents				
Clonazepam	0.25 mg	2 mg, at bedtime	30–40 hr	Tolerance, sedation
Oxazepam	10 mg	40 mg, at bedtime	5–10 hr	Same as for clonazepam
Zaleplon	5 mg	20 mg, at bedtime	1 hr (possibly longer with hepatic dysfunction)	Same as for clonazepam
Zolpidem	5 mg	20 mg, at bedtime	l.6 hr (possibly longer in elderly patients or with hepatic dysfunction)	Same as for clonazepam
Triazolam	0.125 mg	0.5 mg, at bedtime	2–4 hr	Same as for clonazepam
Antiepileptic agents				
Gabapentin	300 mg	3600 mg, in 3 divided doses 1500 mg once daily	5–7 hr (possibly longer with renal dysfunction)	Sedation, dizzines, fatigue, somnolence, ataxia
Opiates				
Propoxyphene	100–200 mg	600 mg, in 2 or 3 divided doses	6–12 hr (possibly longer with hepatic dysfunction)	Sedation, pruritus, constipation, nauses or vomitting, dry mouth, dependence
Hydrocodone	5 mg	20–30 mg, in 2 or 3 divided doses	3 hr (possibly longer with hepatic dysfunction)	Same as for propoxyphene
Codeine	30 mg	180 mg, in 2 or 3 divided doses	2.5–3 hr (possibly longer with hepatic dysfunction)	Same as for propoxyphene
Tramadol	50 mg	300 mg, in 2 or 3 divided doses	5–8 hr (possibly longer with hepatic or renal dysfunction)	Same as for propoxyphene and augmentation
Oxycodone	5 mg	20–30 mg, in 2 or 3 divided doses	3 hr (possibly longer with renal dysfunction)	Same as for propoxyphene
Oxycodone-XR	10 mg	20–30 mg, in 2 or 3 divided doses	12 hr (possibly longer with renal dysfunction)	Same as for propoxyphene
Methadone[*]	2 5 mg	20 mg, in 2 divided doses	16–22 hr (possibly longer with hepatic dysfunction or long-term use)	Same as for propoxyphene
Morphine sulphate-XR	15 mg	30–45 mg, in 2 or 3 divided doses	4 hr (possibly longer with hepatic dysfunction)	Same as for propoxyphene

[*]Medicine should be started at least two hours before bedtime or the anticipated onset of symptoms.
Used with permission from New England Journal of Medicine.[17]

Dopaminergic agents
Mechanism of action, pharmacokinetics, pharmacodynamics

Dopaminergic agents are considered first line therapy for most patients with RLS. These agents can be subdivided into dopamine precursors, ergot derived dopamine agonists, and non-ergot derived dopamine agonists. The dopamine precursor levodopa and the ergot derived dopamine agonists have an unfavorable side effect profile and less efficacy data, and have largely been replaced by the newer non-ergot derived dopamine agonists, pramipexole and ropinirole.

Levodopa is the immediate precursor to dopamine, but unlike dopamine, it crosses the blood brain barrier (BBB).[18] Levodopa undergoes partial metabolism in the GI tract, and inactive metabolites are then renally excreted. The remaining active component is peripherally converted to dopamine by DOPA decarboxylase. Because of the intestinal inactivation and peripheral conversion to dopamine, only 1%–3% of Levodopa administered ultimately enters the CNS. Co-administration with a DOPA decarboxylase inhibitor such as carbidopa prevents metabolism in the peripheral circulation. This reduces systemic side effects and increases CNS concentrations to approximately 10%. Once inside the CNS, levodopa is transported into dopaminergic cells and converted to dopamine. It then acts on the pathways that are thought to cause RLS symptoms.[18] Levodopa has a short half-life of 1.5–2 hours[17] and reaches peak concentration in 0.5 to 2 hours. Intestinal absorption and bioavailability are reduced with protein rich foods, gastric hyperacidity and delayed gastric emptying, making plasma concentrations unpredictable.[19] The pharmacokinetics have not been studied in patients with liver or renal failure.

Ropinirole and pramipexole are nonergot, D2 and D3 dopamine receptor subtype agonists with preferential affinity for D3. Ropinirole also has some in vitro effect on opioid receptors. Both are rapidly absorbed after oral administration.[19]

Ropinirole is metabolized mainly by the hepatic cytochrome P450 1 A2 pathway. Caution is advised during dose titration in patients with hepatic dysfunction or in those taking other cytochrome active medications. Additionally, smoking induces the cytochrome P450 1 A2 system and can result in a lower concentration of ropinirole. It has a half-life of 6–8 hours[17] and reaches peak concentration in 1–2 hours.

Pramipexole undergoes little metabolism and is excreted as active drug in the urine. Adjustment in dosage should be made for patients with renal impairment. It has a half life of 8–10 hours and reaches peak concentration in 1–3 hours.[17]

Clinical efficacy

Several randomized, placebo-controlled trials have established dopaminergic agents as effective therapy for RLS. These agents demonstrate improvements in sleep quality and RLS symptoms, and reduce the frequency of PLMs.

Levodopa was the first dopaminergic agent studied for use in RLS. This agent has been shown to improve symptoms in 6 placebo controlled clinical trials.[20–25] These studies are of 2 to 4 week duration and contain a total of approximately 100 patients. Despite the small number of subjects and short duration of follow-up, most trials demonstrate improvements in the frequency of PLMs. However, improvements in sleep architecture are variable and rarely seen after the first half of the night.

