Draft Comparative Effectiveness Review

Number xx

Treatments for Restless Legs Syndrome

Prepared for:
Agency for Healthcare Research and Quality
U.S. Department of Health and Human Services
540 Gaither Road
Rockville, MD 20850
www.ahrq.gov

Contract No.

Prepared by:

AHRQ Publication No. xx-EHCxxx
<Month Year>

This report is based on research conducted by an Evidence-based Practice Center under contract to the Agency for Healthcare Research and Quality (AHRQ), Rockville, MD (Contract No. xxx-xxxx-xxxxx). The findings and conclusions in this document are those of the author(s), who are responsible for its content, and do not necessarily represent the views of AHRQ. No statement in this report should be construed as an official position of AHRQ or of the U.S. Department of Health and Human Services.

The information in this report is intended to help clinicians, employers, policymakers, and others make informed decisions about the provision of health care services. This report is intended as a reference and not as a substitute for clinical judgment.

This report may be used, in whole or in part, as the basis for the development of clinical practice guidelines and other quality enhancement tools, or as a basis for reimbursement and coverage policies. AHRQ or U.S. Department of Health and Human Services endorsement of such derivative products or actions may not be stated or implied.

Public Domain Notice

This document is in the public domain and may be used and reprinted without special permission. Citation of the source is appreciated.

Disclaimer Regarding 508-Compliance

Persons using assistive technology may not be able to fully access information in this report. For assistance contact info@ahrq.org.

Financial Disclosure Statement

None of the investigators has any affiliations or financial involvement that conflicts with the material presented in this report.

Standard Suggested Citation of Your Report

Preface

The Agency for Healthcare Research and Quality (AHRQ) conducts the Effective Health Care Program as part of its mission to organize knowledge and make it available to inform decisions about health care. As part of the Medicare Prescription Drug, Improvement, and Modernization Act of 2003, Congress directed AHRQ to conduct and support research on the comparative outcomes, clinical effectiveness, and appropriateness of pharmaceuticals, devices, and health care services to meet the needs of Medicare, Medicaid, and the Children's Health Insurance Program (CHIP).

AHRQ has an established network of Evidence-based Practice Centers (EPCs) that produce Evidence Reports/Technology Assessments to assist public- and private-sector organizations in their efforts to improve the quality of health care. The EPCs now lend their expertise to the Effective Health Care Program by conducting comparative effectiveness reviews (CERs) of medications, devices, and other relevant interventions, including strategies for how these items and services can best be organized, managed, and delivered.

Systematic reviews are the building blocks underlying evidence-based practice; they focus attention on the strength and limits of evidence from research studies about the effectiveness and safety of a clinical intervention. In the context of developing recommendations for practice, systematic reviews are useful because they define the strengths and limits of the evidence, clarifying whether assertions about the value of the intervention are based on strong evidence from clinical studies. For more information about systematic reviews, see http://www.effectivehealthcare.ahrq.gov/reference/purpose.cfm

AHRQ expects that CERs will be helpful to health plans, providers, purchasers, government programs, and the health care system as a whole. In addition, AHRQ is committed to presenting information in different formats so that consumers who make decisions about their own and their family's health can benefit from the evidence.

Transparency and stakeholder input from are essential to the Effective Health Care Program. Please visit the Web site (http://www.effectivehealthcare.ahrq.gov) to see draft research questions and reports or to join an e-mail list to learn about new program products and opportunities for input. Comparative Effectiveness Reviews will be updated regularly.

We welcome comments on this CER. They may be sent by mail to the Task Order Officer named below at: Agency for Healthcare Research and Quality, 540 Gaither Road, Rockville, MD 20850, or by e-mail to epc@ahrq.hhs.gov.

Carolyn M. Clancy, M.D.
Director
Agency for Healthcare Research and Quality

Jean Slutsky, P.A., M.S.P.H.
Director, Center for Outcomes and Evidence
Agency for Healthcare Research and Quality

Stephanie Chang, M.D., M.P.H.
Director
Evidence-based Practice Program
Center for Outcomes and Evidence
Agency for Healthcare Research and Quality

Suchitra Iyer, Ph.D.
Task Order Officer
Center for Outcomes and Evidence
Agency for Healthcare Research and Quality

Acknowledgments

Key Informants

Technical Expert Panel

Peer Reviewers

Treatments for Restless Legs Syndrome

Structured Abstract

Context: Restless legs syndrome (RLS) is a neurological disorder characterized by unpleasant sensations in the legs and a distressing, irresistible urge to move them. RLS severity and burden vary widely and the condition may require long-term treatment.

Objective: To review the comparative effectiveness, efficacy, and safety of pharmacological and nonpharmacological treatments for RLS.

Data Sources: Bibliographic databases MEDLINE, EMBASE, Natural (from inception through September 2011); Cochrane Central; grey literature sources including ClinicalTrials.gov, the International Controlled Trials Registry Platform (ICTRP), and the NIH RePORTer.

Review Methods: Eligible studies included randomized controlled trials (RCTs) published in English that lasted at least 4 weeks and compared pharmacological and/or nonpharmacological treatments for RLS with placebo or active treatment and reported International RLS symptom scale scores. We assessed RLS symptom impact, sleep scale scores, disease-specific quality of life, withdrawals, and adverse effects. We included observational studies that assessed long-term (>6 months) adverse effects and treatment withdrawals.

Results: Of the 44 studies included, one active comparator and 25 placebo-controlled RCTs provided efficacy and harms data and 18 observational studies assessed long-term harms and adherence. Studies were typically small and short-duration. Placebo-controlled RCTs (16 trials) in adults with severe primary RLS of long-duration suggest with high strength of evidence that dopamine agonists (pramipexole, rotigotine, ropinirole and cabergoline) improve symptom scores. Studies (k=6) also reported an increase in the percent of subjects who have a clinically important response defined as ≥50 percent reduction from baseline in mean International RLS (RLS) symptom scale scores (IRLS responders) (RR = 1.61; [95% CI: 1.35 to 1.92]), improved patient-reported sleep scale scores (effect size=0.38; [95% CI: 0.29 to 0.46], k=8), and disease-specific quality of life (effect size = -0.40; [95% CI: -0.52 to -0.29], k=7). Dopamine agonist compared to placebo resulted in more patients who experienced at least one adverse event (high strength of evidence) but not more overall study withdrawals (moderate strength of evidence). Long-term augmentation (drug-induced worsening of symptoms) and treatment withdrawal were common. Gamma-aminobutyric acid (GABA) analogs improved symptoms (IRLS responders, RR = 2.13; [95% CI: 1.36 to 3.34], k=2, high strength of evidence) and mean change in IRLS symptom scores (2 trials, moderate strength of evidence) in short-term placebo-controlled trials. Only three studies assessed nonpharmacological interventions. Compression stockings but not the botanical extract valerian improved IRLS symptom scores more than sham or placebo treatments. Strength of evidence was moderate for compression stockings and low for valerian. Exercise improved symptoms more than control though adherence was poor and results were provided only for individuals who completed the program (low strength of evidence).

Only one trial (n=361) compared active treatments. The dopamine agonist cabergoline improved IRLS scores and less frequently resulted in augmentation then levodopa (moderate strength of evidence). Two trials evaluated iron therapy in adults with iron deficiency and provided low strength of evidence of symptom improvement. No studies assessed treatment in pregnant women or those with end-stage renal disease. Observational data indicate that withdrawal from mostly dopamine agonist and levodopa treatment at 1 year or more ranged from 13 to 57%. Treatment withdrawals were due to lack of efficacy in 6-37% as well as augmentation and other adverse events.

Conclusion: Results from randomized controlled trials of individuals with RLS are inadequate to assess comparative treatment effectiveness and harms. Results are mostly limited to short-term, placebo-controlled efficacy studies of dopamine agonists and GABA analogs conducted in a highly selected population of adults with moderate to very severe primary RLS of long-duration. Compared to placebo, dopamine agonists and GABA analogs reduce symptoms and improve patient-reported sleep outcomes and disease-specific quality of life. Adverse effects of pharmacological therapies and long-term treatment withdrawals due to adverse effects or lack of efficacy are common. Applicability of these findings to adults with less severe or less frequent RLS symptoms, individuals with secondary RLS, or to children is unknown.

Contents

Executive Summary ES-1

Introduction 1
Overview 1
Methods of Assessment 3
Areas of Uncertainty 5
Scope and Key Questions 6

Methods 9
Topic Refinement 9
Literature Search Strategy 9
Inclusion and Exclusion Criteria 9
Study Selection 10
Data Extraction 10
Risk of Bias 11
Data Synthesis 11
Strength of the Body Evidence 11
Applicability 12

Results 13
Literature Search 13
Description of Included Studies 13
Study Quality and Publication Bias 14
Key Question 1. What is the comparative effectiveness of treatment for RLS? 14
Key Points 15
Dopamine Agonists 15
GABA-analogs 18
Long-term tolerability and durability 19
Nonpharmacological therapies 19
Comparative Effectiveness of RLS treatments and Dose Response 20
Key Question 2. What are the harms of RLS treatments? 21
Key Points 21
Short-term harms 21
Comparative harms 22
Long-terms harms and withdrawl from treatment 23
Key Question 3. What is the effect of patient characteristics on the benefits and harms of treatment for RLS? 23
Study Quality / Risk of Bias and Applicability 24

Discussion 49
Future Research Recommendations 52

References 54

Acronyms and Abbreviations 58

Tables

Table A. Overall strenth of evidence in studies of dopamine agonists ES-14
Table B. Overall strength of evidence in studies of GABA anologs ES-15
Table C. Overall stength of evidence in studies of Iron supplements ES-15
Table D. Future research recommendations ES-20
Table 1. Pharmacological treatments for RLS 3
Table 2. Methods of Assessment 4
Table 3. Inclusion criteria 10
Table 4. Outcomes evaluated in studies of dopamine agonists 25
Table 5. Baseline characteristis of patients in studies of dopamine agonists 26
Table 6. Overall strength of evidence in studies of dopamine agonists 27
Table 7. IRLS Responders (≥50% score reduction) 30
Table 8. Summary of baseline characteristics for GABA analog trials 36
Table 9. Overall strength of evidence in studies of GABA analogs 37
Table 10. Long-terms harms with dopamine agonists - Augmentation 40
Table 11. Overall strength of evidence in nonpharmacologic trials 43
Table 12. Overall strength of evidence in iron trials 48
Table 13. Future research recommendations 52

Figures

Figure 1 Analytic Framework 8
Figure 2. Flow diagram of search strategy 13
Figure 3 Efficacy outcomes for dopamine agonists (>50% reduction in IRLS score) ... 29
Figure 4. Efficacy outcomes for dopamine agonists (CGI) 31
Figure 5. Efficacy outcomes for dopamine agonists (PGI) 32
Figure 6. Efficacy outcomes for dopamine agonists (mean change from baseline) 33
Figure 7. Efficacy outcomes for dopamine agonists (change in RLS QOL) 34
Figure 8. Efficacy outcomes for GABA analogs (change in sleep / MOS score) 35
Figure 9. Efficacy outcomes for GABA analogs (>50% reduction in IRLS score) 38
Figure 10. Efficacy outcomes for GABA analogs (CGI) 39
Figure 11. Short-term harms with dopamine agonists (any study withdrawal) 44
Figure 12. Short-term harms with dopamine agonists (withdrawals due to AEs) 45
Figure 13. Short-terms harms with GABA analogs (any study withdrawal) 46
Figure 14. Short-term harms with GABA analogs (withdrawals due to AEs) 46
Figure 15. Patients with ≥ 1 adverse effect 47

