# Effective Health Care Program

## Treatment for Restless Legs Syndrome

### *Executive Summary*

## Introduction

Restless legs syndrome (RLS) is a neurological disorder characterized by unpleasant sensations in the legs and a distressing, irresistible urge to move them. RLS can result in reduced quality of life and interrupt sleep, leading to daytime fatigue. However, effective treatment options are not well established and there is little guidance on diagnosis and treatment. A comprehensive review of the effectiveness and harms of treatments for RLS could lead to improved care for individuals with the syndrome.

RLS is defined and diagnosed based solely on clinical criteria. The essential diagnostic criteria for RLS were established by the International Restless Legs Syndrome Study Group in 1995[1] and revised in 2003.[2] RLS symptoms are triggered by rest or inactivity and worsen at night. Movement such as walking, stretching, or bending the legs provides partial or complete relief. Yet, relief is temporary, and symptoms return when movement ceases.[3]

RLS varies in symptom severity and frequency. Mild RLS may cause minor annoyance, but severe RLS can interfere with work, social activities, function, and emotional well-being. RLS-induced

### Effective Health Care Program

The Effective Health Care Program was initiated in 2005 to provide valid evidence about the comparative effectiveness of different medical interventions. The object is to help consumers, health care providers, and others in making informed choices among treatment alternatives. Through its Comparative Effectiveness Reviews, the program supports systematic appraisals of existing scientific evidence regarding treatments for high-priority health conditions. It also promotes and generates new scientific evidence by identifying gaps in existing scientific evidence and supporting new research. The program puts special emphasis on translating findings into a variety of useful formats for different stakeholders, including consumers.

The full report and this summary are available at **www.effectivehealthcare. ahrq.gov/reports/final.cfm**.

sleep disruption may lead to poor daytime functioning, anxiety, and depression. Sleep deprivation and daytime fatigue are common reasons RLS patients seek treatment.[3]

**AHRQ**
**Agency for Healthcare Research and Quality**
*Advancing Excellence in Health Care • www.ahrq.gov*

**Effective Health Care**

Prevalence estimates for RLS in the United States range from 1.5 percent to 7.4 percent in adults.[4] The variation reflects different approaches to diagnosing RLS and defining its frequency and severity, and the fact that many RLS questionnaires do not account for individuals who have conditions with similar symptoms. A telephone survey of U.S. adults who answered questions about RLS defined as "symptoms occurring at least twice weekly with moderate to severe impact" found prevalence to be 1.5 percent.[2]

The etiology of primary RLS is unknown, but the disorder also occurs secondary to other conditions such as iron deficiency, end-stage renal disease, and pregnancy.[2] A family history of RLS is common and twin studies have shown heritability estimates of 54 to 83 percent. However, findings from genomewide association studies have been inconsistent.[5] Compared with primary RLS, secondary RLS is less common, often starts later in life, and progresses more rapidly, and it tends to resolve when the underlying condition is treated or resolved.[2] Although mechanistic relationships are not well established, the pathophysiology of RLS may be closely linked to abnormalities in the dopaminergic system and iron metabolism.[3] The clinical course of RLS varies. Periods of remission are common, particularly in younger patients and those with milder disease. Severe restless legs syndrome, however, can be a chronic progressive disorder that may require long-term treatment.[3]

Recommended treatments (nonpharmacologic and pharmacologic options) vary by patient age, comorbidities, preferences, and disease severity.[6] Nonpharmacologic options include: exercise, avoiding RLS precipitants (caffeine, alcohol, antidepressants, antihistamines); exercise; counter stimulus to sensory symptoms (hot or cold baths, limb massage, compression stockings, counter-pulsation devices); herbal medicines and acupuncture; and cognitive behavioral therapy.

Pharmacologic treatment is generally reserved for patients with symptoms that are frequent (several times per week) and that cause moderate to very severe discomfort and bother. The major classes of drugs used are dopaminergic agents, sedative hypnotic agents, anticonvulsant calcium channel (alpha-2-delta) ligands, opiates, and iron. Of these, three dopamine agonists (pramipexole, ropinirole, and rotigotine) and one calcium channel (alpha-2-delta) ligands (gabapentin enacarbil) are FDA approved for treatment of moderate to severe RLS.

Dopamine agonists can result in a treatment complication called augmentation, which is a drug-induced worsening of symptoms. Augmentation is characterized by greater symptom intensity, onset earlier in the day, and shorter latency during inactivity. With augmentation, symptoms may also spread to the arms, trunk, and face.[7] Another long-term adverse effect of dopamine agonists includes impulse-control disorders, which may occur in up to 9 to 17 percent of RLS patients using these drugs.[8]

The primary goal of RLS treatment is to reduce or eliminate symptoms and improve patient function, sleep, and quality of life. For patients with RLS believed to be secondary to other conditions (e.g., iron deficiency), treating the underlying condition first is recommended. RLS associated with pregnancy typically resolves postpartum; however, little is known about women with pregnancy-induced RLS, whose symptoms persist after delivery.[9,10] We conducted a systematic review of the effectiveness and harms of RLS treatments with the primary intent to conduct a comparative effectiveness review.

## Scope and Key Questions

### Scope of the Review

We evaluated the efficacy, safety, and comparative effectiveness of pharmacologic and nonpharmacologic treatments for RLS. Pharmacologic interventions included drugs approved for use (for any condition) in the United States. We included individuals with RLS regardless of age or etiology. Although many patients with RLS also experience semi-rhythmic limb movements, called periodic limb movements (PLMs), while awake or asleep, these movements are not specific to RLS. Sleep disorders such as PLM disorder are a distinct entity and not considered in this review. We evaluated RLS symptom severity and outcome, patient-reported sleep quality, and disease-specific quality of life using patient- and physician-validated scale scores for RLS. We assessed treatment-related harms and adherence.

### Key Questions

We developed Key Questions with input from stakeholder groups representing patients, providers, and technical experts. Key Questions not only addressed short-term efficacy and safety but also assessed longer term benefits and harms (including adherence) because many RLS patients require life-long treatment.

**Key Question 1.** What is the comparative effectiveness of treatments for restless legs syndrome (RLS)?

a. What are the benefits from RLS treatments when compared with placebo or no treatment?

b. What are the benefits from RLS treatments when compared with other active treatments?

c. What is the durability and sustainability of treatment benefits?

**Key Question 2.** What are the harms from RLS treatments?

a. What are the harms from RLS treatments when compared with placebo or no treatment?

b. What are the harms from RLS treatments when compared with other active treatments?

c. What are the long-term harms from treatment?

**Key Question 3.** What is the effect of patient characteristics (age, sex, race, comorbidities, disease severity, etiology, iron status, pregnancy, end-stage renal disease) on the benefits and harms of treatments for RLS?

## Methods

### Literature Search Strategy

We searched the bibliographic databases MEDLINE (via OVID), Embase, and Natural Standards through June 2012 for randomized controlled trials (RCTs) evaluating treatment efficacy and for observational studies (including open-label extensions of RCTs) reporting adverse effects and long-term adherence to RLS treatments. The search algorithm, developed with input from a biomedical librarian and independently reviewed by another librarian, consisted of a combination of search strings that described the condition and search filters designed to retrieve relevant RCTs and observational studies (Appendix A in the full report). To identify completed trials and to check for publication bias, we searched Cochrane Central, the International Controlled Trials Registry Platform (ICTRP), Clinicaltrials.gov, Food and Drug Administration (FDA) Web sites, and the National Institutes of Health (NIH) RePORTer. We included eligible unidentified trials referred by peer reviewers.

### Inclusion and Exclusion Criteria

For treatment efficacy, we included studies if they were RCTs that enrolled individuals with RLS as defined by the International Restless Legs Syndrome Study Group in 1995[1] and revised in 2003.[2] Eligible trials must have been published in English, evaluated pharmacologic and/or nonpharmacologic interventions for RLS, lasted at least 4 weeks, and reported validated RLS symptom or quality-of-life scale scores, clinician and patient global impact scale scores, or measures of sleep quality.

We included observational studies and open-label followup extensions of RCTs reporting long-term (>6 months) adverse effects and adherence. Pharmacologic interventions were limited to drugs approved for use (for any condition) in the United States.

### Study Selection

We identified eligible studies in two stages. In the first stage, two investigators independently reviewed titles and abstracts of all references identified in our literature search. Studies deemed potentially eligible for inclusion by either investigator were further evaluated. In the second stage, two investigators independently reviewed full-text articles to determine whether studies met inclusion criteria. Differences in full-text screening decisions were infrequent and were resolved by discussion or, when necessary, by consultation with a third investigator. For all studies, we documented eligibility status. For excluded studies, we recorded at least one exclusion reason at the full-text screening stage. The excluded articles and the reasons for exclusion are listed in Appendix B in the full report.

### Data Extraction

Data from included studies were abstracted directly into evidence tables by one reviewer and validated by a second reviewer. Disagreements were resolved by consensus or, when needed, by consultation with a third reviewer. We abstracted data on the following:

- Study characteristics, including design (e.g. parallel or crossover, long-term extension studies), eligibility criteria, duration, setting, funding source, blinding, intention-to-treat analysis, reporting of dropouts/ attrition

- Patient characteristics, including age, race, sex, comorbidities, RLS diagnostic criteria, previous RLS medication history, duration of RLS (time since diagnosis), baseline RLS symptom severity and frequency, iron, pregnancy, and end-stage renal disease status

- Intervention/comparator characteristics, including type, dosage, titration, and washout period (for crossover trials)

- Outcomes, including International Restless Legs Syndrome Study Group (IRLS) Rating Scale responders defined as "patients with ≥50 percent reduction in IRLS scale score" (our primary outcome), mean change in IRLS scale score from baseline, percentage of patients with complete remission, percentage of patients reporting "much improved" or "very much improved"

on clinicianassessed global impressions (CGI) or patient assessed global impressions (PGI) scales, RLS quality of life, patient-reported sleep quality, number of individuals experiencing adverse effects, dropouts, dropouts due to adverse effects, treatment discontinuation due to adverse effects, specific adverse effects, and augmentation

### Risk of Bias of Individual Studies

We assessed risk of bias of RCTs using the Cochrane risk of bias tool.[11] We addressed: (1) allocation concealment, (2) blinding methods (participant, investigator, and/or outcome assessor), (3) how incomplete data were addressed, (4) intention-to-treat principle, and (5) whether reasons for dropouts/attrition were reported. Studies were rated as good, fair, or poor quality. Observational studies were not formally assessed for quality.