Several well designed, placebo controlled trials have documented the efficacy of ropinirole in the treatment of RLS.[26–30] These trials incorporated a large number of subjects over an extended period of time, and included patients with at least moderate RLS. They demonstrated an early and sustained benefit for most patients. All but one trial showed improvements in severity as measured by the IRLS,[27–30] and most showed improvements in the Medical Outcomes Study (MOS) sleep scale in domains pertaining to sleep impairment[26–28,30] and in the clinical global impression of improvement (CGI-I).[27–29] However, reductions in daytime sleepiness were less consistent across trials. Two trials demonstrated a reduction in PLMI,[26,27] one of which also showed reduced PLM-associated arousals.[26]

Pramipexole has demonstrated efficacy in placebo controlled trials containing more than 1200 total RLS patients, most with frequent symptoms and at least moderate disease severity.[31–36] Similar to ropinirole, pramipexole reduced the PLMI, but not PLM arousals. It was also shown to reduce PLMs while awake. The

IRLS was consistently improved beyond placebo. Subjective assessments of daytime sleepiness and fatigue were unchanged and effects on sleep architecture were variable, with some trials demonstrating less REM[33] and slow wave sleep.[35]

Studies evaluating the long term efficacy of levodopa in the treatment of RLS with daily symptoms show that 23%–56% of patients ultimately required a change to an alternate agent.[37–39] Most changes were either due to long term treatment ineffectiveness or the development of augmentation. The long term efficacy of the nonergot dopaminergic agents in patients with moderate to severe RLS is better. In a 52 week open label prospective study, 82% of patients responded to an average dose of 1.64 mg ropinirole, rating their symptoms as "very much improved" or "much improved." The IRLS in these patients was reduced by an average of 10 points.[40] Improvements were early and sustained throughout the study period. In a 26 week, open label, prospective trial with pramipexole, 89.7% of patients rated themselves "much better" or "very much better" and early and lasting improvements were seen in IRLS with an average reduction of -16.9 ± 7.8 points. Subjective assessments of sleep quality improved and there was a modest improvement in daytime somnolence.[41] Retrospective data on pramipexole do demonstrate that approximately 40% of patients required a dose increase to twice or three times per day, usually to treat augmentation.[42] With this intervention patient's symptoms were well controlled, and treatment failure or addition of a second line agent was rare.

Safety, side effects, adverse reactions

In clinical trials, adverse events occurred in approximately 60%–85% of patients receiving dopaminergic medications,[20,21,26–28,30–32,34–36,43] but only 5% of patients discontinued therapy. Common side effects include nausea, emesis, dizziness, fatigue, somnolence, and nasal congestion. Nausea is most common, occurs in approximately 40% of patients,[20,21,26–28,30–32,34–36,43] and is the most frequent reason for drug intolerance.

More severe adverse reactions with dopaminergic agents are rare. Dopamine agonists are known to cause postural hypotension and although they were not designed to specifically address this outcome, in pooled placebo controlled trials of RLS patients, hypotension and syncope occurred slightly more with ropinirole than with placebo. However, the overall incidence remained less than 1%.[44] Additionally, A few patients have developed disorders of impulse control while receiving dopaminergic agents for RLS, including pathologic gambling.[45]

Augmentation and rebound are potential consequences of using dopaminergic agents. Augmentation is characterized by worsening of symptoms secondary to sustained treatment. The mechanism for development is not completely understood, but is presumably related to prolonged or increased dopaminergic receptor stimulation. Other data suggest a genetic predisposition to augmentation.[2] This syndrome is well recognized, and a standardized clinical definition called the Max Plank Institute criteria have been published (Table 3).[46]

Table 3. Diagnostic criteria for augmentation.

Augmentation occurs only in patients receiving RLS drug therapy

Essential clinical criteria[*]
- Increase in RLS symptom severity on at least five days during the previous week
- Increase in severity is not caused by other factors, such as change in lifestyle or mental status
- There has been a prior benefit from drug therapy

Additional clinical features[**]
- RLS symptoms worsen after an increase in drug dose and improve after a decrease in dose
- Symptoms occur at least four hours earlier
- Symptoms occur two to four hours earlier with at least one of the following:
  - A shorter latency to symptoms when at rest
  - Extension of symptoms to other body parts
  - A shorter duration of relief from treatment
  - Greater intensity of symptoms
  - Increase in PLM frequency

[*]All three criteria required for diagnosis.
[**]At least one clinical feature must be met.

In randomized, placebo controlled trials, augmentation with levodopa was rarely reported. However, a longer term study with levodopa found 73% of patients experienced augmentation and 50% required a decrease in dosage or transition to an alternative agent.[39] The risk of augmentation with levodopa seems to increase at dosages of 200 mg or greater.[8] Although there is no direct comparison, augmentation is likely more severe and more prevalent with levodopa than with the newer agents pramipexole and ropinirole. In randomized controlled trials, augmentation occurred with pramipexole in up to 6.4% of patients.[32,35] Two long term retrospective studies reported an incidence of approximately 33%.[42,47] Augmentation with pramipexole was almost always relatively mild and easy to manage, leading to very few treatment failures. Ropinirole did not cause augmentation in randomized controlled trials, although some of these trials did exclude patients with a prior history of this syndrome. A one year open label study reported an incidence of augmentation between 2.3%–9.1%, depending on the definition used.[40]

Augmentation must be distinguished from a rebound of RLS symptoms or withdrawal symptoms. Rebound is a worsening of RLS symptoms as the effectiveness of an individual dose of medication wanes, commonly occurring in the early morning. Rebound has been seen in 20% of patients taking levodopa but was not observed in a long term retrospective review of patients receiving pramipexole.[2] The higher occurrence of rebound in patients receiving levodopa is presumably related to its shorter half-life. Withdrawal symptoms occur almost universally in patients after discontinuing medication. It is marked by a temporary worsening of symptoms with return to baseline within a week. The intensity of withdrawal may be related to higher doses and longer durations of treatment.[17] Avoidance of augmentation is advocated by keeping levodopa and dopamine agonists at their minimum effective dose. If augmentation occurs at these doses, the dose should be reduced or the patient switched to another class of medication.