Appendixes

Appendix A. Search Strategy
Appendix B. Excluded Studies
Appendix C. Evidence Tables
Appendix D. Outcomes Tables
Appendix E. Withdrawals and Adverse Events Tables
Appendix F. Baseline Characteristics Tables
Appendix G. Study Quality / Risk of Bias Tables

Effective Health Care

Comparative Effectiveness of Multidisciplinary Postacute Rehabilitation for Moderate to Severe Traumatic Brain Injury in Adults

Executive Summary

The Effective Health 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. Ahrq.gov/reports/final.cfm

Introduction

Restless legs syndrome (RLS) is a neurological disorder characterized by unpleasant sensations in the legs and a distressing, irresistible urge to move them. The condition 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 encompasses a wide spectrum of symptom severity and frequency. Mild RLS may result in only minor annoyance, but severe RLS can interfere with work or social activities and reduce function and emotional well-being. RLS-induced sleep disruption may lead to poor daytime functioning, anxiety, and depression. Sleep deprivation and daytime fatigue are common reasons RLS patients seek treatment.[3]

Prevalence estimates for RLS in the United States range from 2.4 percent to 7.4 percent in adults.[4] The wide 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. One study designed

to characterize the epidemiology of RLS in the U.S. population (a telephone survey of willing adults who answered questions about RLS) defined RLS as "symptoms occurring at least twice weekly with moderate to severe impact" and 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] Compared with primary RLS, secondary RLS is less common, often starts later in life and progresses more rapidly, and tends to resolve when the underlying condition is treated or resolved.[2] Although mechanistic relationships are yet to be 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 and commonly includes periods of remission, particularly in younger patients and those with milder disease. Severe restless legs syndrome, however, is a chronic progressive disorder that may require long-term treatment.[3]

Treatments (nonpharmacological and pharmacological options) vary by patient age, comorbidities, preferences, and disease severity.[5] Nonpharmacological options include: exercise, sleep hygiene, avoiding RLS precipitants (caffeine, alcohol, nicotine, 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.

Pharmacological treatment is generally reserved for patients with symptoms that are frequent (typically several times per week) and moderate to very severe. The major classes of drugs used are dopaminergic agents, sedative hypnotic agents, anticonvulsive agents, opiates, and iron. Of these, two dopamine agonists (pramipexole and ropinirole) and one anticonvulsant (gabapentin) are FDA approved for treatment of moderate to severe RLS.

A complication of long-term treatment with dopamine agonists is a drug-induced worsening of symptoms known as augmentation, 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.[6]

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 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.[7, 8] We conducted a systematic review of the effectiveness and harms of treatments for restless leg syndrome 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 pharmacological and nonpharmacological treatments for RLS. Pharmacological 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 (PLM) while awake or asleep, these movements are not specific to RLS. Sleep disorders such as periodic limb movement disorder are a distinct entity and not considered in this review. We evaluated RLS symptom severity and impact, 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 addressed not only 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 to placebo or no treatment?
b. What are the benefits from RLS treatments when compared to 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 to placebo or no treatment?
b. What are the harms from RLS treatments when compared to 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 September 17, 2011 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). To identify completed trials and to check for publication bias, we searched Cochrane Central, the International Controlled Trials Registry Platform (ICTRP), Clinicaltrials.gov, FDA websites, and the NIH RePORTer.

Inclusion and Exclusion Criteria

For questions related to treatment efficacy, we included studies if they were RCTs that enrolled individuals with RLS, were published in English, evaluated pharmacological and/or nonpharmacological interventions for RLS, lasted at least 4 weeks, and reported validated RLS symptom scale scores (International RLS-IRLS). We included observational studies and open-label followup extensions of RCTs reporting long-term (>6 months) adverse effects and adherence. Pharmacological 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. 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 if 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 and at least one exclusion reason at the full-text screening stage. The excluded articles and the reasons for exclusion are listed in Appendix B.

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 cross-over, 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 cross-over trials)
- Outcomes, including mean change in IRLS scale score from baseline, IRLS responders, i.e., patients with ≥50 percent reduction in IRLS scale score (our primary outcome), percent of patients with complete remission, percent of patients reporting “much improved” or “very much improved” on clinician-assessed global impression (CGI) or patient-assessed global impression (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.[9] 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 (WMD), or risk ratios (RR). Data were pooled and analyzed in Review Manager 5.1 (Review Manager (RevMan) [Computer program]. Version 5.1. Copenhagen: The Nordic Cochrane Centre, The Cochrane Collaboration, 2011). We calculated risk ratios (RR) for dichotomous outcomes and WMD or standardized mean differences (SMD) for continuous outcomes using a random-effects model. We assessed statistical heterogeneity between trials and for subgroups of drugs using the I^2 test. A score of approximately 50% suggests substantial heterogeneity.

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[10]for the following outcomes: mean change in IRLS scale score from baseline; percent of IRLS responders, i.e., patients with $\geq$50 percent reduction in IRLS scale score; percent of patients reporting "much improved" or "very much improved" on clinician-assessed global impression (CGI) or patient-assessed global impression (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 of evidence.

Applicability

We assessed applicability[11] 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 44 studies that fulfilled eligibility criteria and

were included: of these 26 were RCTs (25 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 pharmacological 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 to placebo or no treatment?
b. What are the benefits from RLS treatments when compared to other active treatments?
c. What is the durability and sustainability of treatment benefits?

Key Points

- Randomized controlled trial results were limited to short-term efficacy studies versus placebo or usual care (<6 months).
- Compared to placebo, there was overall high strength of evidence that dopamine agonists (ropinirole, pramipexole, and rotigotine) reduced RLS symptoms, increased the percentage of patients with a clinically important response (≥50 percent reduction in IRLS symptom scale scores or who were "improved" or "much improved" on patient or clinician-reported global impression scale) and improved disease-specific quality of life and patient-reported sleep outcomes.
- There was high strength of evidence that pregabalin increased the percentage of patients with a clinically important response (≥50 percent reduction in IRLS). There was low strength of evidence that gamma-aminobutyric acid (GABA) analogs improved clinician-reported global impression, disease-specific quality of life and patient-reported sleep outcomes compared to placebo.
- Applicability was limited to nonpregnant, white, middle-aged adults with few comorbidities and RLS symptoms that were long term, frequent, and high-moderate to very severe.
- Only three small RCTs[12-14] addressed nonpharmacological interventions. Pneumatic compression devices[12] reduced IRLS symptom scale scores more than sham (moderate strength of evidence). Strength training and treadmill walking[13] improved IRLS symptoms but adherence was poor and results only provided for study completers. The botanical extract valerian[14] was not effective. The strength of evidence for both interventions was low.
- No eligible studies assessed opioids, sedative hypnotics, or tramadol, though these are used clinically for RLS treatment.
- One study[15] found that the dopamine agonist cabergoline improved scores on the IRLS symptom scale and RLS quality of life scale more than Levodopa (moderate strength of evidence). Carbergoline is not approved for treatment of RLS and has limited use in the United States due to increased risk for cardiac valvular disorders.
- Observational studies and long-term open-label followup from RCTs of pharmacological interventions found that withdrawal from treatment at 1 year or

more was common ranging from 13 to 57 percent. Reasons for withdrawal were due to lack of efficacy (6 to 32 percent), and adverse events including augmentation (7 to 62 percent).

Dopamine Agonists

Efficacy of dopamine agonists was evaluated in 16 randomized, double-blind, placebo-controlled studies[16-31] and one comparative effectiveness study.[15]Two of the placebo controlled studies[24, 27] and the only comparative effectiveness trial assessed the dopaminergic analog cabergoline[15] 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. We do not include outcomes or characteristics of the two carbegoline placebo controlled studies [24, 27] with the other dopaminergic trials and do not discuss 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. [15] Only two placebo controlled trials lasted 24 weeks or more,[20, 28] and none exceeded 29 weeks. The mean age of participants was 55 years, and women constituted 64 percent (range 55 to 74) of randomized participants. Participants were overwhelmingly white in the six trials that reported race/ethnicity. [17, 18, 22, 26, 28, 31]

All included RCTs used the IRLS criteria to diagnose RLS. Most studies required at least upper 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, contemplating becoming pregnant, or if they had psychiatric disorders, substance use, 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 = 24.9). RLS duration varied with a mean of 19 years for ropinirole to 2 years for rotigotine trials. Trials enrolled de novo patients and those who had received prior RLS treatments. On average, more than one half (53 percent) 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. Three studies investigated multiple fixed doses of the drug in separate study arms. [19, 28, 31]

IRLS responders (≥50 percent score reduction). Six trials (three pramipexole trials, n = 1007[22, 26, 31]; three rotigotine trials,[19, 25, 28] n=1066) reported the percentage of patients who responded to treatment based on ≥50 percent reduction in IRLS symptom scale score from baseline. Compared to placebo, the percentage of patients with a favorable treatment response was greater with the dopamine agonists, pramipexole and rotigotine (RR = 1.61; [95 percent CI, 1.35 to 1.92]). There was no evidence of subgroup differences. The absolute effect in terms of responders per 100 patients was 25 more (95 percent CI, 14 more to 37 more) in the dopamine agonist treatment group than with placebo (high strength of evidence).

Responders on clinician and patient-rated global impression scale. The proportion of responders (with a rating of "much improved" or "very much improved") on clinician- and patient-reported global scales was higher for dopamine agonists than for placebo (respective risk ratios 1.46; [95 percent CI, 1.35 to 1.58] and 1.66; [95 percent CI, 1.45 to 1.90], [13 trials, n=4,074]). 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 score between treatment and placebo was -4.47; (95 percent CI, -5.41 to -3.52). The magnitude of reduction in IRLS scale scores was slightly greater in studies of rotigotine[19, 25, 28] (-6.07; [95 percent CI, -8.33 to -3.81]) (k=3, n=1286) than in studies of pramipexole[18, 20, 22, 26, 31] (-4.76; [95 percent CI, -6.24 to -3.28]) (k=5, n=1587) or ropinirole[17, 21, 29] (-3.29; [95 percent CI, -4.31 to -2.27]) (k=3, n=483) (p = 0.05 for interaction). We found no clear evidence of a dose effect in the three fixed-dose studies that used different doses in separate arms.[19, 28, 31] The overall strength of evidence was high. Carbergoline[15] 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 percent 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 =7, n=1772). The effect size is considered between small to medium in magnitude (SMD = -0.40; [95 percent CI, -0.52 to -0.29]). Results were similar across studies of pramipexole (k = 2), ropinirole (k=1) and rotigotine (k = 3), for drug subgroup heterogeneity = 0 percent. Overall strength of evidence was high. Dopamine agonists improved patient-reported sleep quality compared to placebo as measured by the Medical Outcomes Study Sleep Problem Index scale (k=8) (standardized mean effect size = 0.38; [95 percent CI, 0.29 to 0.46]. The magnitude of effect was considered small to moderate. Strength of evidence was high.