### Data Synthesis

For trials that included similar populations, interventions, and outcomes and that presented sufficient data, we calculated pooled random-effects estimates of overall effect size, weighted mean differences (WMDs), or risk ratios (RRs). Data were pooled and analyzed in Review Manager 5.1.[12] We calculated RR for dichotomous outcomes and WMD or standardized mean differences (SMDs) for continuous outcomes using a random-effects model. We assessed statistical heterogeneity between trials and for subgroups of drugs using the $I^2$ test and observation of the direction of the effect of the studies. Scores of approximately 50 percent and effect sizes that did not fall on the same side of "no effect" suggested substantial heterogeneity. For the fixed-dose trials, we analyzed only the doses recommended for current clinical practice if possible.

### Strength of the Body of Evidence

We evaluated the overall strength of evidence using methods developed by the Agency for Healthcare Research and Quality Effective Health Care Program[13] for the following outcomes: percentage of IRLS responders, (i.e., patients with >50 percent reduction in IRLS scale score); mean change in IRLS scale score from baseline; percent of patients reporting much improved or very much improved on clinician-assessed CGI or PGI; RLS quality of life; patient-reported sleep quality and daytime sleepiness; number of individuals experiencing adverse effects, and dropouts due to adverse effects. We evaluated individual domains qualitatively and assigned a summary rating of high-, moderate-, or low-strength evidence.

### Applicability

We assessed applicability[14] based on the following criteria: eligibility requirements used to select patient populations; patient characteristics such as demographics, baseline RLS symptom severity and frequency, duration of RLS, history of previous therapy, length of followup, and whether individuals had primary or secondary RLS.

## Results

We organized results by Key Question and by class of drug/therapy. We identified 671 unique publications. Title and abstract screening resulted in 138 potentially relevant publications. Full-text screening resulted in 53 studies that fulfilled eligibility criteria and were included: of these 33 were RCTs (31 placebo or usual care controlled) and 18 were observational studies (including open-label extensions of included RCTs) that reported long-term treatment withdrawals, reasons for withdrawals, or percentage of patients developing augmentation. All RCTs that examined pharmacologic treatments were industry sponsored.

### Key Question 1. What is the comparative effectiveness of treatments for restless legs syndrome (RLS)?

a. **What are the benefits from RLS treatments when compared with placebo or no treatment?**

b. **What are the benefits from RLS treatments when compared with other active treatments?**

c. **What is the durability and sustainability of treatment benefits?**

**Key Points**

- RCT results were limited to short-term efficacy studies versus placebo or usual care (≤6 months).

- Compared with placebo, dopamine agonists (ropinirole, pramipexole, and rotigotine) increased the percentage of patients with a clinically important response (>50% reduction in IRLS symptom scale scores or who were improved or much improved on patient or clinician-reported global impressions scale), reduced RLS symptoms, and improved disease-specific quality of life and patient-reported sleep outcomes (high-strength evidence).

- Alpha-2-delta ligands (gabapentin enacarbil, and pregabalin) increased the percentage of patients with a clinically important response (>50% reduction in

IRLS), improved clinician-reported global impressions (high-strength evidence), disease-specific quality of life and other patient-reported sleep outcomes compared with placebo (low-strength evidence). Gabapentin enacarbil improved sleep adequacy based on the medical outcome scale (MOS)-sleep adequacy domain (high-strength evidence).

- We found no clear evidence of a dose effect for the outcomes of IRLS responders or mean change in IRLS scale scores for either dopamine agonists or alpha-2-delta ligands.

- There is limited indirect comparison evidence that the effect on clinically important response may vary somewhat by specific type of dopamine agonist or alpha-2-delta ligand.

- Intravenous ferric carboxymaltose slightly improved IRLS symptom scale scores and disease-specific quality of life compared to placebo[15] (moderate-strength evidence) and improved patient-reported sleep outcomes (low-strength evidence) in patients without iron deficiency.

- No eligible studies assessed opioids, sedative hypnotics, or tramadol, though these are used clinically for RLS treatment.

- One small crossover trial found no significant improvement in IRLS scores with dopamine agonist pramipexole treatment compared with dual release levodopa/benserazide therapy (low-strength evidence).[16] One study[17] found that the dopamine agonist cabergoline improved scores on the IRLS symptom scale and RLS quality of life scale more than levodopa (moderate-strength evidence).

- Four small RCTs[18-21] addressed nonpharmacologic interventions. Pneumatic compression devices[18] reduced IRLS symptom scale scores more than sham (moderate-strength evidence). Near-infrared light treatment improved IRLS symptom scores more than sham (low-strength evidence).[21] Strength training and treadmill walking[19] improved IRLS symptoms, but adherence was poor (low-strength evidence). The botanical extract valerian[20] was not effective (low-strength evidence).

- Applicability to broader populations may be limited because studies enrolled middle-aged adults who were not pregnant and primarily white and who had few comorbidities and RLS symptoms that were long term, frequent, and high-moderate to very severe.

- Observational studies and long-term open-label followup from RCTs of pharmacologic interventions found that treatment withdrawal due to lack of efficacy at 1 year or more ranged from 6 to 32 percent.

**Dopamine Agonists**

The efficacy of dopamine agonists was evaluated in 18 randomized, double-blind, placebo-controlled studies[22-38] and two comparative effectiveness studies.[16,17] Two of the placebo-controlled studies[30,33] and the only comparative effectiveness trial assessed the dopaminergic analog cabergoline,[17] which is not FDA approved for treatment of RLS and is rarely used in the United States due to FDA warnings about cardiac valvular complications. For this reason, we do not include outcomes or characteristics of the two cabergoline placebo-controlled studies[30,33] with the other dopaminergic trials and we do not discuss them in this summary. We do describe the findings of the comparative effectiveness trial of cabergoline versus levodopa because the primary intent of this report is a comparative effectiveness review.[17]

Only two placebo-controlled trials lasted 24 weeks or more,[26,34] and none exceeded 28 weeks. The mean age of participants was 55 years, and women constituted 65 percent (range 55 to 74) of randomized participants. The majority of participants in the seven trials who reported race/ethnicity were white.[23,24,25,28,32,34,37]

All included placebo-controlled RCTs used the IRLS criteria to diagnose RLS. Most studies required at least high moderate to severe symptom severity (most trials required an IRLS scale score of ≥15 at baseline and some required a score >20) with frequent symptom occurrence and duration of at least 1 month. Patients were typically excluded if they were pregnant; if they were contemplating becoming pregnant; or if they had psychiatric disorders, substance abuse disorders, or other serious medical conditions, including renal insufficiency. Mean symptom severity was severe at baseline for all trials assessed using the IRLS scale score (mean=25.1). RLS duration varied with a mean of 17 years for ropinirole to 2 years for rotigotine trials. Trials enrolled newly diagnosed, not previously treated, patients and those who had received prior RLS treatments.

On average, more than half (60%) of patients in the rotigotine trials had received previous RLS treatment, versus 26 percent and 44 percent, respectively, for pramipexole and ropinirole. Seven trials excluded patients with augmentation/end-of-dose rebound during previous RLS treatment. Study drugs were given orally on a

daily (rather than as needed) basis, with the exception of rotigotine, which was delivered transdermally each day. Most studies used flexible up-titration based on symptom response and adverse effects, with doses ranging from 0.125 to 0.75 mg/day for pramipexole, 0.25 to 4 mg/day for ropinirole, and 1 to 3 mg/day for rotigotine. Four studies investigated multiple fixed doses of the drug in separate study arms.[25,34,37,39]

### *IRLS Responders (≥50% Score Reduction)*

The IRLS Rating Scale is a 10-item scale with scores ranging from 0 (no symptoms) to 40. Scores >30 are considered very severe and ≤10, mild.

Seven trials (three pramipexole trials, n=1,079,[28,32,37] and four rotigotine trials, n=1,139[25,31,34,39]) reported the percentage of patients who responded to treatment based on >50 percent reduction in their IRLS symptom scale score from baseline. Compared with placebo, the percentage of patients with a favorable treatment response was greater with the dopamine agonists, pramipexole and rotigotine (RR=1.60; [95% confidence interval (CI), 1.38 to 1.86]). There was no evidence of a difference in treatment efficacy between these two agents. The absolute effect in terms of responders per 100 patients was 24 more (95% CI, 15 more to 35 more) in the dopamine agonist treatment group than with placebo (high-strength evidence).

### *Responders on Clinician- and Patient-Rated Global Impressions Scale*

The percentage of responders (with a rating of much improved or very much improved) on clinician- and patient-reported global scales, respectively, was higher for dopamine agonists than for placebo (respective RRs 1.45 [95% CI, 1.36 to 1.55]) (k=15 trials, n=4,446) and 1.66 [95% CI, 1.45 to 1.90]) (k=6 trials, n=2,069). The strength of evidence for both of these outcomes was high.