Contraindications

Patients with Parkinson's disease are at an increased risk for melanoma and it has been speculated that levodopa may potentiate this risk. However, a growing body of evidence supports the fact that levodopa incurs no additional risk for the development of malignant melanoma.[48] Currently, levodopa remains contraindicated in patients with skin cancer or suspicious lesions,[44] but, based on this recent evidence, there has been a call to remove this contraindication.[48] Levodopa is also contraindicated in patients with narrow-angle glaucoma or those taking non-selective MAO inhibitors.[44] Ropinirole and pramipexole are only contraindicated in patients with known hypersensitivity to these agents.[44]

Patient therapy

Levodopa has a rapid onset of action and a short half-life. While this increases the risk for rebound, it also facilitates use in those who experience intermittent symptoms not requiring daily therapy, or symptoms that result from a specific event, such as a long car or plane trip. Levodopa is recommended for intermittent, mild to moderate RLS as a medication to control infrequent acute symptoms or isolated PLMs (Table 4).[49] It should be avoided for patients with moderate to severe RLS requiring regular treatment.

Both ropinirole and pramipexole are FDA approved for the treatment of moderate to severe RLS.[44] Because of their favorable side effect profile, they are appropriate for patients who require chronic therapy. There are no comparative trials suggesting that either medication is superior to the other. The choice of

Table 4. RLS pharmacotherapy treatment scheme.[49]

Intermittent RLS	Daily RLS*	Refractory RLS**
Levodopa	Dopamine agonists	Change dopamine agonist
Dopamine agonists	Gabapentin	Change to gabapentin
Gabapentin	Low potency opioids	Change to high potency opioid
Low potency opioids		Add gabapentin, opioid, or benzodiazepine
Benzodiazepines		

*Listed in order of preference.
**Refractory RLS defined as persistent symptoms despite initial monotherapy.

dopamine agonist should be based on the presence of comorbid renal or hepatic disease or the use of additional medications that are metabolized through the CYP P450 1 A2 system.

Antiepileptics
Mechanism of action, pharmacokinetics, pharmacodynamic

Gabapentin is a structural analogue of gamma-Aminobutyric acid (GABA), which freely crosses the blood brain barrier. It is frequently used for neuropathic pain, but is also useful for treating RLS. Its precise mechanism of action is largely unknown. Recently, the $\alpha_2\delta$ subunit of the voltage-gated calcium channel has been proposed as a specific pre-synaptic binding site for gabapentin.[50,51] Activation of this receptor may account for the multiple cellular effects associated with this agent, including increased GABA levels in the human brain, GABAb receptor activation, effects on NDMA receptors, and a reduction in the release of glutamate and other excitatory neurotransmitters. The exact role that this receptor plays in the RLS pathway is not yet clear.

Gabapentin is absorbed in the proximal small bowel via a saturable transport mechanism that has the potential to create a lack of proportionality between higher oral doses and serum drug levels.[52] This limits the benefit of continued upward titration. The half life is approximately 5–7 hours[17] and it is completely excreted in the urine as unchanged drug. The half life is significantly increased in patients with renal insufficiency and dosage adjustment is required for these patients.[53]

Clinical efficacy

Case series and prospective cohort studies have shown efficacy for gabapentin in the treatment of RLS.[53–56] In addition, two randomized, double blind, placebo controlled trials evaluating gabapentin as treatment for RLS have been conducted.[57,58] Combined, these two trials include 40 patients followed over a 6 week duration. One study was conducted exclusively in patients with chronic renal insufficiency who were dialysis dependent. This trial had a crossover design and showed subjective improvements in RLS symptoms with 300 mg of gabapentin.[57] The second study administered 600–2400 mg gabapentin (mean dose 1855 mg) to RLS patients and also revealed subjective benefits, including improvements in the IRLS and measures of sleep quality.[58] The PLMI was reduced, but there was no effect on PLM arousals.

Safety, side effects, adverse reactions

Gabapentin is generally well tolerated. In clinical trials, the most frequently reported reactions were weight gain, dizziness and somnolence.[54,55,57–59] Other reported side effects include nausea, parasthesia, and headache. These reactions rarely led to study withdrawal, were usually reported as mild in severity, and tended to resolve with continued use of the drug. The FDA has recently concluded that antiepileptics, as a class, may increase the risk of suicide, but this outcome has not been reported in RLS trials with gabapentin.[59]

Contraindications

Gabapentin is only contraindicated in patients with known hypersensitivity to the medication.

Patient therapy

One small, four week, open label study has compared gabapentin to ropinirole and demonstrated comparable reductions in the IRLS, PLMs and PLMI.[60] However, in contrast to the dopamine agonists, there are few well designed trials supporting the use of gabapentin for RLS. Gabapentin should therefore be considered a second line agent for the treatment of RLS with daily symptoms. It may be used as primary therapy for intermittent RLS, especially in patients who have pain within their symptom complex. In cases of persistent RLS despite the use of dopamine agonists, gabapentin can be used in addition or as an alternative to these agents.[49]

Opioids
Mechanism of action, pharmacokinetics, pharmacodynamics

All opioid based medications share a common mechanism of action.[61] They stimulate mu receptors located in pre- and postsynaptic positions in the brain, brainstem, spinal cord, and peripheral afferent nerves. Stimulation of presynaptic receptors within terminal, central afferent neurons results in decreased calcium influx, which reduces presynaptic vesicle release of nocioceptive neurotransmitters such as substance P and CGRP. Additionally, stimulation of postsynaptic

mu receptors within secondary afferent relay neurons results in increased potassium conductance, ultimately leading to decreased action potential generation.[61] The specific mechanism by which opioids impact RLS is unknown. Some data do suggest opioid receptor derangement in RLS patients,[62] which may be overcome by exogenous opioid administration.