Gamma-aminobutyric acid (GABA) analogs Efficacy of anticonvulsant drugs was evaluated in four randomized, double-blind, placebo-controlled studies (n = 441).[32-35] All four studies involved gamma-aminobutyric acid (GABA) analogs (gabapentin, two trials; pregabalin, two trials). Trials were short (three 6-week trials[33-35] and one 12-week trial[32]). The mean age of study participants was 51 years. Women constituted 62 percent of all participants randomized. In the two studies that reported race,[34, 35]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 = 23). 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.

Two trials[32, 34] evaluated IRLS responders. Pregabalin compared to placebo increased the proportion of IRLS responders (RR 2.03; [95 percent CI, 1.33 to 3.11]).[34] The absolute effect in terms of responders per 100 patients was 37 more [95 percent CI, 12

more to 76 more]. The strength of evidence was high. The proportion of patients who reported improved or very much improved on the CGI was not significantly greater for the GABA-analog treatment group though there was evidence of heterogeneity between studies (RR = 1.52, 95 percent CI, 0.89 to 2.58, I^2 = 83 percent). The strength of evidence was low. Gabapentin[33, 35] (k = 2) and pregabalin [32, 34](k = 2) reduced symptom severity compared to placebo. The pooled weighted mean change in IRLS score from baseline or at end-of-study between GABA analogs and placebo groups was -4.51; [95 percent CI, -6.60 to -2.42] to -6.46; [95 percent CI, -10.43 to -2.50] respectively (k = 2). The strength of evidence was moderate.

Nonpharmacological therapies

Three small, short-term studies assessed nonpharmacological therapies in adults with moderate to severe RLS.[12-14] A good quality RCT of pneumatic compression devices[12] worn for at least 1 hour each day for 4 weeks starting prior to the time 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). Treadmill walking and lower body resistance exercise performed three times weekly for 12 weeks improved IRLS scale scores (WMD = -9.4 [95 percent CI =-13.9 to -4.9]) compared to usual care (moderate quality study and a low strength of evidence[13]. However, results were reported only for 28 completers from 41 subjects enrolled. In a moderate quality RCT, the botanical preparation valerian[14] at 800 mg daily for 8 weeks did not improve IRLS symptom scale scores more than placebo among 48 adults with frequent and severe RLS symptoms (p = 0.69). The strength of evidence was low.

Comparative Effectiveness of RLS treatments and dose response

One 30-week study (n = 361)[15] found that the dopamine agonist cabergoline improved IRLS symptom scale scores (WMD = -6.80; [95 percent CI, -9.02 to -4.58]) and RLS quality of life more than Levodopa (WMD = -7.10; [95 percent CI, -9.94 to -4.26]) in white adults with severe RLS (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 GABA agonist pregabalin (k=1).

Key Question 2

What are the harms from RLS treatments?

a. What are the harms from RLS treatments when compared to placebo or no treatment?
b. What are the harms from RLS treatments when compared to 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 in patients randomized to dopaminergic agents than to placebo (moderate strength of evidence)
- Study withdrawals due to adverse effects were more common (though not statistically so) with dopamine agonist treatment than placebo (low strength of evidence). Differences 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 to placebo (high strength of evidence)
- Short-term adverse effects from treatment with dopamine agonists compared to placebo were nausea, vomiting, and somnolence (high strength of evidence for all these outcomes)
- Application site reactions were much more common with transdermal rotigotine than with placebo (high strength of evidence)
- Some indirect evidence from placebo controlled trials suggests that fatigue may be more common with ropinirole then pramipexole or rotigotine.
- Data from observation studies indicates 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 1 adverse effect. Patients were less likely to withdraw from dopamine agonist treatment than from placebo treatment (21 versus 23 percent; RR = 0.82; [95 percent CI, 0.68 to 1.00], k=14) (moderate strength of evidence). There was an overall non-significant increase in study withdrawals due to adverse effects associated with dopamine agonist treatment (10 versus 6 percent; RR = 1.36; [95 percent CI, 0.98 to 1.87], k=14) (low strength of evidence). However, there was evidence of between-drug differences for (I^2 = 74 percent, p=0.02) with a nearly 3-fold increase in withdrawals due to adverse events for rotigotine therapy (RR = 2.85; [95 percent CI, 1.40 to 5.80]). More patients reported at least 1 adverse effect with dopamine agonist compared to placebo (RR = 1.17; [95 percent CI, 1.10 to 1.25], k=14) (high strength of evidence).

Short-term adverse effects from treatment with dopamine agonists compared to placebo were nausea (22 versus 7 percent, RR = 3.42 [95 percent CI, 2.56 to 4.56], k=13), vomiting (11 versus 2 percent, RR = 4.84 [95 percent CI, 2.77 to 8.47], k=5) and somnolence (12 versus 6 percent, RR = 2.04; [95 percent CI, 1.50 to 2.76], k=8) (overall strength of evidence was high for these outcomes). Fatigue was numerically but not

statistically significantly greater (12 versus 6 percent, RR = 1.86; [95 percent CI, 0.96 to 3.62], k=7). Application site reactions were much more common with transdermal rotigotine than with placebo, 33 versus 7 percent, respectively (RR = 8.20; [95 percent CI, 2.53 to 26.57], k=3) (high strength of evidence).

Comparative harms

One 30 week good quality randomized trial reported that compared to levodopa, cabergoline[15] resulted in less augmentation and augmentation leading to withdrawal (moderate strength of 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 in 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 pharmacological 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 = 74 percent, p = 0.02). Compared to placebo, fatigue was more common in the single study of ropinirole[30] reporting this outcome than in studies of pramipexole[20, 22, 26, 31] (k = 4) or rotigotine (k = 2)[19, 28] (I^2 = 92.6 percent, p<0.00001). Compared to placebo the relative risk of site reaction[19, 25, 28] (k = 3) was similar across doses of rotigotine ranging from 0.5 to 3.0 mg/day. The relative risk of nausea, fatigue and somnolence for rotigotine, pramipexole and ropinirole versus placebo also did not vary significantly by dose though the numbers of patients and events in each dose subgroup were small, confidence intervals wide and overlapped.

Long-term harms and withdrawal from treatment

We used data from 18 observational studies[36-53] (including open-label extensions of RCTS) that reported least 6 months of followup to assess the percentage individuals withdrawing from pharmacological treatments and reasons for withdrawal (lack of efficacy, adverse events, augmentation, other). 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 percent). Withdrawals of gabapentin and the dopamine agonists were 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?

- No RCTs examined the effect of patient or RLS characteristics on benefits and harms of treatments for primary RLS
- No RCTs enrolled children or 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 of evidence that iron may improve IRLS symptom scale scores and possibly the percentage of adults considered IRLS responders

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 whom had been treated previously, and whose symptoms were frequent and high-moderate to severe.

Two small good quality RCTs evaluated iron therapy (one intravenous and one oral) in patients with RLS secondary to iron deficiency.[54, 55] One 12-week trial of 18 subjects found that compared to placebo, iron reduced IRLS scale scores by 9.16 points (95 percent CI,-15.2 to -3.1). [55]Another trial of intravenous iron sucrose (administered five times over 3 months in 60 subjects) found no difference versus placebo at 12 months in mean change in IRLS scale scores (p = 0.47).[54] 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 percent CI, 1.07 to 3.18]).[54] By 12 months 21 of 31 subjects (68 percent) in the placebo group and nine of 29 (31 percent) in the iron group withdrew.[54] Of these, 19 and five respectively withdrew due to lack of efficacy. The strength of evidence for these outcomes was low.

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. Studies typically excluded patients with psychiatric or other serious comorbid conditions including renal or liver disease and pregnant women or those contemplating becoming pregnant.

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). 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 GABA analogs 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 of patient or RLS characteristics on outcomes.

Table A. Overall strength of evidence for individual outcomes in 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	6	2085	RR 1.61 [1.35 to 1.92]	low	direct	precise	consistent	High
	pramipexole	3	1079	RR 1.46 [1.22 to 1.74]	low	direct	precise	consistent	High
	rotigotine	3	1006	RR 1.83 [1.41 to 2.38]	low	direct	precise	consistent	High
IRLS total score: Mean change from baseline	All trials vs. placebo	12	3347	WMD -4.47 [-5.41 to -3.52]	low	direct	precise	consistent	High
	pramipexole	5	1578	WMD -4.76 [-6.24 to -3.28]	low	direct	precise	consistent	High
	ropinirole	4	1286	WMD -3.29 [-4.31 to -2.27]	low	direct	precise	consistent	High
	rotigotine	3	483	WMD -6.07 [-8.33 to -3.81]	low	direct	precise	consistent	High
	Cabergoline vs. levodopa	1	361	WMD -6.80 [-9.02 to -4.58]	low	direct	precise	unknown	Moderate
Clinical Global Impression responders: (much-very much improved)	All trials vs. placebo	13	4074	RR 1.46 [1.35 to 1.58]	low	direct	precise	consistent	High
	pramipexole	5	1747	RR 1.61 [1.40 to 1.86]	low	direct	precise	consistent	High
	ropinirole	5	1377	RR 1.37 [1.25 to 1.50]	low	direct	precise	consistent	High
	rotigotine	3	950	RR 1.35 [1.16 to 1.57]	low	direct	precise	consistent	High
Patient Global Impression responders: (much-very much improved)	All trials vs. placebo	6	2069	RR 1.66 [1.45 to 1.90]	low	direct	precise	consistent	High
	pramipexole	5	1712	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	7	1779	SMD -0.40 [-0.52 to -0.29]	low	direct	precise	consistent	High
	pramipexole	3	912	SMD -0.43 [-0.61 to -0.25]	low	direct	precise	consistent	High
	ropinirole	1	377	SMD -0.31 [-0.51 to -0.11]	low	direct	precise	unknown	Moderate
	rotigotine	3	483	SMD -0.42 [-0.52 to -0.29]	low	direct	precise	inconsistent	Moderate
	Cabergoline vs. levodopa	1	361	SMD -0.50 [-0.72 to -0.30]	low	direct	precise	unknown	Moderate
Self-rated sleep MOS-SPI-II	All trials vs. placebo	8	2052	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	1237	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
Patients with ≥ 1 adverse event	All trials vs. placebo	14	4248	RR 1.17 [1.10 to 1.25]	low	direct	precise	consistent	High
	pramipexole	5	1790	RR 1.16 [1.04 to 1.29]	low	direct	precise	inconsistent	Moderate
	ropinirole	6	1429	RR 1.18 [1.09 to 1.27]	low	direct	precise	consistent	High