### *IRLS-Mean Change From Baseline*

Treatment with dopamine agonists resulted in a small reduction in symptom severity based on change in IRLS scale scores; the weighted mean difference (WMD) in pooled IRLS scores between treatment and placebo was -4.56 (95% CI, -5.42 to -3.70). The magnitude of reduction in IRLS scale scores was greater in studies of rotigotine[25,31,34,39] (-6.09 [95% CI, -7.71 to -4.46]) (k=4, n=585) than in studies of pramipexole[24,26,28,32,37] (-4.76 [95% CI, -6.24 to -3.28]) (k=5, n=1,587) or ropinirole[23,27,35] (-3.49 [95% CI, -4.44 to -2.54]) (k=4, n=1,517) (p=0.02 for interaction). We found no clear evidence of a dose effect in the three fixed-dose

studies of rotigotine or pramipexole that used different doses in separate arms.[25,34,37] The overall strength of evidence was high. Cabergoline[17] improved IRLS scores more than levodopa in a single trial lasting 30 weeks (n=361) among adults with severe IRLS symptoms (mean IRLS score=25.7) (WMD=-7.0 [95% CI, -9.1 to -4.9]) (moderate strength of evidence).

### *Quality of Life and Patient-Reported Sleep Outcomes*

Dopamine agonist improved RLS-specific quality of life as measured by standardized mean differences in RLS quality of life scale scores (k=9, n=2,140). The effect size was small to medium in magnitude (SMD=-0.37 [95% CI, -0.48 to -0.27]). Results were similar across studies of pramipexole (k=2), ropinirole (k=2) and rotigotine (k=4), for drug subgroup (heterogeneity=0%). Overall strength of evidence was high. Dopamine agonists improved patient-reported sleep quality compared with placebo as measured by the Medical Outcomes Study Sleep Problem Index scale (k=8) (standardized mean effect size=0.38 [95% CI, 0.29 to 0.46]). The magnitude of effect was small to moderate. Strength of evidence was high.

### Alpha-2-Delta Ligands

The efficacy of anticonvulsant drugs was evaluated in seven randomized, double-blind, placebo-controlled studies (n=1,066).[40-45] All studies involved alpha-2-delta ligands (gabapentin enacarbil, four trials; pregabalin, two trials; and gabapentin, one trial). Trials were short (one crossover trial of two 4-week intervals,[46] three 6-week trials,[43-45] and three 12-week trials.[40-42] The mean age of study participants was 51 years. Women constituted 60 percent of all participants randomized. In the four studies that reported race,[40,44-46] study participants were predominantly white. All studies used the IRLS criteria to diagnose RLS. All participants had primary RLS. Mean symptom severity at baseline, assessed using the IRLS scale score, was severe (mean IRLS scale score=24). Mean RLS disease duration was 12 years. Trials reported change in RLS symptom severity as assessed by IRLS scale scores (mean change from baseline or score at end of study) and CGI score though reporting methods precluded pooling all studies. One trial was a maintenance trial in which responders (defined as having an IRLS score <15 that had decreased by ≥6 points compared with baseline and having been rated much improved or very much improved on the CGI) to single-blind gabapentin enacarbil treatment were then randomized to continuing gabapentin enacarbil or placebo in a 12-week double-blind phase.[41]

Three trials[40,42,44] evaluated IRLS responders. Overall, alpha-2-delta ligands increased the percentage of IRLS responders (RR 1.66; [95% CI, 1.33 to 2.09]).[40,42,44] The absolute effect in terms of responders per 100 patients was 25 more (95% CI, 12 more to 41 more). The strength of evidence was high. A significantly greater percentage of patients in the alpha-2-delta ligand group reported improved or very much improved on the CGI (RR=1.60 [95% CI, 1.21 to 2.10]). However, there was evidence of statistical heterogeneity between treatment subgroups. Improvement was significant for gabapentin enacarbil therapy but not for pregabalin treatment (p=0.03 for interaction) (high-strength evidence). Gabapentin enacarbil,[40,43,45] pregabalin (k=2),[42,44] and gabapentin[43] reduced symptom severity compared with placebo. The pooled weighted mean change in IRLS score from baseline between alpha-2-delta ligands and placebo groups was -4.26 (95% CI, -5.75 to -2.77) (k=3). The crossover trial by Winkelman found that mean change in IRLS score from baseline significantly favored gabapentin enacarbil.[46] The mean treatment difference versus placebo was -6.6 points (95% CI, -8.6 to -4.6) (high-strength evidence). In the maintenance trial, patients continuing gabapentin enacarbil therapy were significantly less likely to experience relapse (defined as an increase by ≥6 points from randomization to an IRLS score ≥15 points and a rating of much worse or very much worse on the CGI) than patients allocated to placebo, 9 percent and 23 percent, respectively (RR=0.41 [95% CI, 0.20 to 0.85]).[41]

Gabapentin enacarbil significantly improved sleep adequacy based on the MOS-sleep adequacy domain (SMD=0.53 [95% CI, 0.33 to 0.72], k=2). The magnitude of effect was considered moderate and strength of evidence was high.

### Nonpharmacologic Therapies

Four small, short-term studies assessed nonpharmacologic therapies in adults with moderate to severe RLS.[18-21] A good quality RCT of pneumatic compression devices[18] worn for at least 1 hour each day for 4 weeks starting before the time of day when symptoms typically began found an improvement in IRLS symptom scale scores (p=0.006) and daytime somnolence (p=0.04) and complete resolution of symptoms more than sham devices (moderate strength of evidence). One low-quality RCT evaluated near-infrared light therapy compared with sham treatment. Twelve 30-minute near-infrared light treatment sessions were applied over 4 weeks. Near-infrared light treatment significantly improved IRLS symptom scores more than sham, -13.4 points versus -4.5 points, respectively, with a mean difference (MD) of -9.00 (95% CI=-13.21 to

-4.79).[21] Treadmill walking and lower body resistance exercise performed three times weekly for 12 weeks improved IRLS scale scores (MD= -9.4 [95% CI =-13.9 to -4.9]) compared with usual care (moderate quality study and low- strength evidence).[19] However, results were reported only for 28 completers from 41 subjects enrolled. In a moderate-quality RCT of 48 adults with frequent and severe RLS symptoms, the botanical preparation valerian,[20] at 800 mg daily for 8 weeks, did not improve IRLS symptom scale scores more than placebo (p=0.69). The strength of evidence was low.

### Comparative Effectiveness of RLS Treatment and Dose Response

One small crossover trial (n=39)[16] compared treatment with dopamine agonist pramipexole with dual release levodopa/benserazide in newly diagnosed, previously untreated patients over two 4-week periods. Overall reductions of IRLS scores from baseline trended toward significant improvement with pramipexole treatment, with a mean reduction of 7.2 points compared to 4.0 points for levodopa/benserazide (p=0.054). Patients with severe RLS (38% denoted by an IRLS baseline score >20) showed significant reductions in IRLS scores with pramipexole versus levodopa/benserazide (p=0.047) (low-strength evidence).

One 30-week study (n=361)[17] in white adults with severe RLS found that the dopamine agonist cabergoline improved IRLS symptom scale scores (WMD=-6.80 [95% CI, -9.02 to -4.58]) and RLS quality of life more than levodopa (WMD=-7.10 [95% CI, -9.94 to -4.26]) (IRLS scale score=25.7). The strength of evidence was moderate for both outcomes. We found no clear evidence of a dose effect for the outcomes of IRLS responders and mean change in IRLS scale scores for either dopamine agonists (k=3) or the alpha-2-delta ligands pregabalin (k=1).

### Key Question 2. What are the harms from RLS treatments?

a. **What are the harms from RLS treatments when compared with placebo or no treatment?**

b. **What are the harms from RLS treatments when compared with other active treatments?**

c. **What are the long-term harms from treatment?**

### Key Points

• Study withdrawals (due to any reason) from RCTs were slightly less common with dopamine agonist treatments than with placebo (moderate-strength evidence).

- Study withdrawals due to adverse effects were more common with dopamine agonist treatment than with placebo (moderate-strength evidence). Differences between treatments were primarily due to an increase in withdrawals related to adverse effects (application site reactions) reported in three trials of transdermal rotigotine.

- More patients randomized to dopamine agonist had at least one adverse effect compared with placebo (high-strength evidence).

- Short-term adverse effects from treatment with dopamine agonists compared with placebo were nausea, vomiting, somnolence, and fatigue (high-strength evidence for all these outcomes).

- Application site reactions were much more common with transdermal rotigotine than with placebo (high-strength evidence).

- Study withdrawals (due to any reason) were less common in patients randomized to alpha-2-delta ligands than to placebo (high-strength evidence).

- Somnolence, unsteadiness or dizziness, and dry mouth were much more common with alpha-2-delta ligands than with placebo (high-strength evidence for all these outcomes).

- Incidences of diarrhea and blood phosphorus decrease were reported with intravenous iron therapy.

- No adverse events, except for a few cases of nausea, were reported in the trial evaluating bupropion.

- One small crossover trial reported higher incidences of augmentation and rebound (RLS symptoms in the early morning) with dual release levodopa/benserazide therapy versus pramipexole.

- Data from observation studies indicate that long-term augmentation ranged from 2.5 percent to 60 percent and varied markedly by type of dopamine agonist, followup time, study design, and method used to ascertain augmentation. We found no clear pattern to explain this variability.

- Withdrawal from mostly dopamine agonist and levodopa treatment was common, occurring in 13 percent to 57 percent of subjects due either to lack of efficacy or adverse effects. Most studies reported treatment withdrawals greater than 20 percent at 1 year.

**Short-Term Harms**

We evaluated three measures of short-term treatment harms from randomized placebo controlled trials: any study withdrawal, study withdrawal due to adverse effects, and patients reporting at least one adverse effect. Patients were less likely to withdraw from dopamine agonist treatment than from placebo treatment (20% vs. 24%; RR=0.79; [95% CI, 0.66 to 0.94], k=16) (moderate-strength evidence). There was an overall significant increase in study withdrawals due to adverse effects associated with dopamine agonist treatment (10% vs. 6%; RR=1.37 [95% CI, 1.03 to 1.82], k=16) (high-strength evidence). Risk of withdrawal due to adverse events appeared to differ between dopamine agonists ($I^2$=73%, p=0.02), with the highest increase associated with rotigotine therapy (RR=2.50 [95% CI, 1.33 to 4.70]). More patients reported at least one adverse effect with dopamine agonist compared with placebo (RR=1.19; [95% CI, 1.12 to 1.28], k=16) (high-strength evidence).