Opioids can be divided into naturally occurring, semisynthetic, and synthetic compounds.[61] The individual agents have a range of pharmacokinetic and pharmacodynamic profiles and different routes of delivery, but all produce analgesia and some degree of sedation. Several opioids have been used to treat RLS, but only a few, including oxycodone, tramadol, and methadone have evidence to support their use.[63–65]

Oxycodone has a rapid onset of effect and remains active for approximately 3 to 6 hours. Methadone has an onset of action of approximately one hour and is effective for 4 to 8 hours. Repetitive dosing produces a longer duration of effect. Tramadol is a mu receptor agonist which also inhibits reuptake of norepinephrine and serotonin. Onset of action is one hour and duration of effect is approximately 8 hours.[44] All three agents undergo hepatic metabolism through the cytochrome P450 system and adjustments in dosage or avoidance of medication are necessary in patients with severe hepatic dysfunction. They are also all renally excreted as active drug and metabolite, requiring dosage adjustments in severe renal insufficiency.[44]

Clinical efficacy

There are few well designed trials documenting the effects of opioids in RLS. Oxycodone was evaluated in a 4 week, randomized, placebo controlled, double-blinded crossover trial.[63] In this trial, oxycodone in dosages from 2.5 mg to 25 mg (average 15.9 mg), lead to improvements in sensory discomfort and symptoms of motor restlessness, a reduction in daytime drowsiness, and PLMs. In a case series of patients with severe RLS who had failed treatment with dopaminergic agents, methadone lead to significant improvements in RLS symptoms in the majority of subjects.[64] Improvement in symptoms was sustained for almost two years in 60% of subjects. Similarly, in a small, open label trial, tramadol improved subjective symptoms over an extended period of time.[65] In a small, retrospective study using opioid monotherapy as either

initial treatment or for dopamine agonist failure, clinical efficacy persisted for a prolonged duration.[66] After six years, 20/36 patients remained on opioid monotherapy. The remainder discontinued opioids due to side effects or lack of benefit. These studies indicate a moderate rate of long term efficacy with opioids as treatment for RLS and support their use as initial monotherapy in selected cases or as an alternative or adjunctive medication to other agents.

Safety, side effects, adverse reactions

Opioids as a class have well known and significant side effects, including respiratory depression, worsening of sleep apnea, the development of tolerance and addiction. However, in one long term retrospective trial, only one patient out of 36 receiving opioid monotherapy for RLS developed addiction and tolerance.[66] Likewise, a short term trial of patients with preexisting sleep apnea did not experience worsening of their sleep disordered breathing and no patients developed new onset sleep apnea while using oxycodone.[63] Interestingly, a case report and a retrospective study both report augmentation with the use of tramadol monotherapy for RLS, a phenomenon usually confined to the use of dopaminergic agents.[65–68] Other frequently reported side effects of opioid RLS therapy include daytime fatigue, confusion, and constipation. Opioids promote histamine release which may cause hypotension or bronchospasm in some patients.

Contraindications

Opioids should be used with caution in patients with liver or renal insufficiency, a history of substance abuse or those with acute psychiatric instability or a high suicide risk.[44] They are contraindicated in patients receiving naltrexone therapy.

Patient therapy

As described, there are few placebo controlled trials that support the use of opioids for RLS, so the choice of a specific agent and dose should be individualized. Low potency opioids at the minimum effective dose can be used to treat intermittent or daily RLS, and are usually given as a third line agent for monotherapy or as an adjunct for patients failing to achieve symptom control with other agents. They should be given in tablet form and should have a long enough half life to remain effective throughout the night. Opioids

should not be withheld simply for concern over the development of addiction, but care should be taken when prescribing to patients with a history of substance abuse or dependency.

Benzodiazepines and non-benzodiazepine sedative-hypnotics
Mechanism of action, pharmacokinetics, pharmacodynamics

Benzodiazepines are a group of medications which bind to the $GABA_A$ receptor, located throughout the CNS, and facilitate endogenous GABA binding. This increases GABA potency and causes neuronal chloride conductance and hyperpolerization, which inhibits neuronal depolarization.[69] Clinically, this depressant effect leads to anxiolysis and hypnosis.

Clonazepam is the benzodiazepine most studied in the treatment of RLS.[19] It has a rapid onset of action and a long elimination half life of 30–40 hours.[17] It is metabolized through hepatic glucuronidation and sulfate conjugation and is renally excreted as conjugated, inactive metabolite. No dosage changes are needed for renal or hepatic impairment.[44]

Zolpidem is a sedative hypnotic which also works through the GABA receptor system. It specifically binds to the α subunit of the $GABA_A$ receptor, also known as the benzodiazepine-1 receptor. This preferential binding leads to sedation and hypnosis with relatively little anxiolysis. Zolpidem has an onset of action of 30 minutes with a 3 to 6 hour duration of action. It is metabolized through the cytochrome P450 system and is renally excreted as parent drug and inactive metabolite.[44] Small dosage changes are necessary in severe hepatic impairment.[44]

Clinical efficacy

Few randomized controlled trials have studied the use of benzodiazepines for RLS and the existing trials show mixed results. One randomized, placebo controlled, double blind crossover trial of 6 patients showed no improvements in the CGI after 8 weeks.[70] In another 3 week trial of similar design, clonazepam improved subjective sleep quality and sensory discomfort.[71] Finally, a three day, single blind, placebo-controlled trial of 10 patients demonstrated improved sleep efficiency on PSG and subjective sleep quality, but did not show a reduction in PLMs.[72]

Zolpidem was evaluated in a small, open-label case series for use in patients with moderate to severe idiopathic RLS who had failed treatment with levopoda or benzodiazepines. The study followed 8 patients for 12 to 30 months. All eight patients experienced complete resolution of symptoms within one week and the benefits were sustained for the duration of the study.[73]

Safety, side effects, adverse reactions

Adverse reactions and side effects of clonazepam, when used for RLS, have not been extensively reported. When used for other indications, daytime somnolence is common with clonazepam. In a pooled analysis of studies using clonazepam for indications other than RLS, somnolence occurred in 37% of patients.[44] Although relatively uncommon, in up to 7% or patients, depression, ataxia, falls, and memory disturbance were also reported.[44] Like opioids, these medications carry a risk of abuse and dependency.