	rotigotine	3	1029	RR 1.23 [0.93 to 2.38]	low	direct	imprecise	consistent	Moderate
	Cabergoline vs. levodopa	1	361	RR 1.07 [0.97 to 1.19]	low	direct	precise	unknown	Moderate
Any study withdrawal	All trials vs. placebo	14	4253	RR 0.82 [0.68 to 1.00]	low	direct	precise	inconsistent	Moderate
	pramipexole	5	1792	RR 0.71 [0.50 to 1.01]	low	direct	imprecise	inconsistent	Low
	ropinirole	6	1432	RR 0.91 [0.72 to 1.14]	low	direct	imprecise	consistent	Moderate
	rotigotine	3	1029	RR 0.92 [0.56 to 1.50]	low	direct	imprecise	inconsistent	Low
	Cabergoline vs. levodopa	1	361	RR 0.92 [0.72 to 1.16]	low	direct	imprecise	unknown	Low
Study withdrawals due to an adverse event	All trials vs. placebo	14	4252	RR 1.36 [0.98 to 1.87]	low	direct	imprecise	inconsistent	Low
	pramipexole	5	1791	RR 0.97 [0.69 to 1.35]	low	direct	imprecise	consistent	Moderate
	ropinirole	6	1432	RR 1.41 [0.89 to 2.22]	low	direct	imprecise	consistent	Moderate
	rotigotine	3	1029	RR 2.85 [1.40 to 5.80]	low	direct	precise	consistent	High
	Cabergoline vs. levodopa	1	361	RR 1.50 [0.95 to 2.37]	low	direct	imprecise	inconsistent	Low
Nausea	All trials vs. placebo	13	3879	RR 3.42 [2.56 to 4.56]	low	direct	precise	consistent	High
	pramipexole	4	1421	RR 2.63 [1.78 to 3.90]	low	direct	precise	consistent	High
	ropinirole	6	1429	RR 4.36 [2.75 to 6.91]	low	direct	precise	consistent	High
	rotigotine	3	1029	RR 2.79 [1.34 to 5.79]	low	direct	precise	consistent	High
Vomiting	Ropinirole	5	1377	RR 4.84 [2.77 to 8.47]	low	direct	precise	consistent	High
Somnolence	All trials vs. placebo	8	2314	RR 2.04 [1.50 to 2.76]	low	direct	precise	consistent	High
	pramipexole	2	673	RR 1.65 [0.85 to 3.23]	low	direct	imprecise	consistent	Moderate
	ropinirole	4	1070	RR 2.29 [1.56 to 3.36]	low	direct	precise	consistent	High
	rotigotine	2	571	RR 1.73 [0.84 to 3.57]	low	direct	imprecise	consistent	Moderate
Application site reactions	Rotigotine	3	1029	RR 8.20 [2.53 to 26.57]	low	direct	precise	consistent	High

MOS-SPI-II = Medical Outcomes Scale- Sleep Problems Index II; RR = relative risk; SMD = standardized mean difference; WMD = weighted mean difference (a negative SMD and WMD indicates that the active treatment is more effective then placebo)

Table B. Overall strength of evidence for individual outcomes in studies of GABA analogs

Outcome	Number of trials	n	Summary statistics, [95% CI]	Risk of bias	Directness	Precision	Consistency	Evidence rating
IRLS Responders (≥50% score reduction)	2	182	RR 2.03 [1.33 to 3.11]	low	direct	precise	consistent	High
IRLS total score: Mean change from baseline	2	264	WMD -4.51 [-6.60 to -2.42]	moderate	direct	precise	consistent	Moderate
IRLS total score: Mean score at endpoint	2	102	WMD -6.56 [-9.27 to -3.86]	moderate	direct	precise	consistent	Moderate
Clinical Global Impression: Responders (much improved)	2	341	RR 1.52 [0.89 to 2.58]	moderate	direct	imprecise	inconsistent	Low
Self-rated sleep MOS-SPI-II	1	47	SMD 0.29 [-0.29 to 0.86]	low	direct	imprecise	unknown	Low
Patients with ≥ 1 adverse event	3	417	RR 1.38 [0.90 to 2.12]	low	direct	imprecise	inconsistent	Low
Any study withdrawal	3	417	RR 0.81 [0.49 to 1.34]	low	direct	imprecise	consistent	Moderate
Study withdrawals due to an adverse event	3	417	RR 3.18 [1.17 to 8.66]	low	direct	precise	consistent	High

Table C. 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	Evidence rating
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

RR = risk ratio; WMD = weighted mean difference.
* post-hoc analysis

Discussion

The main intent of this report was to conduct a comparative effectiveness review on treatments for restless leg syndrome. However, we identified only one randomized controlled trial that directly compared two treatment options. This single study assessed two drugs no longer widely used for this condition (cabergoline and levodopa). The included studies are insufficient to conduct reliable indirect comparisons from which to draw valid information about comparative benefits and harms. Thus, we could not make accurate conclusions about the comparative effectiveness and harms of treatments for RLS. However, results from small, placebo-controlled randomized trials of short duration suggest that dopamine agonists (ropinirole, pramipexole, and rotigotine) and anticonvulsant GABA analogs (gabapentin and pregabalin) reduce symptoms, increase the percentage of IRLS responders, and improve disease-specific quality of life and patient-reported sleep outcomes.

Randomized controlled trial evidence regarding treatments for restless legs syndrome is limited in quality and quantity, and applicability is largely unknown for long-term outcomes and for those who have mild to moderate RLS symptoms or who are pregnant or who have iron deficiency or end-stage renal disease. All RCTs were short in duration and enrolled highly selected populations with symptoms that were very severe to high-moderate, frequent, and long-standing. Studies of pharmacological therapies consisted mainly of dopaminergic agents, while a few studies assessed GABA analogs. 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.[5] Few nonpharmacological therapies were assessed, and they were limited to a single small study each.

Exclusion criteria were many, and subjects were typically recruited from RLS clinics not primary care or mental health settings; both settings are frequent clinical settings for initial 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 enrolled individuals under age 18, and the vast majority of individuals were white. The long-term benefits, adherence, and harms as well as the comparative effectiveness and harms of commonly used and FDA-approved treatments are not well known. Future trials of other therapies are needed, because current evidence suggests that available options have limited short- and long-term effectiveness and frequently result adverse effects and treatment discontinuation.

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. Although symptom scales and are widely used in research studies, their use in clinical settings is less clear and likely very limited. Furthermore, despite that RCT study subjects met consensus definitions of RLS, these criteria are not routinely used in clinical settings to diagnose, assess severity, or initiate therapy. Thus,

the applicability of results from these RCTs to individuals seen, diagnosed and treated in primary care or mental health settings is not established. Outcomes were not stratified by patient and RLS characteristics, and we could not determine whether findings vary by these factors.

Only one RCT directly compared pharmacologic options, specifically cabergoline to levodopa (two agents not widely used currently for RLS treatment). 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 GABA agonist pregabalin (k = 1). Because studies reported a large placebo response, we urge caution in using information from uncontrolled studies as the basis for recommending 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 RLS symptom scale scores found no benefit with oral iron therapy in adults with RLS and normal iron stores. 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 who are unable to initiate or tolerate dopaminergic agents, or for whom these drugs have failed, recommended treatments include off-label opioids (morphine, oxycodone and methadone), sedative hypnotics, and tramadol. None of these are FDA approved for treatment of RLS and have the potential for long-term abuse especially given the subjective nature of RLS symptoms and large placebo response seen in other pharmacological studies. We found no eligible studies evaluating these agents. A single crossover study of 11 patients assessed oxycodone versus placebo and reported improvement in leg sensation, motor restlessness, and alertness.

The RCT evidence base for RLS treatments is mostly limited to short-term, placebo-controlled efficacy studies of dopamine agonists and anticonvulsant GABA analogs conducted in highly selected patient populations with longstanding, high moderate to very severe primary RLS. We found no data from randomized controlled trials on the comparative benefits or harms of these drugs. Only two small studies of iron therapy addressed secondary RLS due to iron deficiency, providing low strength of evidence that iron replacement therapy may improve symptoms. Assessment of nonpharmacological interventions was limited to three trials, one on exercise, one on compression stockings, and one on the herb valerian. These provided low strength evidence for a benefit with compression stockings and exercise but not with valerian.

No studies 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. No studies meeting our inclusion criteria assessed opioids, sedative hypnotics, or tramadol, all of which are recommended in treatment algorithms[5] and presumably used in clinical practice.

Results from small, placebo-controlled randomized trials of short duration suggest that dopamine agonists (ropinirole, pramipexole, and rotigotine) and anticonvulsant GABA analogs (gabapentin and pregabalin) reduce symptoms, increase the percentage of IRLS responders, and improve disease-specific quality of life and patient-reported sleep outcomes. 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. Applicability is limited to nonpregnant adults who have high-moderate to very severe RLS and no major comorbidities. Long-term studies reporting withdrawals due to loss of efficacy or side effects suggest that for many RLS patients, the benefits of pharmacological 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 long-term treatment with dopaminergic drugs.

Nonpharmacological interventions such as exercise and compression stockings were assessed in only one study each. While results suggested these interventions may improve symptoms, the studies were very small and short-term. The exercise therapy trial had high patient drop out (30 percent). Further, the authors reported outcomes only for individuals who completed the study. Thus, their findings are limited in both quality and applicability. No RCTs have examined other recommended nonpharmacological therapies such as psychotherapy or hot or cold baths.

Evaluating any treatment for RLS 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 scale scores 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, for whom a chronic, progressive disorder may require daily treatment for decades. Even nonpharmacological interventions and other treatments for those with milder symptoms are often long-term. Yet, the evidence base 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 highly selected population of RLS patients must 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. 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 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 efficacy studies of dopamine agonists and GABA analogs conducted in a highly selected population of adults with moderate to very severe primary RLS of long-duration. Compared to placebo, dopamine agonists and GABA analogs reduce symptoms 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 GABA analogs are common. We found no high quality data on comparative effectiveness and harms of commonly used treatments, little data on nonpharmacological interventions or the effect of patient or RLS characteristics on outcomes. Applicability to adults with less frequent or less severe (mild to moderate) RLS symptoms, children, or those with secondary RLS is unknown.

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 pharmacological treatments and dopamine agonists in particular	• More studies of nonpharmacological treatments.
	• Many classes of drugs used in clinical practice such as opioids and sedative hypnotics have not been evaluated in clinical trials.	• Studies of classes of drugs other than dopamine agonists such as opioids and sedative hypnotics.
	• We found no evidence for effectiveness of therapies in specific subgroups such as children, older adults with multimorbidities, or individuals with secondary RLS.	• Studies of effectiveness of drugs in specific sub-groups such as children, older adults, and individuals with secondary RLS.
Long-term durability of treatment benefits	• Long-term durability of treatment benefits remains an unaddressed concern.	• Long-term studies that establish the time frame over which treatment benefits are sustained for different types of 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.	• Studies that report effectiveness of treatments for various subgroups of patients such as those with different disease duration, patients *de novo* to treatment, and those for whom previous treatment failed.
Augmentation	• Augmentation is a significant harm with long-term 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. • 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. • 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. • Report outcomes such as proportions of patients with remission of symptoms (IRLS score=0), patient-reported sleep outcomes and quality of life. • 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.