Short-term adverse effects from treatment with dopamine agonists compared with placebo were nausea (23% vs. 7%, RR=3.31 [95% CI, 2.53 to 4.33], k=15), vomiting (7% vs. 2%, RR=4.48 [95% CI, 2.68 to 7.48], k=8), and somnolence (12% vs. 6%, RR=2.04; [95% CI, 1.50 to 2.76], k=8) (overall high-strength evidence for these outcomes). Application site reactions were much more common with transdermal rotigotine than with placebo (29% vs. 3%; RR=8.32 [95% CI, 3.45 to 20.05], k=4) (high-strength evidence).

Patients allocated to alpha-2-delta ligand therapy were less likely to withdraw from treatment due to any reason than patients allocated to placebo (12% vs. 18%; RR=0.68 [95% CI, 0.47 to 0.98], k=4) (high-strength evidence). Compared with placebo, alpha-2-delta ligand treatment was associated with an overall nonsignificant increase in study withdrawals due to adverse effects (8% vs. 4%; RR=1.86 [95% CI, 0.95 to 3.63], k=4) (moderate-strength evidence).

Compared with placebo, certain short-term adverse effects were significantly greater with alpha-2-delta ligand treatment: somnolence (19% vs. 3%, RR=5.37 [95% CI, 2.38 to 12.12], k=5), unsteadiness or dizziness (17% vs. 4%, RR=4.11 [95% CI, 2.19 to 7.71], k=4), and dry mouth (6% vs. 1%; RR=3.31 [95% CI, 1.09 to 10.05], k=4) (overall high-strength evidence for these outcomes).

Three subjects each reported diarrhea (12.5%) and blood phosphorus decrease (12.5%) with intravenous iron

therapy.[15] No subjects in the placebo arm reported these events. Two patients allocated to bupropion and one to placebo discontinued treatment due to nausea.[47] No other adverse events were reported.

## Comparative Harms

One small moderate-quality crossover trial (n=39)[16] of two 4-week periods reported higher incidences of augmentation and rebound (RLS symptoms in the early morning) with dual release levodopa/benserazide therapy versus pramipexole treatment in newly diagnosed, not previously treated patients (Appendix G in the full report). Higher incidences of nausea, headache, and vomiting were associated with pramipexole.

One 30-week good-quality randomized trial reported that compared with levodopa, cabergoline[17] resulted in less augmentation and augmentation leading to withdrawal (moderate-strength evidence). The drugs did not differ with regard to any study withdrawals. Cabergoline is not approved for treatment of RLS and is rarely used in the United States due in part to FDA warnings about increased risk of cardiac valvular abnormalities and other adverse effects.

We observed subgroup differences across types of dopamine agonist for certain adverse effects. However, we urge caution in regard to direct comparisons, because these are based on subgroup differences observed in placebo-controlled trials, not on direct comparisons between drugs. Study and patient characteristics may account for some or all of the between-study differences we observed (or for the lack of differences in other adverse effects). Withdrawals due to application site reactions were unique to transdermal rotigotine; all other studied pharmacologic agents are taken orally. Application site reactions were the main factor leading to more withdrawals in studies of rotigotine than in studies of pramipexole or ropinirole ($I^2$=73%, p=0.02). Compared with placebo, the risk ratio of site reaction[25,31,34,39] (k=4) was similar across doses of rotigotine, ranging from 0.5 to 3.0 mg/day. The risk ratio of nausea, fatigue, and somnolence for rotigotine, pramipexole, and ropinirole versus placebo did not vary significantly by dose, although the numbers of patients and events in each dose subgroup were small; confidence intervals were wide and overlapped.

## Long-Term Harms and Withdrawal From Treatment

We used data from 18 observational studies[48-65] (including open-label extensions of RCTs) that reported at least 6 months of followup to assess the percentage of individuals withdrawing from pharmacologic treatments and reasons for withdrawal (e.g., lack of efficacy, adverse events, and augmentation). Followup duration ranged from 6 months to 10 years. Data were available for gabapentin (one study), opioids (multiple opioids, one study; methadone, one study) and dopamine agonists. Withdrawal from treatment was common, occurring in 13 percent to 57 percent of subjects. The highest withdrawals were in studies of levodopa (withdrawals all greater than 40%). Withdrawal from gabapentin and the dopamine agonists was typically greater than 20 percent. About half of withdrawals were due to adverse events, including augmentation; 20 percent to 30 percent of withdrawals were due to lack of efficacy.

## Key Question 3. What is the effect of patient characteristics (age, sex, race, comorbidities, disease severity, etiology, iron status, pregnancy, end-stage renal disease) on the benefits and harms of treatments for RLS?

### Key Points

- No RCTs examined the effect of patient or RLS characteristics on benefits and harms of treatments for primary RLS.

- No RCTs enrolled children or any women who were pregnant or recently postpartum, and nearly all specifically excluded these individuals.

- No eligible studies enrolled individuals with end-stage renal disease, and almost all specifically excluded these individuals.

- Two small randomized trials of iron therapy versus placebo in adults with iron deficiency provided low-strength evidence that iron may improve both the percentage of adults considered IRLS responders and the IRLS symptom scale scores.

We found almost no evidence addressing the effect of patient characteristics on benefits and harms of treatments for RLS. While studies generally provided baseline sex, age, race, disease severity, and primary and secondary RLS etiologies, results were not stratified by these characteristics. No study evaluated patients exclusively based on sex, age, race, comorbidities, disease severity/duration, or prior treatment characteristics. On average, trials enrolled middle-aged white adults (mostly women) with primary RLS of long duration, many of whom had been treated previously, and whose symptoms were frequent and high-moderate to severe.

Studies typically excluded patients with psychiatric or other serious comorbid conditions, including patients

with renal or liver disease and women who are pregnant or contemplating becoming pregnant. No studies assessed treatments in pregnant women, and no eligible studies assessed treatments in patients with end-stage renal disease. The minimum age for entry to studies was always at least 18 years, thus we found no information on treatment of RLS in children or adolescents.

Two small, good quality RCTs evaluated iron therapy (one intravenous and one oral) in patients with RLS secondary to iron deficiency.[66,67] One 12-week trial of 18 subjects found that compared with placebo, iron reduced IRLS scale scores by 9.16 points (95% CI, -5.2 to -3.1).[67] Another trial of intravenous iron sucrose (administered five times over 3 months to 60 subjects) found no difference versus placebo at 12 months in mean change in IRLS scale scores (p=0.47).[66] A post hoc analysis at 11 weeks found an increase in the percentage of subjects considered IRLS responders among those randomized to iron (RR=1.85; [95% CI, 1.07 to 3.18]).[66] By 12 months, 21 of 31 subjects (68%) in the placebo group and 9 of 29 (31%) in the iron group withdrew.[66] Of these, 19 and 5, respectively withdrew due to lack of efficacy. The strength of evidence for these outcomes was low.

### Study Quality/Risk of Bias and Applicability

Nearly all of the pharmacologic trials (dopamine agonist, anticonvulsants, and iron therapies) were considered of good quality (having a low risk of bias) (Tables A-C). A funnel plot of all the 12 placebo-controlled dopamine agonist trials reporting mean change in the IRLS total score from baseline showed no asymmetry (Egger intercept 2-sided p=0.35). The applicability of the included evidence for RLS treatments is limited. Included studies were mostly short-term, placebo-controlled efficacy studies of dopamine agonists and alpha-2-delta ligands conducted in a highly selected population of adults with moderate to very severe primary RLS of long duration. Applicability to adults with less frequent or less severe (mild to moderate) RLS symptoms, children, or those with secondary RLS is unknown. Furthermore, studies did not address long-term effectiveness, the comparative effectiveness, and harms of commonly used treatments, or the effect the patient or RLS characteristics have on outcomes.

## Discussion

The primary intent of this report was to conduct a comparative effectiveness review on treatments for restless legs syndrome. However, we identified only two RCTs that directly compared treatment options. Included studies did not permit reliable indirect comparisons from which to draw robust conclusions about comparative benefits and harms. Results from small, placebo-controlled randomized trials of generally short duration demonstrated that dopamine agonists (ropinirole, pramipexole, and rotigotine) and anticonvulsant alpha-2-delta ligands (gabapentin enacarbil, gabapentin, and pregabalin) increase the percentage of individuals responding to treatment, as defined by a 50-percent reduction in the IRLS symptom scale score or reporting improved or much improved on the CGI or PGI scores, reduced RLS symptoms, and an improved disease-specific quality of life and patient-reported sleep outcomes. However, adverse effects of pharmacologic therapies and long-term treatment withdrawals due to adverse effects or lack of efficacy are common.

Evidence is lacking about the long-term effectiveness in, and applicability to, adults with less severe or less frequent RLS symptoms, children, or individuals with secondary RLS, including women who are pregnant or intending to become pregnant and adults with iron deficiency or end-stage renal disease. Studies of pharmacologic therapies consisted mainly of dopaminergic agents; a few studies assessed alpha-2-delta ligands. All studies administered therapies daily rather than as needed. Although the effectiveness, harms, and adherence to as needed therapy are unknown, current recommendations note this as an option.[6] Few nonpharmacologic therapies were assessed, and no individual nonpharmacologic treatment was studied in more than a single trial. RCTs enrolled highly selected populations with symptoms that were very severe to high-moderate, frequent, and long-standing.