Contraindications

Clonazepam is contraindicated in patients with hypersensitivity to the medication and in patients with severe liver failure or narrow-angle glaucoma.[44] Clonazepam can worsen sleep disordered breathing and should be used with caution or avoided in these patients. Zolpidem is contraindicated in patients with history of drug hypersensitivity.[44]

Patient therapy

Benzodiazepines and sedative hypnotics may be used in patients with intermittent RLS. Because these medications are known to induce sleep, they should be considered in patients experiencing insomnia due to their RLS. Clonazepam has a long half-life, potentially leading to persistent daytime somnolence and should be avoided in patients requiring daily RLS therapy. Likewise, these medications should typically not be used as monotherapy in refractory RLS, but can be effective when added to dopamine agonists.

Special Patient Populations
Iron deficiency

Case controlled series and open label studies suggest that oral and intravenous iron therapy reduce RLS symptoms in iron deficient patients, but not in those

with normal iron stores.[19] Additionally, a 4 week double blind, randomized trial demonstrated significant improvement in RLS symptoms in dialysis dependent patients receiving iron.[74] Prior to initiating treatment for RLS, patients should be evaluated for iron deficiency and treated if necessary. If oral iron becomes intolerable due to gastrointestinal side effects, intravenous therapy can be considered. Intravenous iron therapy can cause an anaphylactoid reaction in 3% of patients[19] and close monitoring is necessary during infusion. Patients receiving iron replacement therapy should have serial ferritin levels drawn to prevent iron overload.

End stage renal disease

RLS is common in patients with renal failure. In a study of 601 dialysis dependent patients, the IRLSSG screening criteria identified moderate to severe RLS in 21.5%.[75] RLS in dialysis dependent patients has been associated with premature discontinuation of dialysis, lower quality of life, and increased mortality.[12] While most studies establish only an association between uremic renal failure and RLS, end stage renal disease likely plays a causative role in the pathogenesis of RLS. Patients with end stage renal disease tend to experience symptom remission after transplant, only to have RLS recur with subsequent graft failure.[12,76]

As described, some randomized trials with levodopa and gabapentin have included this population, and an open label trial showed benefit with clonazepam.[77] The larger and more recently published studies excluded patients with renal failure. As a result, the impact that renal failure has on the pharmacologic treatment of RLS is somewhat unclear. Treatment of anemia with iron and erythropoietin can improve RLS symptoms in dialysis patients[78] and should be considered prior to initiating medications. If pharmacologic therapy is started, the choice of agent is based on the same patient related factors that drive treatment decisions in idiopathic RLS. However, if dopamine agonists are used, ropinirole is the preferred agent as pramipexole requires dose adjustments in patients with renal insufficiency.

Pregnancy

Iron deficiency related to pregnancy is an independent risk factor for RLS, but pregnant patients are also at risk when iron stores are normal. One study reported a prevalence of 27% in a cohort of pregnant patients, with symptoms concentrated in the third trimester and resolving after child birth.[10] No trials have specifically addressed the safety and efficacy of pharmacologic treatment for RLS during pregnancy, and conservative measures are recommended until delivery. Impaired sleep can lead to adverse obstetric outcomes though, and dopamine agonists or levodopa can be used for severe cases.[8] These medications are pregnancy class C and may interfere with lactation.

Children

Few studies have evaluated the pharmacologic treatment of RLS in children. If children do require medication, ropinirole was shown to be effective in a post hoc analysis of four randomized trials and could be considered.[79] Children with RLS and attention deficit hyperactivity disorder (ADHD) may experience improvement in ADHD when RLS is treated.[8]

Drug Induced RLS

Because serotonin reuptake inhibitors and tricyclic antidepressants are associated with RLS symptoms, managing the patient with depression and RLS can be difficult. In general, if depression occurs after RLS is controlled, starting antidepressants will usually not lead to RLS relapse. If RLS and depression occur concurrently, treating RLS first may alleviate both conditions. If RLS occurs after starting an antidepressant, the medication should be discontinued if possible. If patients with RLS require an alternative antidepressant, bupropion is a good option because it has been shown to increase levels of dopamine, but not serotonin,[80] and in one small study, it reduced PLM frequency.[81] Other medications known to exacerbate RLS should be avoided when possible.[13]

Additional Agents
Ergot-derived dopamine agonists

The ergot-derived dopamine agonists, pergolide and cabergoline, have been shown to reduce PLMs and improve the IRLS in well designed clinical trials.[82–84] However, ergot-derivatives are associated with an increased risk of cardiac valve and pulmonary fibrosis.[85] Unlike non-ergot derived dopamine agonists, ergot derivatives are strong agonists of the

5-hydroxytryptamine 2B (5-HT2b) receptor which is located within heart valves. Stimulation of this receptor produces mitogenic effects in fibromyoblasts which may potentially result in clinically significant fibrosis.[86] A recent nested, case-control analysis confirmed an increased risk of cardiac valve regurgitation with the use of pergolide and cabergoline, but not with the non-ergot dopamine agonists.[86] Fibrosis has never been a complication of therapy in RLS trials with these agents, but it has never been specifically assessed. Due to concern for this significant complication, pergolide has been withdrawn from the market in the United States[87] and cabergoline is not recommended as a first line agent for RLS. If used, regular surveillance with a cardiopulmonary exam and perhaps echocardiography is warranted.

Antiepileptics: valprioc acid and carbamazipine

Valproic acid and carbamazipine are antiepileptics that were each shown to improve RLS symptoms in a randomized controlled trial.[24,88] However, these trials were conducted prior to the use of validated outcome measures. Also, both medications can cause rare, but serious adverse side effects including Stevens-Johnson syndrome, pancytopenia, liver failure, and coagulopathy.[19] Due to the limited data and potential for adverse reactions, these agents should be avoided as treatment for RLS.