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.
4. García-Borreguero D, Egatz R, Winkelmann J, et al. Epidemiology of restless legs syndrome: The current status. Sleep medicine reviews. 2006 Jul;10(3):153-67.
5. 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.
6. Garcia-Borreguero D, Williams AM. Dopaminergic augmentation of restless legs syndrome. Sleep Med Rev. 2010 Oct;14(5):339-46. PMID 20219397.
7. 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.
8. Manconi M, Govoni V, De Vito A, et al. Restless legs syndrome and pregnancy. Neurology. 2004 Sep 28;63(6):1065-9. PMID 15452299.
9. Higgins JPT, Green S, eds. Cochrane handbook for systematic reviews of interventions: The Cochrane Collaboration; 2008.
10. 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.
11. Atkins D, Chang S, Gartlehner G, et al. Assessing the Applicability of Studies When Comparing Medical Interventions. Quality AfHRa; December 2010. http://www.effectivehealthcare.ahrq.gov/index.cfm/search-for-guides-reviews-and-reports/?pageaction=displayProduct&productID=603#2412.
12. 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.
13. 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.
14. 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.
15. 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.
16. 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.
17. 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.
18. 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.
19. 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.
20. 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.

21. 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.
22. 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.
23. 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.
24. 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.
25. 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.
26. 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.
27. 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.
28. 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.
29. 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.
30. 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.
31. 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.
32. 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.
33. 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.
34. 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.
35. 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.
36. 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.
37. 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.
38. 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.
39. Ferini-Strambi L. Restless legs syndrome augmentation and pramipexole treatment. Sleep Medicine. 2002 Nov;3 Suppl:S23-5. PMID 14592163.

40. 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.
41. 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.
42. 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.
43. 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.
44. 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.
45. 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.
46. 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.
47. 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.
48. Ondo WG. Methadone for refractory restless legs syndrome. Movement Disorders. 2005 Mar;20(3):345-8. PMID 15580610.
49. 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.
50. 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.
51. 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.
52. 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.
53. 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.
54. 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.
55. 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.

Introduction

Overview

Restless legs syndrome (RLS), or Willis-Ekbom disease, is a neurological disorder that characterized by unpleasant or painful sensations in the legs and a distressing, irresistible urge to move them.[56] RLS symptoms worsen during inactivity and at night. Partial or complete relief may result from movement such as walking, stretching, or bending of the legs. Yet, the relief is temporary and symptoms return when movement ceases. If the disease progresses, symptoms may occur earlier in the day and intensify even further at night and/or extend beyond the legs to the arms and/or trunk. The clinical course of RLS varies, and periods of remission are common, particularly in younger patients and those with milder disease. Severe restless legs syndrome, however, is a chronic progressive disorder that may require long-term treatment.[3]

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[57] and revised in 2003.[58]} Any RLS diagnosis requires that the all four essential criteria be met: 1) An urge to move the legs, usually accompanied by uncomfortable or unpleasant sensations in the legs; 2) Unpleasant sensations or the urge to move begin or worsen during periods of rest or inactivity such as lying or sitting; 3) Unpleasant sensations or urge to move are partly or totally relived by movement such as walking, bending, stretching, etc., at least as long as the activity continues; and 4) Unpleasant sensations or the urge to move are worse in the evening or at night than during the day, or only occur in the evening or night. In other words, to meet the four essential criteria, patients should have characteristic sensory or motor symptoms that are provoked or made worse by rest, improve with movement, and worsen or occur only in the evening or at night.

The etiology of RLS is unknown, but it may occur secondary to other conditions such as iron deficiency, end-stage renal disease, and pregnancy.[58] Secondary RLS often starts later in life than does primary RLS. It is also associated with more rapid progression than and often resolves when the underlying condition is treated.[58] Although mechanistic relationships are yet to be established, pathophysiology of RLS may be closely linked to abnormalities in the dopaminergic system and iron metabolism.[3]

The severity of RLS varies. Mild RLS may result in only minor annoyance; however, severe RLS can have a crippling impact on quality of life.[59] It can interfere with work or social activities and reduce function and emotional well-being. RLS-induced sleep disruption may lead to poor daytime functioning, anxiety, and depression. Sleep deprivation and daytime fatigue are the most common reasons RLS patients seek treatment.[59]

Prevalence estimates for RLS range from 2.4 to 10 percent in adults, and are higher for women and older people.[4] Different approaches to diagnosing RLS and defining its severity lead to the large variance in prevalence estimates, as does the fact that many RLS questionnaires do not account for individuals with other conditions with similar symptoms (e.g., neuropathies, pain syndromes). Also notable is that these prevalence estimates include RLS patients with a wide spectrum of disease severity; when restricted to the RLS population with clinically significant disease requiring medical attention, the prevalence estimates are much lower. For example, in a U.S. study, Allen et.al.[2] used validated diagnostic tools and estimated that 7.4 percent of the population fulfilled all four of the diagnostic criteria. However, exclusion of secondary causes

and mimic conditions resulted in a prevalence estimate of 2.4 percent for primary RLS. The prevalence estimate for RLS sufferers, characterized as those having symptoms at least twice weekly with moderate to severe impact, was a much lower 1.5 percent. In this group, 34.4 percent had moderate symptoms, 54.2 percent had severe symptoms, and 11.5 percent had very severe symptoms. We draw attention to these distinctions because questions related to RLS severity and impact underlie many of the uncertainties encountered in clinical practice; accuracy in assessing RLS severity and impact is key to evaluating the need for treatment and the applicability of treatments to patients with different degrees of disease severity.

Treatments (nonpharmacological and pharmacological options) vary by patient age and the severity of RLS. Nonpharmacological options include: exercise, sleep hygiene, avoiding potential RLS precipitants (caffeine, alcohol, nicotine, antidepressants, antihistamines); counter stimuli to sensory symptoms (hot or cold bath, limb massage, compression stockings, counter-pulsation devices); herbal medicines and acupuncture; and cognitive behavioral therapy. Pharmacological treatment is generally reserved for patients with moderate to severe RLS. The major classes of drugs used are dopaminergic agents, sedative hypnotic agents, anticonvulsive agents, opiates, and iron. Information on these treatments is shown in Table 1. Of these drugs, two dopamine agonists (pramipexole and ropinirole) and one anticonvulsant drug (gabapentin) are FDA approved for treatment of moderate to severe RLS. A significant treatment complication with long-term use of dopaminergic agents is a drug-induced worsening of symptoms known as augmentation. Augmentation is characterized by more intense symptoms with earlier onset, shorter latency, and that may spread to other body parts (usually the arms, but also the trunk and face).[6]

The primary goal of RLS treatment is to manage symptoms and improve patient function and quality of life. Except for the limitations on pharmacological therapy imposed by pregnancy, and the use of iron replacement for those with iron deficiency, treatment options are unlikely to vary for primary and secondary forms of RLS.[5] For patients with RLS secondary to pregnancy, iron deficiency, or end-stage renal disease, the recommendation is to treat the associated condition first whenever possible. Clinical experience suggests that RLS associated with pregnancy resolves postpartum in most patients; however, therapy has not been evaluated this population, and very little is known about women with pregnancy-induced RLS whose symptoms persist after delivery.[7]

Table 1. Pharmacologic treatments for RLS

	Generic Name	US Trade Name	FDA Approval for RLS
Dopaminergic agents	Levodopa	Sinemet®	
	Ropinirole	Requip®	Yes
	Pramipexole	Mirapex®	Yes
	Rotigotine	Neupro®	
Sedative-hypnotics	Clonazepam	Rivotril®	
	Temazepam	Restoril®	
	Oxazepam	Serax®	
Anticonvulsants	Gabapentin Enacarpil	Horizant®	Yes
	Gabapentin	Neurontin®	
	Pregabalin	Lyrica®	
Opioids	Hydrocodone	-Vicodin® -Lortab®	
	Codeine	Tylenol # 3 w/codeine®	
	Tramadol	-Ultram® -Tramal®	
	Oxycodone or oxycodone-XR	-Tylox® -Percodan® -Oxycontin®	
	Methadone	-Methadose® -Dolophine®	
	Morphine Sulphate-XR	Depodur®	
Iron			

Methods of Assessment

Several scales are used to assess RLS severity, impact, and specific health outcomes such as patient-reported sleep outcomes, quality of life, and harms (Table 2).[60] Use of these scales is limited almost exclusively to clinical research and possibly specialty settings. They are used only rarely in primary care. The International Restless Leg Study group (IRLS) scale is most widely reported.[61]The IRLS is a 10-item scale with scores ranging from 0 (no symptoms) to 40. Scores >30 are considered very severe and 10 or less, mild. The minimum change in scale score that translates to clinically significant improvement in patients has not been defined for these scales. In the absence of such definition, responder criteria that could potentially be meaningful to patients—and that have face validity and are identifiable to patients and providers—could be used. Such criteria include: 1) resolution of symptoms (IRLS scale score=0); 2) percent of patients with reduction of symptoms from very severe or severe to mild (IRLS<10); 3) 50 percent or greater change in IRLS score from baseline; or 4) percent of patients who are much improved or very much improved on the clinician-assessed global impressions scale or patient-assessed global impressions scale.

Table 2. Methods of Assessment

Domain	Scale	Components of Scale	Attributes
Severity and Impact of Disease	International RLS Study group scale (IRLS)[61]	• Intensity (5 items) • Frequency (1 item) • Consequences of RLS (4 questions on sleep quality, daytime tiredness, mood, and quality of life)	• Scale with 10 items with each item rated on a 5 point scale (0 = no symptoms, 4 = very severe or frequent symptoms) • Scores are combined to give a global assessment. 0: No RLS 1-10: mild RLS 11-20: moderate RLS 21-30: severe RLS 31-40: very severe RLS • Assessed together by patient and investigator
Severity of Disease and Therapeutic effects	Clinical Global Impressions (CGI)[60]	• Disease severity (1 item) • Improvement from baseline (1 item) • Therapeutic effect (1 item) • Side-effects of treatment (1 item)	• Individual items are rated on a 7-point scale. Scores are not combined; often just one component of the scale (e.g. Improvement) is assessed • Assessed by clinician
Quality of Life	Restless Legs Quality of Life Instrument (RLS-QLI) [60]	• Social function (4 items) • Daily function (6 items) • Sleep quality (4 items) • Emotional well-being (3 items)	• 17 items rated on a 5 point scale
	Hopkins RLS Quality of Life Questionnaire (RLSQoL)[60]	• Daily function (8 items) • Social activities and travel arrangements (2 items) • Morning activities and concentration (5 items) • Sleep and sexual activity (3 items)	• I8 items rated on a 5 point scale
	RLS Quality of Life Questionnaire (Qol-RLS)	• Daily activities • Emotional well-being • Social interactions • Sleep	• 12 items rated on a 6-point scale
Patient-reported day time sleepiness and	Epworth Sleepiness Scale [62]	• Daytime sleepiness	• 8-item, 4-point questionnaire measuring daytime somnolence in different situations. • A score greater than 10 is characterized as “sleepy” and a score greater than 18 is considered “very sleepy”
sleep quality	Medical Outcomes Study Sleep Scale[63]	• Sleep initiation • Maintenance • Quality • Quantity • Adequacy • Daytime somnolence	• 12 items that measures multiple aspects of sleep
	Pittsburgh Sleep Quality Index[64]	• Sleep quality • Latency • Duration • Efficiency • Disturbance • Use of sleep medication • Daytime dysfunction	• Score ranges from 0 to 21; Total score≤5 indicates good sleep quality and a total score >5 indicates poor sleep quality

Augmentation	Augmentation Severity Rating Scale (ASRS)[65]	•	• 3 items (9 point: 0 = no sign of augmentation, 8 = signs of severe augmentation) are used to assess severity of augmentation • A cutoff of at least 5 points in the total score is recommended as a screener for augmentation

Areas of Uncertainty

Clinicians face uncertainty related to defining RLS, assessing disease severity, and evaluating the risk/benefits of treatment. While these challenges apply to both primary care and specialty settings, they may be more pronounced in primary care. Specific issues that affect clinical practice include:

- **Reliable diagnosis requires use of standard criteria and distinguishing RLS from other disorders.** RLS is diagnosed based on clinical history using standard criteria. "Mimic" conditions sometimes satisfy the standard RLS criteria, and must be ruled out by examination. Many patients with RLS also experience semi-rhythmic limb movements called periodic limb movements (PLM) while awake or asleep. However, these movements are not RLS and they may occur among older adults, in those taking antidepressants, and as a result of certain neurological and sleep disorders (e.g., narcolepsy).[66] RLS is distinct from sleep disorders such as periodic limb movements disorder (PLMD).