Exclusion criteria were many, and subjects were typically recruited from RLS clinics rather than primary care or mental health settings; both settings are frequent sites for detection and management of individuals with RLS. Enrollees had greater disease severity, frequency, and duration than was reported by the estimated 1.5 percent of individuals described as RLS sufferers based on a telephone survey of adults who agreed to be interviewed about RLS. No RCTs assessed patients with mild or moderate disease, and few lasted longer than 6 months. None of the enrolled individuals were under age 18, and the majority of individuals were White.

We included studies that reported validated RLS symptom scale measures assessing overall disease severity, impact, quality of life, patient- and physician-reported global assessment, and sleep quality. However, thresholds establishing a clinically important effect size are unknown.

# Table A. Overall strength of evidence for individual outcomes in placebo-controlled studies of dopamine agonists

| Outcome | Treatments | Number of Trials | n | Summary Statistics [95% CI] | Risk of Bias | Directness | Precision | Consistency | Evidence Rating |
|---|---|---|---|---|---|---|---|---|---|
| IRLS responders (≥50% score reduction) | All trials vs. placebo | 7 | 2,218 | RR 1.60 [1.38 to 1.86] | Low | Direct | Precise | Consistent | High |
| | pramipexole | 3 | 1,079 | RR 1.46 [1.22 to 1.74] | Low | Direct | Precise | Consistent | High |
| | rotigotine | 4 | 1,139 | RR 1.76 [1.47 to 2.10] | Low | Direct | Precise | Consistent | High |
| IRLS total score: mean change from baseline | All trials vs. placebo | 14 | 3,578 | WMD -4.56 [-5.42 to -3.70] | Low | Direct | Precise | Consistent | High |
| | pramipexole | 5 | 1,578 | WMD -4.76 [-6.24 to -3.28] | Low | Direct | Precise | Consistent | High |
| | ropinirole | 5 | 1,517 | WMD -3.49 [-4.44 to -2.54] | Low | Direct | Precise | Consistent | High |
| | rotigotine | 4 | 585 | WMD -6.09 [-7.71 to -4.46] | Low | Direct | Precise | Consistent | High |
| Clinician-assessed Global Impressions responders: (much–very much improved) | All trials vs. placebo | 15 | 4,446 | RR 1.45 [1.36 to 1.55] | Low | Direct | Precise | Consistent | High |
| | pramipexole | 5 | 1,747 | RR 1.61 [1.40 to 1.86] | Low | Direct | Precise | Consistent | High |
| | ropinirole | 6 | 1,608 | RR 1.37 [1.25 to 1.50] | Low | Direct | Precise | Consistent | High |
| | rotigotine | 4 | 1,091 | RR 1.37 [1.22 to 1.54] | Low | Direct | Precise | Consistent | High |
| Patient-assessed Global Impressions responders: (much–very much improved) | All trials vs. placebo | 6 | 2,069 | RR 1.66 [1.45 to 1.90] | Low | Direct | Precise | Consistent | High |
| | pramipexole | 5 | 1,712 | RR 1.72 [1.45 to 2.05] | Low | Direct | Precise | Consistent | High |
| | ropinirole | 1 | 357 | RR 1.52 [1.29 to 1.79] | Moderate | Direct | Precise | Unknown | Moderate |
| RLS quality of life | All trials vs. placebo | 9 | 2,140 | SMD -0.37 [-0.48 to -0.27] | Low | Direct | Precise | Consistent | High |
| | pramipexole | 3 | 912 | SMD -0.43 [-0.61 to -0.25] | Low | Direct | Precise | Consistent | High |
| | ropinirole | 2 | 643 | SMD -0.30 [-0.45 to -0.14] | Low | Direct | Precise | Consistent | High |
| | rotigotine | 4 | 585 | SMD -0.37 [-0.60 to -0.13] | Low | Direct | Precise | Consistent | High |
| Self-rated sleep MOS-SPI-II | All trials vs. placebo | 8 | 2,052 | SMD 0.38 [0.29 to 0.46] | Low | Direct | Precise | Consistent | High |
| | pramipexole | 1 | 356 | SMD 0.36 [0.15 to 0.57] | Low | Direct | Precise | Unknown | Moderate |
| | ropinirole | 4 | 1,237 | SMD 0.37 [0.24 to 0.49] | Low | Direct | Precise | Consistent | High |
| | pramipexole | 3 | 459 | SMD 0.43 [0.24 to 0.61] | Low | Direct | Precise | Consistent | High |

## Table A. Overall strength of evidence for individual outcomes in placebo-controlled studies of dopamine agonists (continued)

| Outcome | Treatments | Number of Trials | n | Summary Statistics [95% CI] | Risk of Bias | Directness | Precision | Consistency | Evidence Rating |
|---|---|---|---|---|---|---|---|---|---|
| Any study withdrawal | All trials vs. placebo | 16 | 4,860 | RR 0.79 [0.66 to 0.94] | Low | Direct | Precise | Inconsistent | Moderate |
| | *pramipexole* | 5 | 1,792 | RR 0.71 [0.50 to 1.01] | Low | Direct | Imprecise | Inconsistent | Low |
| | *ropinirole* | 7 | 1,698 | RR 0.84 [0.67 to 1.06] | Low | Direct | Imprecise | Consistent | Moderate |
| | *rotigotine* | 4 | 1,370 | RR 0.83[0.54 to 1.26] | Low | Direct | Imprecise | Inconsistent | Low |
| Study withdrawals due to an adverse event | All trials vs. placebo | 16 | 4,860 | RR 1.37 [1.03 to 1.82] | Low | Direct | Precise | Consistent | High |
| | *pramipexole* | 5 | 1,791 | RR 0.97 [0.69 to 1.35] | Low | Direct | Imprecise | Consistent | Moderate |
| | *ropinirole* | 7 | 1,698 | RR 1.48 [0.99 to 2.20] | Low | Direct | Imprecise | Consistent | Moderate |
| | *rotigotine* | 4 | 1,370 | RR 2.50 [1.33 to 4.70] | Low | Direct | Precise | Consistent | High |
| Patients with ≥1 adverse event | All trials vs. placebo | 16 | 4,854 | RR 1.19 [1.12 to 1.28] | Low | Direct | Precise | Consistent | High |
| | *pramipexole* | 5 | 1,790 | RR 1.16 [1.04 to 1.29] | Low | Direct | Precise | Inconsistent | Moderate |
| | *ropinirole* | 7 | 1,695 | RR 1.20 [1.10 to 1.32] | Low | Direct | Precise | Consistent | High |
| | *rotigotine* | 4 | 1,369 | RR 1.25 [1.00 to 1.59] | Low | Direct | Precise | Consistent | High |

CI = confidence interval; IRLS = International Restless Legs Syndrome Study Group Rating Scale; MOS-SPI-II = Medical Outcomes Scale- Sleep Problems Index II; RLS = restless legs syndrome; RR = risk ratio; SMD = standardized mean difference; WMD = weighted mean difference (a negative SMD and WMD indicates that the active treatment is more effective than the placebo)

# Table B. Overall strength of evidence for individual outcomes in placebo-controlled studies of alpha-2-delta ligands

| Outcome | Treatments | Number of Trials | n | Summary Statistics [95% CI] | Risk of Bias | Directness | Precision | Consistency | Evidence Rating |
|---|---|---|---|---|---|---|---|---|---|
| IRLS responders (≥50% score reduction) | All trials vs. placebo | 3 | 503 | RR 1.66 [1.33 to 2.09] | Low | Direct | Precise | Consistent | High |
| | Gabapentin enacarbil | 1 | 321 | RR 1.54 [1.18 to 2.01] | Low | Direct | Precise | Unknown | Moderate |
| | Pregabalin | 2 | 182 | RR 2.03 [1.33 to 3.11] | Low | Direct | Precise | Consistent | High |
| IRLS total score: mean change from baseline | All trials vs. placebo | 3 | 475 | WMD -4.26 [-5.75 to -2.77] | Low | Direct | Precise | Consistent | High |
| | Gabapentin enacarbil | 2* | 431 | WMD -4.18 [-5.76 to -2.60] | Low | Direct | Precise | Consistent | High |
| | Pregabalin | 1 | 44 | WMD -4.90 [-9.41 to -0.39] | Low | Direct | Precise | Unknown | Moderate |
| Clinical global impressions: responders (much improved) | All trials vs. placebo | 3 | 662 | RR 1.60 [1.21 to 2.10] | Low | Direct | Precise | Consistent | High |
| | Gabapentin enacarbil | 2** | 538 | RR 1.80 [1.51 to 2.14] | Low | Direct | Precise | Consistent | High |
| | Pregabalin | 1 | 124 | RR 1.14 [0.80 to 1.64] | Low | Direct | Imprecise | Unknown | Low |
| RLS quality of life | All trials vs. placebo | 2 | 263 | SMD 0.27 [-0.17 to 0.70] | Low | Direct | Imprecise | Inconsistent | Low |
| | Gabapentin enacarbil | 1 | 220 | SMD 0.42 [0.16 to 0.69] | Low | Direct | Precise | Unknown | Moderate |
| | Pregabalin | 1 | 122 | SMD -0.05 [-0.65 to 0.55] (300 mg dose)† | Low | Direct | Imprecise | Unknown | Low |
| Self-rated sleep MOS-sleep adequacy | Gabapentin enacarbil | 2 | 431 | SMD 0.53 [0.33 to 0.72] | Low | Direct | Precise | Consistent | High |

**Table B. Overall strength of evidence for individual outcomes in placebo-controlled studies of alpha-2-delta ligands (continued)**

| Outcome | Treatments | Number of Trials | n | Summary Statistics [95% CI] | Risk of Bias | Directness | Precision | Consistency | Evidence Rating |
|---|---|---|---|---|---|---|---|---|---|
| Any study withdrawal | All trials vs. placebo | 5 | 936 | RR 0.71 [0.52 to 0.99] | Low | Direct | Precise | Consistent | High |
| | Gabapentin enacarbil | 3 | 741 | RR 0.70 [0.49 to 1.00] | Low | Direct | Precise | Consistent | High |
| | Pregabalin | 2 | 195 | RR 0.79 [0.37 to 1.68] | Low | Direct | Imprecise | Inconsistent | Low |
| Patients with ≥1 adverse event | All trials vs. placebo | 5 | 933 | RR 1.17 [0.1.00 to 1.36] | Low | Direct | Imprecise | Consistent | Moderate |
| | Gabapentin enacarbil | 3 | 738 | RR 1.09 [0.1.00 to 1.19] | Low | Direct | Precise | Consistent | High |
| | Pregabalin | 2 | 195 | RR 1.67 [0.74 to 3.80] | Low | Direct | Imprecise | Consistent | Moderate |

CI = confidence interval; IRLS = International Restless Legs Syndrome Study Group Rating Scale; MD = mean difference; MOS = medical outcome scale; RLS = restless legs syndrome; RR = risk ratio; SMD = standardized mean difference; WMD = weighted mean difference

*An additional crossover trial (Winkleman 2011) also reported significant improvement versus placebo (MD in improvement from baseline was -6.57 [95% CI -8.58 to -4.57].