Gabapentin precursor: XP13512

XP13512 is a gabapentin precursor recently studied for use in 222 patients with at least moderate RLS in a 12 week double-blind, randomized, placebo controlled trial.[89] This agent is absorbed throughout the small bowel, thus overcoming limitations in gabapentin absorption and providing a more reliable dose-proportional exposure. More patients on XP13512 had improvement in their IRLS compared to placebo, and there were few significant side effects. Furthermore, improvements with this drug were of similar magnitude to what was achieved in trials with ropinirole and pramipexole. More studies are necessary with this agent, perhaps comparing it to gabapentin and other RLS agents to determine whether it offers a clinical advantage in RLS treatment.

Conclusion

RLS is a common, yet under recognized, sleep disorder which often impacts quality of life. Fortunately there are several pharmacotherapeutic options from different medication classes that have proven efficacious in RLS. There are few studies that directly compare the different agents used for the treatment of RLS, and therapy should be individualized based on symptom severity and side effect profile. Pharmacotherapy should be used to provide relief of symptoms while minimizing adverse drug effects, with particular attention to the development and management of augmentation. Further study of the physiologic mechanisms underlying RLS and its associated conditions may lead to improved recognition, development of novel agents, and better long term pharmacologic outcomes.

Disclosures

This manuscript has been read and approved by all authors. This paper is unique and not under consideration by any other publication and has not been published elsewhere. The authors report no conflicts of interest. The views expressed in this review are those of the authors and do not necessarily reflect the official policy or position of the Department of the Army, Department of Defense, nor the U.S. Government. The authors confirm that they have permission to reproduce any copyrighted material.

References

1. Teive HA, et al. Professor Karl-Axel Ekbom and restless legs syndrome. *Parkinsonism Relat Disord*. 2009;15(4):254–7.
2. Allen RP, et al. Restless legs syndrome: diagnostic criteria, special considerations, and epidemiology. A report from the restless legs syndrome diagnosis and epidemiology workshop at the National Institutes of Health. *Sleep Med*. 2003; 4(2):101–19.
3. Abetz L, et al. The reliability, validity and responsiveness of the International Restless Legs Syndrome Study Group rating scale and subscales in a clinical-trial setting. *Sleep Med*. 2006;7(4):340–9.
4. Walters AS, et al. Validation of the International Restless Legs Syndrome Study Group rating scale for restless legs syndrome. *Sleep Med*. 2003; 4(2):121–32.
5. Hening WA, et al. An update on the dopaminergic treatment of restless legs syndrome and periodic limb movement disorder. *Sleep*. 2004;27(3):560–83.
6. Montplaisir J, et al. Periodic leg movements are not more prevalent in insomnia or hypersomnia but are specifically associated with sleep disorders involving a dopaminergic impairment. *Sleep Med*. 2000;1(2):163–7.
7. Hening W, et al. Impact, diagnosis and treatment of restless legs syndrome (RLS) in a primary care population: the REST (RLS epidemiology, symptoms, and treatment) primary care study. *Sleep Med*. 2004;5(3):237–46.
8. Satija P, Ondo WG. Restless legs syndrome: pathophysiology, diagnosis and treatment. *CNS Drugs*. 2008;22(6):497–518.

9. Gamaldo CE, Earley CJ. Restless legs syndrome: a clinical update. *Chest*. 2006;130(5):1596–604.

10. Manconi M, et al. Restless legs syndrome and pregnancy. *Neurology*. 2004;63(6):1065–9.

11. Allen RP, Earley CJ. Restless legs syndrome: a review of clinical and pathophysiologic features. *J Clin Neurophysiol*. 2001;18(2):128–47.

12. Kavanagh DS, Siddiqui CC. Geddes, Restless legs syndrome in patients on dialysis. *Am J Kidney Dis*. 2004;43(5):763–71.

13. Oertel WH, et al. State of the art in restless legs syndrome therapy: practice recommendations for treating restless legs syndrome. *Mov Disord*. 2007;22 Suppl 18:S466–75.

14. Lohmann-Hedrich K, et al. Evidence for linkage of restless legs syndrome to chromosome 9p: are there two distinct loci? *Neurology*. 2008;70(9):686–94.

15. Trenkwalder C, et al. The restless legs syndrome. *Lancet Neurol*. 2005;4(8):465–75.

16. Earley CJ, et al. Abnormalities in CSF concentrations of ferritin and transferrin in restless legs syndrome. *Neurology*. 2000;54(8):1698–700.

17. Earley CJ. Clinical practice. Restless legs syndrome. *N Engl J Med*. 2003;348(21):2103–9.

18. Damrauer SJ, Galanter D. Cardozo. In: D. Golan, et al. editors. Principles of Pharmacology: The Pathophysiologic Basis of Drug Therapy. Baltimore: Lippincott Williams & Wilkins; 2005:161–179.

19. Trenkwalder C, et al. Treatment of restless legs syndrome: an evidence-based review and implications for clinical practice. *Mov Disord*. 2008;23(16):2267–302.

20. Benes H, et al. Rapid onset of action of levodopa in restless legs syndrome: a double-blind, randomized, multicenter, crossover trial. *Sleep*. 1999;22(8):1073–81.

21. Trenkwalder C, et al. L-dopa therapy of uremic and idiopathic restless legs syndrome: a double-blind, crossover trial. *Sleep*. 1995;18(8):681–8.

22. Walker SL, Fine A, Kryger MH. L-DOPA/carbidopa for nocturnal movement disorders in uremia. *Sleep*. 1996;19(3):214–8.

23. Kaplan PW, et al. A double-blind, placebo-controlled study of the treatment of periodic limb movements in sleep using carbidopa/levodopa and propoxyphene. *Sleep*. 1993;16(8):717–23.

24. Eisensehr I, et al. Treatment of idiopathic restless legs syndrome (RLS) with slow-release valproic acid compared with slow-release levodopa/benserazid. *J Neurol*. 2004;251(5):579–83.

25. Brodeur C, et al. Treatment of restless legs syndrome and periodic movements during sleep with L-dopa: a double-blind, controlled study. *Neurology*. 1988;38(12):1845–8.