  The use of standard criteria is common in clinical research and possibly in specialty practice. However, in primary care, the standard criteria may be less consistently applied. As a result, patients may be misdiagnosed, misclassified, receive unnecessary or ineffective treatment, or not receive necessary care. Direct-to-consumer advertising may result in RLS patients previously unidentified receiving appropriate diagnosis and therapy, but it may also result in requests for potentially inappropriate pharmacological treatments for RLS-like symptoms.
- **Assessing comparative risk/benefits of treatment** RLS encompasses a broad spectrum of symptom severity and impact. Because the clinical significance of RLS is due to its impact on an individual's quality of life and function, treatments should focus on the balance of symptomatic benefits with treatment harms. Pharmacological treatments have the potential for adverse events and costs and are not curative; therefore, such therapy is generally indicated only when the disease significantly impacts quality of life.[5], [67] For the larger group of individuals with mild or moderate symptoms, treatment harms remain a concern. In addition, long-term risks and benefits of treatment are unclear. In particular, for older adults with multiple morbidities, the benefits and risks of RLS treatments must be evaluated in the context of overall health effect and potential for adverse events or interactions with concomitant medications. Current recommendations suggest an algorithmic approach for the management of restless leg syndrome.[5] However, little is known about the scientific validity of such an approach or the comparative effectiveness and harms of currently recommended treatment options.
- **Measuring changes in disease status and impact of treatment** Lack of objective measures for assessing disease status presents a challenge in clinical practice.[60], Typically, clinical interviews are used to assess disease severity and treatment-induced changes in disease

status. In research settings, the same assessments are made using specific rating scales such as the International Restless Legs Study Group (IRLS) scale and Clinical Global Impressions (CGI) scale.[60] However, the results of RLS severity scales cannot be meaningfully interpreted in the absence of clearly defined "minimum clinically important differences" (MCIDs).

- **Long-term effectiveness, adherence, and harms of treatment.** There is limited understanding of long-term outcomes of treatments for both primary and secondary RLS. RLS is often a long-term to life-long condition, yet interventions are often assessed in short-term studies. Thus, accurately assessing long-term outcomes is important.

Scope and Key Questions

Scope of the Review

We evaluated the effectiveness, harms, and comparative effectiveness and harms of treatments for individuals with RLS. We assessed outcomes in the domains of: disease severity and impact, patient-reported sleep quality, and quality of life. We did not evaluate polysomnographic or other intermediate laboratory measures of leg movements or sleep.

The definitions of population, intervention/comparator, outcomes, timing, and setting for this review were:

Population. Individuals with restless legs syndrome regardless of age. Major subgroups included older adults (age 65 or greater) with comorbidities and children (age <18 years). Patient characteristics of interest, which may modify RLS disease course and treatment outcomes, included: age, race/ethnicity, gender, RLS severity (including duration), prior treatment status, comorbidities, etiology (i.e., primary or secondary RLS), iron status, pregnancy, and end-stage kidney disease (ESRD).

Interventions. We evaluated the following interventions:

- Pharmacological treatments (dopaminergic agents, sedative-hypnotics, anticonvulsants, opioids, and iron supplementation)
- Nonpharmacological treatments (exercise, hot or cold bath, limb massage, sleep hygiene, acupuncture, herbal medicines, cognitive behavioral therapy, counter pulsation devices, compression stockings, eliminating precipitants of RLS)
  Interventions could include combination of one of more of pharmacological or nonpharmacological treatments.

Comparators. Placebo, no treatment, or active comparator

Outcomes.

Primary outcome. Percentage of patients with ≥ 50 percent change in mean International RLS (IRLS) symptom scale score from baseline or remission of symptoms (IRLS score = 0).

Secondary outcomes. Mean change in symptom severity and impact assessed using International RLS (IRLS) rating scale. Proportion of patients reporting improved or much improved on clinician assessed global change index (CGI scale score) or patient assessed global change index (PGI scale score); quality of life as measured by disease-specific scale (e.g., Restless Legs Quality Of Life Instrument, Hopkins RLS Quality Of Life Questionnaire, RLS Quality Of Life Questionnaire); Patient-reported sleep outcomes measured using a validated

sleep scale to measure daytime sleepiness or somnolence (Epworth Sleepiness Scale) and sleep quality (Medical Outcomes Study Sleep Problems Index or Pittsburgh Sleep Quality Index)

Harms of treatment

Primary measure. Number of individuals experiencing any adverse event

Secondary measures. Dropouts, dropouts due to adverse effects, treatment discontinuation due to adverse events, specific adverse events including augmentation

Timing. We analyzed studies with a minimum of 4 weeks treatment, defining short-term as < 6 months, intermediate as 6 to 24 months, and long term as > 24 months.

Setting. We included studies in outpatient settings.

Key Questions

Key questions were developed with input from stakeholder groups representing patients, providers, and technical experts. Among the many areas of uncertainty identified, a critical issue was understanding whether treatment benefits and adherence were sustained over time (durability). Our key questions therefore address long-term tolerability, sustainability, and harms of treatments.

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

d. What are the benefits from RLS treatments when compared to placebo or no treatment?
e. What are the benefits from RLS treatments when compared to other active treatments?
f. What is the durability and sustainability of treatment benefits?

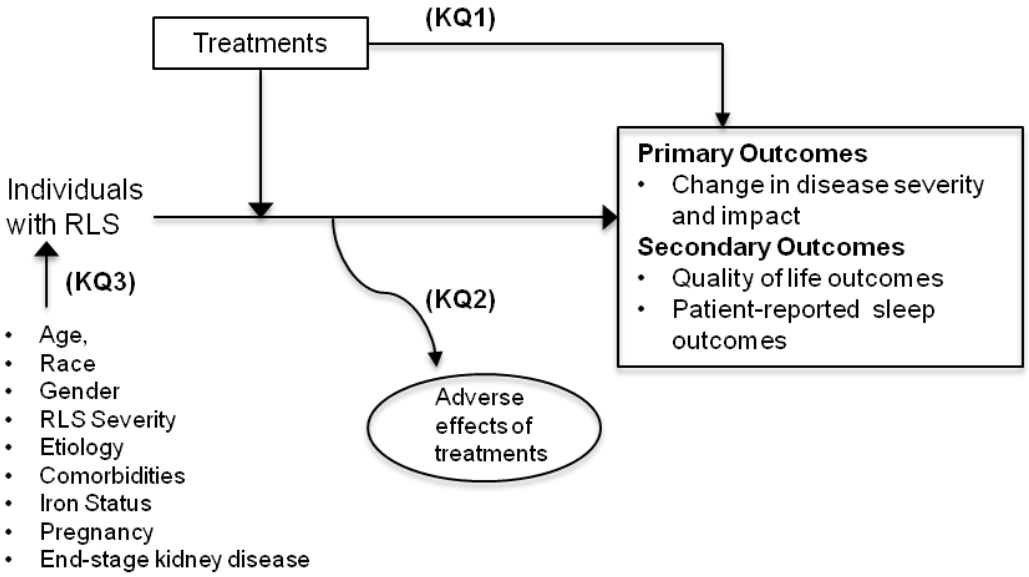
Key Question 2. What are the harms from RLS treatments?

d. What are the harms from RLS treatments when compared to placebo or no treatment?
e. What are the harms from RLS treatments when compared to other active treatments?
f. 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?

The analytical framework for our key questions is shown in Figure 1.

Figure 1. Analytical framework



Methods

We conducted the comparative effectiveness review (CER) of treatments for restless legs syndrome (RLS) following the methods suggested in the AHRQ Methods Guide for Effectiveness and Comparative Effectiveness Reviews (available at http://www.effectivehealthcare.ahrq.gov/methodsguide.cfm). The main sections in this chapter reflect the elements of the protocol publicly posted on the AHRQ Effective Health Care program Web site, and they correspond to the PRISMA checklist.[68]The methods and analyses were determined *a priori.*

Topic Refinement and Review Protocol

The topic for this CER was nominated by a public process available through the Effective Health Care Web site. Investigators developed preliminary key questions with input from various stakeholder groups representing patients, providers, and content experts. The key questions were posted on AHRQ's Web site for public comments for 4 weeks from August 2, 2011 to August 30, 2011. Public comments and input from the Technical Expert Panel (TEP), convened to provide methodological and content expertise, aided the development of the final and protocol.

Literature Search Strategy

We searched the bibliographic databases MEDLINE (via OVID), EMBASE, and Natural Standards from inception through September 17, 2011 for randomized controlled trials evaluating treatment efficacy and observational studies reporting adverse effects of treatments of RLS. In addition, we reviewed regulatory documents from the FDA website to evaluate harms of treatment. The search algorithm, developed with input from a biomedical librarian and independently reviewed by another librarian, consisted of a combination of search strings that describe the condition and search filters designed to retrieve relevant RCTs and observational studies (Appendix A). To identify completed trials and to check for publication bias, we searched Cochrane Central, the International Controlled Trials Registry Platform (ICTRP), and the NIH RePORTer.

Inclusion and Exclusion Criteria

For questions related to treatment efficacy, we included studies if they were RCTs that enrolled individuals with RLS, were published in English, evaluated pharmacological and/or nonpharmacological interventions for RLS, lasted at least 4 weeks, and reported validated RLS symptom scale scores (International RLS-IRLS). We included observational studies and open-label followup extensions of RCTs that reported long-term (>6 months) adverse effects and adherence. Pharmacological interventions were limited to drugs approved for use (for any condition) in the United States. Specific eligibility criteria are listed in Table 3.