**An additional crossover trial (Winkleman 2011) also reported significant improvement versus placebo (Gabapentin enacarbil 74% much improved or very much improved versus 36% for placebo).

†Fixed-dose trial (5 doses, 50-450 mg), range of SMDs from -0.05 to -0.43. No dose was significantly superior to placebo.

**Table C. Overall strength of evidence for iron trials for the treatment of secondary RLS**

| Outcome | Number of Trials | N | Summary Statistics [95% CI] | Risk of Bias | Directness | Precision | Consistency | Strength of Evidence |
|---|---|---|---|---|---|---|---|---|
| IRLS responders (≥50% score reduction)* | 1 | 60 | RR 1.85 [1.07 to 3.18] | Low | Direct | Precise | Unknown | Low* |
| IRLS total score: mean change from baseline | 2 | 78 | WMD -5.25 [-12.44 to 1.95] | Low | Direct | Imprecise | Inconsistent | Low |

CI = confidence interval; IRLS = International Restless Legs Syndrome Study Group Rating Scale; RR = risk ratio; WMD = weighted mean difference

*Post hoc analysis

Although symptom scales are widely used in research studies, their use in clinical settings is less clear and likely limited. Furthermore, despite the fact that RCT study subjects met consensus definitions of RLS, these criteria may not be automatically used in clinical settings to diagnose, assess the severity of, or initiate therapy for RLS. Thus, we do not know the applicability of results from these RCTs to individuals seen, diagnosed, and treated in primary care or mental health settings. Outcomes were not stratified by patient and RLS characteristics, and we could not determine whether findings varied by these factors. Other scale scores are often reported. We focused on outcomes that are most widely used, appear to have the greatest face validity and have clinically meaningful impact especially relevant to patients diagnosed and treated in the United States.

Only two RCTs directly compared pharmacologic options; specifically, cabergoline to levodopa, and pramipexole to dual-release levodopa/benserazide. We found no clear evidence of a dose effect for the outcomes of IRLS responders and mean change in IRLS scale scores for either dopamine agonists (k=3) or the alpha-2-delta ligands (k=2). Because studies reported a large placebo response, we urge caution in using information from uncontrolled studies as the basis for increasing drug doses or altering administration timing if symptom response is inadequate. Similarly, we urge caution in attributing benefits that might be observed in clinical settings to dose adjustment.

Few studies assessed individuals with secondary RLS. No studies enrolled pregnant women. Only two studies assessed the effect of iron therapy on RLS symptoms in adults with iron deficiency. These studies were small, short, and had methodological flaws; however, they suggested that iron therapy may improve symptoms in these individuals. A single study that did not meet our eligibility criteria because it did not use validated IRLS symptom scale scores found no benefit with oral iron therapy in adults with RLS and normal iron stores.[15] Another small short-term RCT assessed intravenous iron versus placebo in patients on hemodialysis with normal iron stores. This study found no benefit. We identified one other study in adults with RLS believed secondary to end-stage renal disease. This study compared gabapentin to placebo, did not report validated RLS symptom scale scores, and showed no benefit with the drug.

For individuals unable to initiate or tolerate dopaminergic agents, or for whom these drugs have failed, recommended pharmacologic treatments include off-label opioids (morphine, oxycodone, and methadone), sedative hypnotics, and tramadol. None of these are FDA approved for treatment of RLS, and all have the potential for long-term abuse, especially given the subjective nature of RLS symptoms and the large placebo response seen in other pharmacologic studies. We found no eligible studies evaluating these agents. A single, placebo-controlled, crossover study of 11 patients found oxycodone improved leg sensation, motor restlessness, and alertness. Randomized controlled studies should be initiated to evaluate the benefits of these therapies not approved for RLS treatment by the FDA in individuals who are refractive to standard pharmacologic treatment.

We found no RCT data on the comparative benefits or harms of dopamine agonists and anticonvulsant alpha-2-delta ligands. Only two small studies of iron therapy addressed secondary RLS due to iron deficiency, providing low-strength evidence that iron replacement therapy may improve symptoms. Assessment of nonpharmacologic interventions was limited to four trials. These provided low-strength evidence for a benefit with compression stockings, near infrared light, and exercise, but not for valerian.

No RCTs assessed the effect of patient characteristics on treatment benefits and harms. We found no evidence on effectiveness of these interventions in children, older adults with multiple morbidities, pregnant or recently postpartum women, or individuals with end-stage renal disease. All pharmaceutical trials were industry sponsored.

Trials reported a large placebo effect, thus future studies require adequate blinding. Moreover, clinicians and patients should be aware of such a large placebo response. Long-term studies reporting withdrawals due to loss of efficacy or side effects suggest that for many RLS patients, the benefits of pharmacologic treatment are not sustained over time, and that these treatments result in adverse effects and are often discontinued. Augmentation, a drug-induced exacerbation of the disease, can occur with dopaminergic drugs.

Evaluating RLS treatments requires determining the change in scale scores that constitutes a minimum clinically important difference. These thresholds have not been established for the IRLS scale score and other scales commonly reported in RLS research. Further, high-quality research is needed to determine whether treatment benefits observed in short-term studies are maintained, and whether the therapies are tolerated long term. The target populations for these drugs are patients with moderate to severe RLS, who may require daily treatment for decades. Even nonpharmacologic interventions and other treatments for those with milder symptoms are often long term. Yet,

evidence is limited to short-term efficacy trials or observational studies among highly selected individuals.

Given such limited evidence, patients and providers face uncertainty regarding the benefits and risks of RLS treatments for individuals whose symptoms are less severe, less frequent, of shorter duration, or diagnosed based on criteria that differ from RLS consensus definitions. Results from short-term efficacy trials in a highly selected population of RLS patients should be carefully interpreted for their applicability to the more heterogeneous population of RLS patients in primary care settings. Applicability concerns are even more salient in light of direct-to-consumer marketing that has raised awareness of potential RLS symptoms.[68] The populations in clinical trials had RLS of high-moderate to severe intensity for many years, and many of these patients had received previous unsuccessful drug treatment for RLS. In contrast, individuals presenting to primary care with RLS like-symptoms may have milder symptoms or other conditions with symptoms that mimic RLS (e.g., periodic leg movement disorders, nocturnal leg cramps, vascular or neurogenic claudication). They may also be younger, older, or have more comorbidities than subjects included in available RCTs.

In conclusion, randomized controlled trial evidence for RLS treatments is mostly limited to short-term, placebo-controlled studies of dopamine agonists and alpha-2-delta ligands conducted in a highly selected population of adults with high moderate to very severe primary RLS of long duration. Compared with placebo, dopamine agonists and alpha-2-delta ligands increase the percentage of individuals responding, reduce RLS symptom scores, and improve patient-reported sleep outcomes, disease-specific quality of life, and overall RLS impact. Both short- and long-term adverse effects and treatment withdrawals due to adverse effects or lack of efficacy for dopamine agonists and alpha-2-delta ligands are common. We found no high-quality data on comparative effectiveness and harms of commonly used treatments, little data on nonpharmacologic interventions or the effect of patient or RLS characteristics on outcomes. Applicability is unknown for adults with less frequent or less severe RLS symptoms, children, or those with secondary RLS.