26. Allen R, et al. Ropinirole decreases periodic leg movements and improves sleep parameters in patients with restless legs syndrome. *Sleep*. 2004;27(5):907–14.

27. Bogan RK, et al. Ropinirole in the treatment of patients with restless legs syndrome: a US-based randomized, double-blind, placebo-controlled clinical trial. *Mayo Clin Proc*. 2006;81(1):17–27.

28. Walters AS, et al. Ropinirole is effective in the treatment of restless legs syndrome. TREAT RLS 2: a 12-week, double-blind, randomized, parallel-group, placebo-controlled study. *Mov Disord*. 2004;19(12):1414–23.

29. Adler CH, et al. Ropinirole for restless legs syndrome: a placebo-controlled crossover trial. *Neurology*. 2004;62(8):1405–7.

30. Trenkwalder C, et al. Ropinirole in the treatment of restless legs syndrome: results from the TREAT RLS 1study, a 12 week, randomised, placebo controlled study in 10 European countries. *J Neurol Neurosurg Psychiatry*. 2004;75(1):92–7.

31. Ferini-Strambi L, et al. Effect of pramipexole on RLS symptoms and sleep: a randomized, double-blind, placebo-controlled trial. *Sleep Med*. 2008;9(8):874–81.

32. Jama L, et al. A dose-ranging study of pramipexole for the symptomatic treatment of restless legs syndrome: polysomnographic evaluation of periodic leg movements and sleep disturbance. *Sleep Med*. 2009;10(6):630–6.

33. Montplaisir J, et al. Restless legs syndrome improved by pramipexole: a double-blind randomized trial. *Neurology*. 1999;52(5):938–43.

34. Oertel WH, et al. Efficacy of pramipexole in restless legs syndrome: a six-week, multicenter, randomized, double-blind study (effect-RLS study). *Mov Disord*. 2007;22(2):213–9.

35. Partinen M, et al. Efficacy and safety of pramipexole in idiopathic restless legs syndrome: a polysomnographic dose-finding study—the PRELUDE study. *Sleep Med*. 2006;7(5):407–17.

36. Winkelman JW, et al. Efficacy and safety of pramipexole in restless legs syndrome. *Neurology*. 2006;67(6):1034–9.

37. Trenkwalder C, et al. One-year treatment with standard and sustained-release levodopa: appropriate long-term treatment of restless legs syndrome? *Mov Disord*. 2003;18(10):1184–9.

38. Becker PM, Jamieson AO, Brown WD. Dopaminergic agents in restless legs syndrome and periodic limb movements of sleep: response and complications of extended treatment in 49 cases. *Sleep*. 1993;16(8):713–6.

39. Allen RP, Earley CJ. Augmentation of the restless legs syndrome with carbidopa/levodopa. *Sleep*. 1996;19(3):205–13.

40. Garcia-Borreguero D, et al. A 52-week open-label study of the long-term safety of ropinirole in patients with restless legs syndrome. *Sleep Med*. 2007;8(7–8):742–52.

41. Partinen M, et al. Open-label study of the long-term efficacy and safety of pramipexole in patients with Restless Legs Syndrome (extension of the PRELUDE study). *Sleep Med*. 2008;9(5):537–41.

42. Winkelman JW, Johnston L. Augmentation and tolerance with long-term pramipexole treatment of restless legs syndrome (RLS). *Sleep Med*. 2004;5(1):9–14.

43. Bliwise DL, et al. Randomized, double-blind, placebo-controlled, short-term trial of ropinirole in restless legs syndrome. *Sleep Med*. 2005;6(2):141–7.

44. Lagrow B, editor. Physicians' Desk Reference. 63 ed. 2009, Physicians' Desk Reference Inc.: Montvale, NJ. 3315.

45. Tippman-Peikert M, et al. Pathologic gambling in patients with restless legs syndrome treated with dopaminergic agonists. *Neurology*. 2007;68(4):301–3.

46. Garcia-Borreguero D, et al. Diagnostic standards for dopaminergic augmentation of restless legs syndrome: report from a World Association of Sleep Medicine-International Restless Legs Syndrome Study Group consensus conference at the Max Planck Institute. *Sleep Med*. 2007;8(5):520–30.

47. Silber MH, Girish M, Izurieta R. Pramipexole in the management of restless legs syndrome: an extended study. *Sleep*. 2003;26(7):819–21.

48. Vermeij JD, et al. Parkinson's disease, levodopa-use and the risk of melanoma. *Parkinsonism Relat Disord*. 2009;15(8):551–3.

49. Silber MH, et al. An algorithm for the management of restless legs syndrome. *Mayo Clin Proc*. 2004;79(7):916–22.

50. Griffin R, Woolf C. In: D. Golan, et al. editors. Principles of Pharmacology: The Pathophysiologic Basis of Drug Therapy. Baltimore: Lippincott Williams & Wilkins; 2005:229–43.

51. Sills GJ. The mechanisms of action of gabapentin and pregabalin. *Curr Opin Pharmacol*. 2006;6(1):108–13.

52. Stewart BH, et al. A saturable transport mechanism in the intestinal absorption of gabapentin is the underlying cause of the lack of proportionality between increasing dose and drug levels in plasma. *Pharm Res*. 1993;10(2):276–81.

53. Tan J, et al. Gabapentin in treatment of restless legs syndrome in peritoneal dialysis patients. *Perit Dial Int*. 2006;26(2):276–8.

54. Mellick GA, Mellick LB. Management of restless legs syndrome with gabapentin (Neurontin). *Sleep*. 1996;19(3):224–6.

55. Happe S, et al. Treatment of idiopathic restless legs syndrome (RLS) with gabapentin. *Neurology*. 2001;57(9):1717–9.

56. Adler CH. Treatment of restless legs syndrome with gabapentin. *Clin Neuropharmacol*. 1997;20(2):148–51.

57. Thorp ML, Morris CD, Bagby SP. A crossover study of gabapentin in treatment of restless legs syndrome among hemodialysis patients. *Am J Kidney Dis*. 2001;38(1):104–8.