Table 3. Inclusion criteria

Domain	Criteria for Inclusion
Population	• Individuals diagnosed with RLS
Intervention	• Pharmacological and nonpharmacological treatments for RLS
Comparison	• Placebo (or sham treatment), no treatment, or other active comparator
Outcomes	• Change in RLS symptom severity and impact (mean change from baseline in IRLS scale scores) •
Setting	• Outpatient settings
Timing	• For RCTs reporting efficacy outcomes, at least 4 weeks • For observational studies reporting adverse events, from 6 months to decades
Study Design	• RCTs and observational studies reporting adverse events; open-label followup studies for RCTs
Publication dates	• Through September 17, 2011
Language	• English

Study Selection

Bibliographic database search results were downloaded to an Endnote™ reference management system. We identified eligible studies in two stages. In the first stage, two investigators independently reviewed titles and abstracts of all references. Studies deemed eligible for inclusion by either investigator were further evaluated. In the second stage, two investigators independently reviewed full text to determine if studies met inclusion criteria. Differences in full-text screening decisions were resolved by discussion or, when necessary, by consultation with a third investigator. Eligibility status and at least one exclusion reason were documented for all studies evaluated at the full-text screening stage. For randomized controlled trials, reasons for exclusion were coded as: non-English language study; not a relevant study design; no relevant intervention or comparator; no relevant outcome; and trial duration <4 weeks. The excluded articles and the reason for exclusion are listed in Appendix B.

Data Extraction

One reviewer extracted data from included studies directly into evidence tables (Appendix C) and a second reviewer validated the data. Disagreements were resolved by consensus or, when needed, by consultation with a third reviewer. We abstracted data on:

- Study characteristics: design (parallel or cross-over), eligibility criteria, study duration, setting, and funding source.
- Patient characteristics: age, race, sex, RLS diagnostic criteria, previous RLS medication history, duration of RLS (time since diagnosis), baseline severity, iron status, and frequency of ESRD.
- Intervention/comparator: type of intervention, dosage, titration, washout period (for cross-over trials).
- Outcomes: Mean change in IRLS scale score from baseline, percent of patients with ≥50 percent reduction in IRLS scale score (responders; our primary outcome); percent of patients with complete remission; percent of patients reporting much improved or very much improved on clinician assessed global impressions scale (CGI) or patient assessed global impression scale (PGI); RLS quality of life; patient-reported sleep quality; number of individuals experiencing adverse effects; drop-outs; drop-outs due to AE; treatment

discontinuation due to adverse effects; percent experiencing augmentation, percent experiencing specific adverse effects.

Risk of Bias of Individual Studies

We assessed risk of bias of RCTs using the Cochrane risk of bias tool[9] 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. We rated studies as good, fair, or poor quality. A rating of good (having good internal validity or low risk of bias) generally indicated that the trial reported adequate allocation concealment, used some blinding methods, analyzed by intent-to-treat, and reported reasons for dropouts/attrition. We then used study quality for the individual RCTs to determine the overall risk of bias to assess strength of evidence for each particular outcome.

Data Synthesis

For trials with similar populations, interventions, and outcomes and that presented sufficient data, we calculated pooled random-effects estimates of overall effect size, weighted mean differences, or risk ratios (RR). We used Review Manager 5.1 to pool and analyze the data.[69] We calculated risk ratios (RR) for dichotomous outcomes and weighted mean (WMD) or standardized mean (SMD) differences for continuous outcomes using a random-effects model. We assessed statistical heterogeneity between trials and for subgroups of drugs using the I^2 test. A score of approximately 50% suggests substantial heterogeneity. Publication bias was assessed through inspection of funnel plots and the Egger intercept test.[70]

Strength of the Body of Evidence

We evaluated the overall strength of evidence using methods developed by the Agency for Healthcare Research and Quality and the Effective Health Care Program[10] for the following outcomes: mean change in IRLS scale score from baseline; percent of IRLS responders, i.e., patients with $\geq$50 percent reduction in IRLS scale score; percent of patients reporting “much improved” or “very much improved” on clinician-assessed global impression (CGI) or patient-assessed global impression (PGI); quality of life; patient-reported sleep quality; number of individuals experiencing adverse effects, and dropouts due to adverse effects. We evaluated strength of the evidence on four required domains:

1. Risk of bias. Low, medium, or high
2. Consistency. Consistent, inconsistent, or unknown/not applicable (e.g., only one study for the respected outcome evaluated)
3. Directness. Direct or indirect
4. Precision, based on the confidence intervals surrounding an effect estimate. The confidence intervals for an imprecise estimate would be wide enough to include clinically distinct conclusions.

We evaluated individual domains qualitatively and assigned a summary rating of high, moderate, or low strength of evidence. An overall rating of high strength of evidence would imply that the included studies were RCTs with a low risk of bias, with consistent, direct, and precise domains. Generally for outcomes with multiple studies, evidence was downgraded to moderate strength of evidence if there was either medium/high risk of bias (low quality RCTs), imprecision, indirectness, or inconsistency and low if two or more of the domains were deemed inadequate. Outcomes with only a single trial were usually rated moderate if there was a low risk of bias, and had direct and precise domains.

Applicability

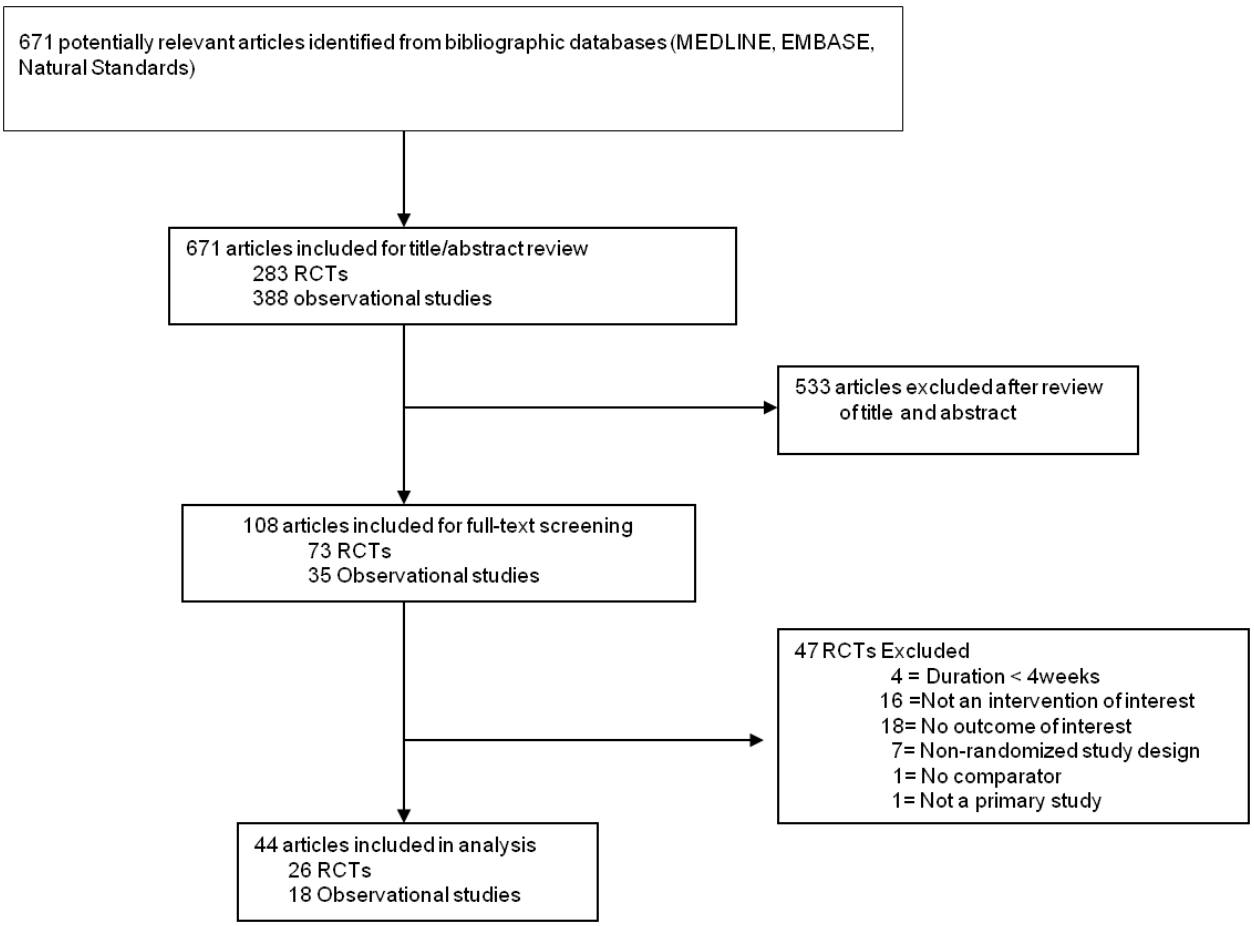
We assessed applicability separately from strength of evidence based on the following criteria: eligibility requirements used to select patient populations; characteristics of population enrolled such as demographics, baseline RLS severity, duration and etiology (primary or secondary) of RLS, history of previous therapy, and the length of followup.[11] We qualitatively compared this to population-based studies that assessed the demographic characteristics and severity and frequency of individuals with RLS.

Results

Literature Search

Results of the literature search and screening process are shown in Figure 2. We identified 671 unique publications. Title and abstract screening resulted in 108 potentially relevant publications. Full-text screening resulted in 44 studies that fulfilled eligibility criteria. Of these, 26 were RCTs 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 who developed augmentation.

Figure 2. Flow diagram of search strategy



Description of Included Studies

Of the 44 studies included[12-34, 36-47, 49-55, 71, 72], 25 placebo-controlled RCTs[12-14, 16-34, 54, 55, 72] and one [15] direct comparison RCT provided efficacy and harms data, and 18 observational studies[36-47, 49-53, 71] contributed data on long-term harms. Of the 26 RCTs included, 23 evaluated pharmacological treatments[15-24, 26-34, 46, 54, 55, 72] and three evaluated nonpharmacological

treatments.[12-14] Pharmaceutical agents evaluated were dopamine agonists (17),[15-24, 26-31, 46] anticonvulsants (4),[32-34, 72] and iron therapy (2).[54, 55] Dopamine agonists evaluated were ropinirole (6),[16, 17, 21, 23, 29, 30] pramipexole (5),[18, 20, 22, 26, 31]rotigotine (3),[19, 25, 28] and cabergoline (3).[15, 24, 27] Anticonvulsants were gabapentin (2),[33, 72] or pre-gabalin (2).[32, 34] Nonpharmacological studies evaluated exercise (1),[13] a botanical extract of the herb valerian (1),[14] and a pneumatic compression device (1).[12] Except for the two small trials of iron therapy[54, 55] and the three trials evaluating nonpharmacological treatments[12-14], all trials were industry sponsored.

Studies typically enrolled adults age 18 to 70 or 80 and used extensive exclusion criteria, specifically excluding pregnant women or those at risk for pregnancy and those with severe liver or renal disease. Additional frequent exclusions involved patients who had previously been in RLS drugs and or had adverse events or failure to respond. Studies did not report comorbidities. Most studies required an IRLS scale score of $\geq$15 (at least mild to moderate severity) and frequent symptoms (>2 to 3 times/week) for a prolonged period. Three studies[21, 28, 29] enrolled patients with IRLS scale scores of >20 (severe or very severe). One small study (n = 22)[32] enrolled subjects with an IRLS scale score of >10.