### Future Research Recommendations

Table D summarizes our recommendations for future research based on the gaps identified in this review.

| Table D. Future research recommendations | | |
|---|---|---|
| **Topical Issues** | **Specific Research Gaps** | **Recommendations** |
| Limited evidence base | • Evidence base consists almost exclusively of pharmacologic treatments, and dopamine agonists in particular.<br><br>• Many classes of drugs used in clinical practice such as opioids and sedative hypnotics have not been evaluated in clinical trials.<br><br>• We found no evidence for effectiveness of therapies in specific subgroups such as children, older adults with multimorbidities, or individuals with secondary RLS. | • Randomized trials of nonpharmacologic treatments including herbal therapy, mind-body medicine, and manipulative treatments.<br><br>• Randomized trials of classes of drugs other than dopamine agonists, such as opioids and sedative hypnotics.<br><br>• Randomized trials of effectiveness of drugs in specific patient subgroups such as children, older adults, and individuals with secondary RLS. |
| Long-term durability of treatment benefits | • Long-term durability of treatment benefits remains unknown. | • High-quality, long-term, open-label extension studies from randomized trials that establish the time frame over which treatment benefits are sustained for different drugs and in specific group of patients. |
| Impact of patient characteristics on treatment outcomes | • We found no studies that address how patient characteristics, such as disease duration and previous therapy, affect treatment outcomes. | • Randomized trials that report effectiveness of treatments for subgroups of patients such as those with different disease duration, those new to treatment, and those for whom previous treatment failed. |

| Table D. Future research recommendations (continued) | | |
|---|---|---|
| **Topical Issues** | **Specific Research Gaps** | **Recommendations** |
| Augmentation | • Augmentation is a significant harm with dopaminergic therapy and can lead to treatment discontinuation; yet, little is known about patient characteristics that may lead to augmentation. | • Long-term studies of augmentation with dopaminergic therapy. Potential study designs could include RCTs, prospective observational studies, and retrospective observational studies, including case-control studies.<br><br>• Studies that evaluate specific patient characteristics such as iron status and disease severity that may make patients susceptible to augmentation with dopaminergic therapy. |
| **Methodological Issues** | **Findings** | **Research Needs** |
| Outcome measures | • It is not clear if the degree of benefit as established by symptom scale scores such as IRLS scale translate to meaningful improvement for patients.<br><br>• The clinical relevance of objective measures of assessment such as polysomnography is not clear. | • Establish minimum important differences in scale scores that translate to clinically significant improvement for individual patients.<br><br>• Report outcomes such as proportions of patients with remission of symptoms (IRLS score=0), patient-reported sleep outcomes, and quality of life.<br><br>• Establish clinical relevance of polysomnography and other objective outcomes (perform studies correlating polysomnography outcomes to clinically significant changes such as remission of symptoms). |
| Time frame for evaluation of treatments | • Most clinical trials were of short duration (typically 12 weeks) yet RLS patients whose symptoms are severe confront a chronic, progressive disease that may require lifelong treatment. | • Longer term (>6 months) studies to establish if treatment benefits are sustained over time and to ascertain long-term harms such as augmentation. |
| Severity of disease | • Clinical trials include patients with moderate to very severe disease typically by specifying a cut-off in IRLS scale score (IRLS score>15). | • Evaluate and report treatment effectiveness for RLS patients with different degrees of symptom severity. (e.g., categories of severity by IRLS scale scores: 1-10: mild; 11-20: moderate; 21-30: severe; 31-40: very severe). |
| Assessment of augmentation with dopaminergic therapy | • Considerable variation in reported prevalence of augmentation by type of drug, time frame of evaluation, and method of assessment. | • Assess augmentation with different dopaminergic drugs using standard criteria and methods of assessment. |

IRLS = International Restless Legs Syndrome Study Group Rating Scale; RCT = randomized controlled trial; RLS = restless legs syndrome

# References

1. Walters AS. Toward a better definition of the restless legs syndrome: The International Restless Legs Syndrome study group. Movement Disorders. 1995 Sep;10(5):634-42. PMID:8552117.

2. Allen RP, Picchietti D, Hening WA, 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 Medicine. 2003 Mar;4(2):101-19. PMID: 14592341.

3. Trenkwalder C, Paulus W. Restless legs syndrome: pathophysiology, clinical presentation and management. Nature Reviews Neurology. 2010 Jul;6(6):337-46. PMID: 20531433.

4. García-Borreguero D, Egatz R, Winkelmann J, et al. Epidemiology of restless legs syndrome: the current status. Sleep Medicine Reviews. 2006 Jun;10(3):153-67. PMID: 16762806.

5. Leschziner G, Gringras P. Restless legs syndrome. BMJ. 2012;344:e3056. PMID: 22623643.

6. Silber MH, Ehrenberg BL, Allen RP, et al. An algorithm for the management of restless legs syndrome. Mayo Clinic proceedings. Mayo Clinic. 2004 Jul;79(7):916-22. PMID: 15244390.

7. Garcia-Borreguero D, Williams AM. Dopaminergic augmentation of restless legs syndrome. Sleep Med Rev. 2010 Oct;14(5):339-46. PMID: 20219397.

8. Cornelius JR, Tippmann-Peikert M, Slocumb NL, et al. Impulse control disorders with the use of dopaminergic agents in restless legs syndrome: a case-control study. Sleep. 2010 Jan;33(1):81-7. PMID: 20120624.

9. Cesnik E, Casetta I, Turri M, et al. Transient RLS during pregnancy is a risk factor for the chronic idiopathic form. Neurology. 2010 Dec 7;75(23):2117-20. PMID: 21135386.

10. Manconi M, Govoni V, De Vito A, et al. Restless legs syndrome and pregnancy. Neurology. 2004 Sep 28;63(6):1065-9. PMID: 15452299.

11. Higgins JPT, Green S, eds. Cochrane handbook for systematic reviews of interventions: The Cochrane Collaboration; 2008.

12. Centre TNC. Reveiw Manager. Version 5.0 ed. Copenhagen: The Cochrane Collaboration; 2008.

13. Owens DK, Lohr KN, Atkins D, et al. AHRQ series paper 5: grading the strength of a body of evidence when comparing medical interventions--agency for healthcare research and quality and the effective health-care program. Journal of Clinical Epidemiology. 2010 May;63(5):513-23. PMID: 19595577.

14. Atkins D, Chang S, Gartlehner G, et al. Assessing the Applicability of Studies When Comparing Medical Interventions. Quality AfHRa; December 2010. www.effectivehealthcare.ahrq.gov/index.cfm/search-for-guides-reviews-and-reports/?pageaction=displayProduct&productID=603#2412.

15. Allen RP, Adler CH, Du W, et al. Clinical efficacy and safety of IV ferric carboxymaltose (FCM) treatment of RLS: a multi-centred, placebo-controlled preliminary clinical trial. Sleep Medicine. 2011 Oct;12(9):906-13. PMID: 21978726.

16. Bassetti CL, Bornatico F, Fuhr P, et al. Pramipexole versus dual release levodopa in restless legs syndrome: a double blind, randomised, cross-over trial. Swiss Medical Weekly. 2011;141:w13274. PMID: 22101745.

17. Trenkwalder C, Benes H, Grote L, et al. Cabergoline compared to levodopa in the treatment of patients with severe restless legs syndrome: results from a multi-center, randomized, active controlled trial. Movement Disorders. 2007 Apr 15;22(5):696-703. PMID: 17274039.

18. Lettieri CJ, Eliasson AH. Pneumatic compression devices are an effective therapy for restless legs syndrome: a prospective, randomized, double-blinded, sham-controlled trial. Chest. 2009 Jan;135(1):74-80. PMID: 19017878.

19. Aukerman MM, Aukerman D, Bayard M, et al. Exercise and restless legs syndrome: a randomized controlled trial. Journal of the American Board of Family Medicine: JABFM. 2006 Sep-Oct;19(5):487-93. PMID: 16951298.

20. Cuellar NG, Ratcliffe SJ. Does valerian improve sleepiness and symptom severity in people with restless legs syndrome? Alternative Therapies in Health & Medicine. 2009 Mar-Apr;15(2):22-8. PMID: 19284179.

21. Mitchell UH, Myrer JW, Johnson AW, et al. Restless legs syndrome and near-infrared light: An alternative treatment option. Physiotherapy Theory & Practice. 2011 Jul;27(5):345-51. PMID: 20977377.

22. Adler CH, Hauser RA, Sethi K, et al. Ropinirole for restless legs syndrome: a placebo-controlled crossover trial. Neurology. 2004 Apr 27;62(8):1405-7. PMID: 15111683.

23. Bogan RK, Fry JM, Schmidt MH, et al. Ropinirole in the treatment of patients with restless legs syndrome: a US-based randomized, double-blind, placebo-controlled clinical trial. Mayo Clinic Proceedings. 2006 Jan;81(1):17-27. PMID: 16438474.

24. Ferini-Strambi L, Aarskog D, Partinen M, et al. Effect of pramipexole on RLS symptoms and sleep: a randomized, double-blind, placebo-controlled trial. Sleep Medicine. 2008 Dec;9(8):874-81. PMID: 18952497.

25. Hening WA, Allen RP, Ondo WG, et al. Rotigotine improves restless legs syndrome: a 6-month randomized, double-blind, placebo-controlled trial in the United States. Movement Disorders. 2010 Aug 15;25(11):1675-83. PMID: 20629075.

26. Hogl B, Garcia-Borreguero D, Trenkwalder C, et al. Efficacy and augmentation during 6 months of double-blind pramipexole for restless legs syndrome. Sleep Medicine. 2011 Apr;12(4):351-60. PMID: 21354368.

27. Kushida CA, Geyer J, Tolson JM, et al. Patient- and physician-rated measures demonstrate the effectiveness of ropinirole in the treatment of restless legs syndrome. Clinical Neuropharmacology. 2008 Sep-Oct;31(5):281-6. PMID: 18836346.

28. Montagna P, Hornyak M, Ulfberg J, et al. Randomized trial of pramipexole for patients with restless legs syndrome (RLS) and RLS-related impairment of mood. Sleep Medicine. 2011 Jan;12(1):34-40. PMID: 20965780.

29. Montplaisir J, Karrasch J, Haan J, et al. Ropinirole is effective in the long-term management of restless legs syndrome: a randomized controlled trial. Movement Disorders. 2006 Oct;21(10):1627-35. PMID: 16874755.

30. Oertel WH, Benes H, Bodenschatz R, et al. Efficacy of cabergoline in restless legs syndrome: a placebo-controlled study with polysomnography (CATOR). Neurology. 2006 Sep 26;67(6):1040-6. PMID: 16931508.

31. Oertel WH, Benes H, Garcia-Borreguero D, et al. Rotigotine transdermal patch in moderate to severe idiopathic restless legs syndrome: a randomized, placebo-controlled polysomnographic study. Sleep Medicine. 2010 Oct;11(9):848-56. PMID: 20813583.

32. Oertel WH, Stiasny-Kolster K, Bergtholdt B, et al. Efficacy of pramipexole in restless legs syndrome: a six-week, multicenter, randomized, double-blind study (effect-RLS study). Movement Disorders. 2007 Jan 15;22(2):213-9. PMID: 17133582.