58. Garcia-Borreguero D, et al. Treatment of restless legs syndrome with gabapentin: a double-blind, cross-over study. *Neurology*. 2002;59(10):1573–9.

59. Kuehn MB. FDA warns of adverse events linked to smoking cessation drugs and antiepileptics. *JAMA*. 2008;229(10):1121.

60. Happe S, et al. Gabapentin versus ropinirole in the treatment of idiopathic restless legs syndrome. *Neuropsychobiology*. 2003;48(2):82–6.

61. Griffin R, Woolf C. In: D. Golan, et al. editors. Principles of Pharmacology: The Pathophysiologic Basis of Drug Therapy. Baltimore: Lippincott Williams & Wilkins; 2005:229–43.

62. Walters AS, et al. Does the endogenous opiate system play a role in the Restless Legs Syndrome? A pilot post-mortem study. *J Neurol Sci*. 2009;279(1–2):62–5.

63. Walters AS, et al. Successful treatment of the idiopathic restless legs syndrome in a randomized double-blind trial of oxycodone versus placebo. *Sleep*. 1993;16(4):327–32.

64. Ondo WG. Methadone for refractory restless legs syndrome. *Mov Disord*. 2005;20(3):345–8.

65. Lauerma H, Markkula J. Treatment of restless legs syndrome with tramadol: an open study. *J Clin Psychiatry*. 1999;60(4):241–4.

66. Walters AS, et al. Long-term follow-up on restless legs syndrome patients treated with opioids. *Mov Disord*. 2001;16(6):1105–9.

67. Vetrugno R, et al. Augmentation of restless legs syndrome with long-term tramadol treatment. *Mov Disord*. 2007;22(3):424–7.

68. Earley CJ, Allen RP. Restless legs syndrome augmentation associated with tramadol. *Sleep Med*. 2006;7(7):592–3.

69. Chou J, Strichartz G, Lo E. In: D. Golan, et al. editors. Principles of Pharmacology: The Pathophysiologic Basis of Drug Therapy. Baltimore: Lippincott Williams & Wilkins; 2005:139–60.

70. Boghen D, et al. The treatment of the restless legs syndrome with clonazepam: a prospective controlled study. *Can J Neurol Sci*. 1986;13(3):245–7.

71. Montagna P, et al. Clonazepam and vibration in restless legs syndrome. *Acta Neurol Scand*. 1984;69(6):428–30.

72. Saletu M, et al. Restless legs syndrome (RLS) and periodic limb movement disorder (PLMD): acute placebo-controlled sleep laboratory studies with clonazepam. *Eur Neuropsychopharmacol*. 2001;11(2):153–61.

73. Bezerra ML, Martinez JV. Zolpidem in restless legs syndrome. *Eur Neurol*. 2002;48(3):180–1.

74. Sloand JA, et al. A double-blind, placebo-controlled trial of intravenous iron dextran therapy in patients with ESRD and restless legs syndrome. *Am J Kidney Dis*. 2004;43(4):663–70.

75. Gigli GL, et al. Restless legs syndrome in end-stage renal disease. *Sleep Med*. 2004;5(3):309–15.

76. Azar SA, Hatefi R, Talebi M. Evaluation of effect of renal transplantation in treatment of restless legs syndrome. *Transplant Proc*. 2007;39(4):1132–3.

77. Read DJ, Feest TG, Nassim MA. Clonazepam: effective treatment for restless legs syndrome in uraemia. *Br Med J (Clin Res Ed)*. 1981;283(6296):885–6.

78. Benz RL, et al. A preliminary study of the effects of correction of anemia with recombinant human erythropoietin therapy on sleep, sleep disorders, and daytime sleepiness in hemodialysis patients (The SLEEPO study). *Am J Kidney Dis*. 1999;34(6):1089–95.

79. Allen RP, Ritchie SY. Clinical efficacy of ropinirole for restless legs syndrome is not affected by age at symptom onset. *Sleep Med*. 2008;9(8):899–902.

80. Stahl SM. The psychopharmacology of energy and fatigue. *J Clin Psychiatry*. 2002;63(1):7–8.

81. Nofzinger EA, et al. Bupropion SR reduces periodic limb movements associated with arousals from sleep in depressed patients with periodic limb movement disorder. *Clin Psychiatry*. 2000;61(11):7–8.

82. Staedt J, et al. Pergolide: treatment of choice in restless legs syndrome (RLS) and nocturnal myoclonus syndrome (NMS). A double-blind randomized crossover trial of pergolide versus L-Dopa. *J Neural Transm*. 1997;104(4–5):461–8.

83. Trenkwalder C, et al. Efficacy of pergolide in treatment of restless legs syndrome: the PEARLS Study. *Neurology*. 2004;62(8):1391–7.

84. Oertel WH, et al. Efficacy of cabergoline in restless legs syndrome: a placebo-controlled study with polysomnography (CATOR). *Neurology*. 2006;67(6):1040–6.

85. Andersohn F, Garbe E. Cardiac and noncardiac fibrotic reactions caused by ergot-and nonergot-derived dopamine agonists. *Mov Disord*. 2009;24(1):129–33.

86. Schade R, et al. Dopamine agonists and the risk of cardiac-valve regurgitation. *N Engl J Med*. 2007;356(1):29–38.

87. Stiles S. Pergolide withdrawn from US market. Medscape Medical News, 2007. Available at: http://www.fda.gov/Drugs/DrugSafety/PublicHealth Advisories/UCM051285 Accessed Apr 1 2010.

88. Telstad W, et al. Treatment of the restless legs syndrome with carbamazepine: a double blind study. *Br Med J (Clin Res Ed)*. 1984;288(6415):444–6.

89. Kushida CA, et al. Randomized, double-blind, placebo-controlled study of XP13512/GSK1838262 in patients with RLS. *Neurology*. 2009;72(5):439–46.