33. Stiasny-Kolster K, Benes H, Peglau I, et al. Effective cabergoline treatment in idiopathic restless legs syndrome.[Summary for patients in Neurology. 2004 Dec 28;63(12):E21-2; PMID: 15623673]. Neurology. 2004 Dec 28;63(12):2272-9. PMID: 15623686.

34. Trenkwalder C, Benes H, Poewe W, et al. Efficacy of rotigotine for treatment of moderate-to-severe restless legs syndrome: a randomised, double-blind, placebo-controlled trial. Lancet Neurology. 2008 Jul;7(7):595-604. PMID: 18515185.

35. Trenkwalder C, Garcia-Borreguero D, Montagna P, et al. Ropinirole in the treatment of restless legs syndrome: results from the TREAT RLS 1 study, a 12 week, randomised, placebo controlled study in 10 European countries. Journal of Neurology, Neurosurgery & Psychiatry. 2004 Jan;75(1):92-7. PMID: 14707315.

36. Walters AS, Ondo WG, Dreykluft T, 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. Movement Disorders. 2004 Dec;19(12):1414-23. PMID: 15390050.

37. Winkelman JW, Sethi KD, Kushida CA, et al. Efficacy and safety of pramipexole in restless legs syndrome. Neurology. 2006 Sep 26;67(6):1034-9. PMID: 16931507.

38. Benes H, Mattern W, Peglau I, et al. Ropinirole improves depressive symptoms and restless legs syndrome severity in RLS patients: a multicentre, randomized, placebo-controlled study. Journal of Neurology. 2011 Jun;258(6):1046-54. PMID: 21188406.

39. Oertel WH, Benes H, Garcia-Borreguero D, et al. Efficacy of rotigotine transdermal system in severe restless legs syndrome: a randomized, double-blind, placebo-controlled, six-week dose-finding trial in Europe. Sleep Medicine. 2008 Mar;9(3):228-39. PMID: 17553743.

40. Lee DO, Ziman RB, Perkins AT, et al. A randomized, double-blind, placebo-controlled study to assess the efficacy and tolerability of gabapentin enacarbil in subjects with restless legs syndrome. Journal of Clinical Sleep Medicine. 2011 Jun 15;7(3):282-92. PMID: 21677899.

41. Bogan RK, Bornemann MAC, Kushida CA, et al. Long-term maintenance treatment of restless legs syndrome with gabapentin enacarbil: a randomized controlled study.[Erratum appears in Mayo Clin Proc. 2010 Jul;85(7):693-4]. Mayo Clinic Proceedings. 2010 Jun;85(6):512-21. PMID: 20511481.

42. Allen R, Chen C, Soaita A, et al. A randomized, double-blind, 6-week, dose-ranging study of pregabalin in patients with restless legs syndrome. Sleep Medicine. 2010 Jun;11(6):512-9. PMID: 20466589.

43. Garcia-Borreguero D, Larrosa O, de la Llave Y, et al. Treatment of restless legs syndrome with gabapentin: a double-blind, cross-over study. Neurology. 2002 Nov 26;59(10):1573-9. PMID: 12451200.

44. Garcia-Borreguero D, Larrosa O, Williams AM, et al. Treatment of restless legs syndrome with pregabalin: a double-blind, placebo-controlled study. Neurology. 2010 Jun 8;74(23):1897-904. PMID: 20427750.

45. Kushida CA, Becker PM, Ellenbogen AL, et al. Randomized, double-blind, placebo-controlled study of XP13512/GSK1838262 in patients with RLS. Neurology. 2009 Feb 3;72(5):439-46. PMID: 19188575.

46. Winkelman JW, Bogan RK, Schmidt MH, et al. Randomized polysomnography study of gabapentin enacarbil in subjects with restless legs syndrome. Movement Disorders. 2011 Sep;26(11):2065-72. PMID: 21611981.

47. Bayard M, Bailey B, Acharya D, et al. Bupropion and restless legs syndrome: a randomized controlled trial. Journal of the American Board of Family Medicine: JABFM. 2011 Jul-Aug;24(4):422-8. PMID: 21737767.

48. Allen RP, Ondo WG, Ball E, et al. Restless legs syndrome (RLS) augmentation associated with dopamine agonist and levodopa usage in a community sample. Sleep Medicine. 2011 May;12(5):431-9. PMID: 21493132.

49. Benes H, Garcia-Borreguero D, Allen R, et al. Augmentation in long-term therapy of the restless legs syndrome with transdermal ritigotine-a retrospective systematic analysis of two large open-label 1 year trials. Movement Disorders. 2009;Suppl 1:S348.

50. Ellenbogen AL, Thein SG, Winslow DH, et al. A 52-week study of gabapentin enacarbil in restless legs syndrome. Clinical Neuropharmacology. 2011 Jan-Feb;34(1):8-16. PMID: 21242741.

51. Ferini-Strambi L. Restless legs syndrome augmentation and pramipexole treatment. Sleep Medicine. 2002 Nov;3 Suppl:S23-5. PMID: 14592163.

52. Frauscher B, Gschliesser V, Brandauer E, et al. The severity range of restless legs syndrome (RLS) and augmentation in a prospective patient cohort: association with ferritin levels. Sleep Medicine. 2009 Jun;10(6):611-5. PMID: 19200780.

53. Garcia-Borreguero D, Grunstein R, Sridhar G, et al. A 52-week open-label study of the long-term safety of ropinirole in patients with restless legs syndrome. Sleep Medicine. 2007 Nov;8(7-8):742-52. PMID: 17512789.

54. Godau J, Spinnler N, Wevers A-K, et al. Poor effect of guideline based treatment of restless legs syndrome in clinical practice. Journal of Neurology, Neurosurgery & Psychiatry. 2010 Dec;81(12):1390-5. PMID: 20884674.

55. Hogl B, Garcia-Borreguero D, Kohnen R, et al. Progressive development of augmentation during long-term treatment with levodopa in restless legs syndrome: results of a prospective multi-center study. Journal of Neurology. 2010 Feb;257(2):230-7. PMID: 19756826.

56. Inoue Y, Kuroda K, Hirata K, et al. Long-term open-label study of pramipexole in patients with primary restless legs syndrome. Journal of the Neurological Sciences. 2010 Jul 15;294(1-2):62-6. PMID: 20451927.

57. Montplaisir J, Fantini ML, Desautels A, et al. Long-term treatment with pramipexole in restless legs syndrome. European Journal of Neurology. 2006 Dec;13(12):1306-11. PMID: 17116213.

58. Oertel W, Trenkwalder C, Benes H, et al. Long-term safety and efficacy of rotigotine transdermal patch for moderate-to-severe idiopathic restless legs syndrome: a 5-year open-label extension study. Lancet Neurology. 2011 Aug;10(8):710-20. PMID: 21705273.

59. Ondo W, Romanyshyn J, Vuong KD, et al. Long-term treatment of restless legs syndrome with dopamine agonists. Archives of Neurology. 2004 Sep;61(9):1393-7. PMID: 15364685.

60. Ondo WG, Lai D. Association between restless legs syndrome and essential tremor. Movement Disorders. 2006 Apr;21(4):515-8. PMID: 16250022.

61. Silber MH, Girish M, Izurieta R. Pramipexole in the management of restless legs syndrome: an extended study. Sleep. 2003 Nov 1;26(7):819-21. PMID: 14655914.

62. Silver N, Allen RP, Senerth J, et al. A 10-year, longitudinal assessment of dopamine agonists and methadone in the treatment of restless legs syndrome. Sleep Medicine. 2011 May;12(5):440-4. PMID: 21239226.

63. Trenkwalder C, Collado Seidel V, Kazenwadel J, et al. One-year treatment with standard and sustained-release levodopa: appropriate long-term treatment of restless legs syndrome? Movement Disorders. 2003 Oct;18(10):1184-9. PMID: 14534925.

64. Walters AS, Winkelmann J, Trenkwalder C, et al. Long-term follow-up on restless legs syndrome patients treated with opioids. Movement Disorders. 2001 Nov;16(6):1105-9. PMID: 11748742.

65. Winkelman JW, Johnston L. Augmentation and tolerance with long-term pramipexole treatment of restless legs syndrome (RLS). Sleep Medicine. 2004 Jan;5(1):9-14. PMID: 14725821.

66. Grote L, Leissner L, Hedner J, et al. A randomized, double-blind, placebo controlled, multi-center study of intravenous iron sucrose and placebo in the treatment of restless legs syndrome. Movement Disorders. 2009 Jul 30;24(10):1445-52. PMID: 19489063.

67. Wang J, O'Reilly B, Venkataraman R, et al. Efficacy of oral iron in patients with restless legs syndrome and a low-normal ferritin: A randomized, double-blind, placebo-controlled study. Sleep Medicine. 2009 Oct;10(9):973-5. PMID: 19230757.

68. Woloshin S, Woloshin S, Schwartz LM, et al. Giving legs to restless legs: a case study of how the media helps make people sick. PLoS Medicine. 2006;3(4):e170. PMID: 16597175.

## Full Report

This executive summary is part of the following document: Wilt TJ, MacDonald R, Ouellette J, Tacklind J, Khawaja I, Rutks I, Butler M, Fink HA. Treatment for Restless Legs Syndrome. Comparative Effectiveness Review No. 86. (Prepared by the Minnesota Evidence-based Practice Center under Contract No. 290-2007-10064-I.) AHRQ Publication No.12(13)-EHC147-EF. Rockville, MD: Agency for Healthcare Research and Quality. November 2012. www.effectivehealthcare.ahrq.gov/reports/final.cfm

## For More Copies

For more copies of Treatment for Restless Legs Syndrome: Comparative Effectiveness Review Executive Summary No. 86 (AHRQ Pub. No. 12(13)-EHC147-1), please call the AHRQ Publications Clearinghouse at 800–358–9295 or email ahrqpubs@ahrq.gov.