We did not include studies of the drug cabergoline (an ergot-derived dopamine agonist) in our main analysis, because cabergoline has been shown to increase the risk for cardiac valvular disorders and is not FDA approved for treatment of RLS. We analyzed 25 placebo-controlled RCTs and one active controlled RCT for efficacy outcomes. Our pooled analysis included 14 studies of dopamine agonists and four studies of anticonvulsant GABA analogs.

Study Quality and Publication bias

We report our assessment of individual study trial quality in Appendix G. Nearly all of the pharmacologic trials (dopamine agonist, anticonvulsants, and iron therapies) were of good quality or had low risk of bias. Blinding of participants and investigators was reported for every trial with the exception of the study assessing exercise.[13] Allocation concealment was adequate in most trials. Intention to treat analysis, as defined as analyzing patients on the basis of the treatment they were originally allocated to, was often not done in the dopamine agonist trials. Treatment and/or post-baseline data were often required for the efficacy analyses. Nearly all of the included studies adequately described reasons for study withdrawal. All of the pharmacologic trials received funding from industry and two trials noted that the study sponsor was involved in the study design and data analysis and interpretation.[25, 28]We assessed for publication bias by constructing funnel plots of dopamine agonist trials that reported mean change in IRLS total scores. We attempted to minimize publication bias by using multiple search strategies and databases, handsearching references and soliciting input about potentially key studies from our Technical Expert Panel members. 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). (Appendix D. Figure 8)

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 to placebo or no treatment?
b. What are the benefits from RLS treatments when compared to other active treatments?
c. What is the durability and sustainability of treatment benefits?

Key Points

- Randomized controlled trial results were limited to short-term efficacy studies versus placebo or usual care (<6 months).
- Compared to placebo, there was overall high strength of evidence that dopamine agonists (ropinirole, pramipexole, and rotigotine) reduced RLS symptoms, increased the percentage of patients with a clinically important response (≥50 percent reduction in IRLS symptom scale scores or who were "improved" or "much improved" on patient or clinician-reported global impression scale) and improved disease-specific quality of life and patient-reported sleep outcomes.
- There was high strength of evidence that pregabalin increased the percentage of patients with a clinically important response (≥50 percent reduction in IRLS). There was low strength of evidence that gamma-aminobutyric acid (GABA) analogs (gabapentin and pregabalin) improved clinician-reported global impression, disease-specific quality of life and patient-reported sleep outcomes compared to placebo.
- Applicability was limited to nonpregnant, white, middle-aged adults with few comorbidities and RLS symptoms that were long term, frequent, and high-moderate to very severe.
- Only three small randomized controlled trials addressed nonpharmacological interventions. Pneumatic compression devices reduced IRLS symptom scale scores more than sham (moderate strength of evidence). Strength training and treadmill walking improved IRLS symptoms versus usual care, but adherence was poor and results were provided only for study completers. The botanical extract valerian was not more effective than placebo. The strength of evidence was low for strength training and valerian.
- No randomized trials assessed opioids, sedative hypnotics, or tramadol, though these are used in clinical practice for RLS treatment.
- One study found that the dopamine agonist cabergoline improved scores on the IRLS symptom scale and RLS quality of life scale more than Levodopa (moderate strength of evidence). Carbergoline is not approved for treatment of RLS and has limited use in the United States due to increased risk for cardiac valvular disorders.
- Observational studies and long-term open-label followup from RCTs of pharmacological interventions found that withdrawal from treatment at 1 year or more was common, ranging from 13 to 57 percent. Reasons for withdrawal were lack of efficacy (6 to 32 percent), and adverse effects including augmentation (7 to 62 percent).

Dopamine Agonists

Efficacy of dopamine agonists was evaluated in 14 randomized, double-blind, placebo-controlled studies. Only two trials lasted 24 weeks or more, and none exceeded 29 weeks. The mean age of participants was 55 years, and women constituted 64 percent (range 55 to 74) of randomized participants. Participants were overwhelmingly white in the six trials that reported race/ethnicity. Two additional randomized trials assessed cabergoline. However, this drug is not approved for treatment of RLS and has limited use in the United States due to increased risk for cardiac valvular disorders. Therefore, we do not include findings from these two trials in our main analysis of dopaminergic drugs.

All studies used the IRLS criteria to diagnose RLS (Table 4). Most studies required at least high-moderate symptom severity with frequent symptom occurrence and duration of at least 1 month. Patients were typically excluded if they were pregnant, contemplating becoming pregnant, or had psychiatric disorders, substance use, 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 = 24.9). RLS duration varied with a mean of 19 years for ropinirole to 2 years for rotigotine trials. Trials enrolled *de novo* patients and those who had received prior RLS treatments. On average, over one half (53 percent) 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, with utilized 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. Three studies investigated multiple fixed doses of drug treatments in separate study arms.

Study and patient characteristics (Tables 4-6) that we evaluated were fairly similar across the dopaminergic agents except the following: 1) study length: rotigotine trials had longest duration of followup (mean = 26.1 week), 2) duration of RLS symptoms: subjects in ropinirole trials had longest mean symptom duration (19.1 years), and 3) previous RLS treatment: the percentage of subjects receiving prior RLS pharmacological treatment was lowest in pramipexole studies (21.0 percent). There was evidence of incomplete outcome reporting (Table 4). All 14 studies reported on mean change from baseline in the IRLS total score. Twelve studies provided data sufficient for pooling. The second most frequently reported outcome was the Clinical Global Impression (CGI) (k = 13). Patient-reported sleep quality based on measures of RLS sleep scale scores were reported in nine studies though different scales were used across studies. Our primary outcome (IRLS responders defined having ≥ 50 percent reduction in IRLS scale scores, Table 7) was reported in only six studies, none of which assessed ropinirole.

IRLS responders (≥50 percent score reduction) (Table 7). Six trials (three pramipexole trials, n=1079; three rotigotine trials, n=1006) reported the percentage of patients who responded to treatment based on ≥50 percent reduction in IRLS symptom scale score from baseline (Figure 3). Compared to placebo, the percentage of patients with a favorable treatment response was greater with the dopamine agonists, pramipexole and rotigotine (RR = 1.61; [95 percent CI, 1.35 to 1.92]). The absolute effect in terms of responders per 100 patients was 25 more (95 percent CI, 14 more to 37 more) in the dopamine agonist treatment group than with placebo (high strength of evidence). Results suggested some effect heterogeneity between drugs (I^2 = 50.8 percent, p = 0.15), with a larger effect seen in studies involving rotigotine (RR = 1.83; [95 percent CI, 1.41 to 2.38], 26 more responders per 100 patients) than in studies of pramipexole (RR=1.46; [95 percent CI, 1.22 to 1.74], 21 more per 100) (Table 6).

We observed a large placebo response with 25 percent to 57 percent of patients randomized to placebo having a ≥ 50 percent reduction in IRLS scale scores compared to placebo. We did not find clear evidence of a dose response based on two studies of rotigotine that assessed the effect of different doses on IRLS responders.(Appendix D) Doses ranged from 0.5 mg per day to 3.0 mg per day. In the study by Hening,[19] risk ratios increased from 1.28 to 1.79 versus placebo for doses of 0.5 mg to 3.0 mg per day, but 95 percent confidence intervals were wide and overlapped

across doses used. The results versus placebo were statistically significant for all doses except the 0.5 mg per day dose (RR = 1.28; [95 percent CI, 0.92 to 1.78]). The study by Trenkwalder[28] examined doses of 1.0, 2.0 and 3.0 mg/day. The effects were large and statistically significant at all studied doses. Risk ratios versus placebo ranged from 2.04 for the 1.0 mg/day dose to 2.18 for the 3.0 mg/day dose.

Responders on clinician and patient-rated global impression scale (Figures 4 and 5). The proportion of responders (with a rating of "much improved" or "very much improved") on clinician and patient-reported global scales was higher for dopamine agonists than for placebo (respective risk ratios 1.46; [95 percent CI, 1.35 to 1.58] (k=13, n=4074) and 1.66; [95 percent CI, 1.45 to 1.90] (k=9, n=2069). The overall strength of evidence for both of these outcomes was high. We found borderline evidence of between-drug differences for clinician-rated global impression (CGI) outcomes (I^2 = 51.1 percent, p=0.13), but not patient-rated global impression (PGI) outcomes (I^2 = 6.5 percent, p = 0.30). Trials of pramipexole (k=5) demonstrated slightly larger effects on clinician-rated global impression scores (RR = 1.61; [95 percent CI, 1.40 to 1.86]) than studies of either ropinirole (k=5) or rotigotine (k=3).

IRLS-mean change from baseline (Figure 6). Dopamine agonists resulted in a small reduction in symptom severity and impact; the weighted mean difference (WMD) in pooled IRLS score between treatment and placebo was -4.47; (95 percent CI, -5.41 to -3.52) (k=12, n=3347). We found evidence of effect heterogeneity between drugs (I^2 = 67.0 percent, p = 0.05). The magnitude of reduction in IRLS scale scores was slightly greater in studies of rotigotine (-6.07; [95 percent CI, -8.33 to -3.81]) (k=4, n=1286) than in studies of pramipexole (-4.76; [95 percent CI, -6.24 to -3.28]) (k=5, n=1587) or ropinirole (-3.29; [95 percent CI, -4.31 to -2.27]) (k=3, n=483). We found no clear evidence of a dose effect in the three fixed-dose studies (1 study of pramipexole and 2 of rotigotine) that used different doses in separate arms. (Appendix D) Doses of pramipexole ranged from 0.25 mg/day to 0.75 mg/day. In the two studies of rotigotine, doses ranged from 0.5 mg/day to 3.0 mg/day. While mean differences in IRLS scale scores increased slightly with higher doses, the absolute effect was less than four points and the confidence intervals around the estimates for doses overlapped. The overall strength of evidence was high.

RLS remitters. (Appendix D) Three studies reported on the number of individuals in whom RLS symptoms completely resolved (remitters). Rotigotine increased the percentage of individuals who had remission of RLS compared to placebo based on an IRLS score of zero at the conclusion of the trial (RR = 2.88; [95 percent CI, 1.30 to 6.39). In a crossover study of ropinirole (n=44), eight of 22 (26.4 percent) individuals had remission on ropinirole versus no individuals receiving placebo.

RLS quality of life (Figure 7) Dopamine agonist improved RLS specific quality of life as measured by standardized mean differences in RLS quality of life scale scores (k=7, n=1772). The effect size is considered between small to medium in magnitude (SMD = -0.40; [95 percent CI, -0.52 to -0.29]). Results were similar across studies of pramipexole (k = 2), ropinirole (k=1) and rotigotine (k=3), for drug subgroup heterogeneity = 0 percent. The overall strength of evidence was high.

Patient-reported sleep quality (Figure 8). Dopamine agonists improved patient-reported sleep quality compared to placebo as measured by the Medical Outcomes Study Sleep Problem Index scale (k=8) (standardized mean effect size = 0.38; [95 percent CI, 0.29 to 0.46]. The magnitude of effect was considered small to moderate and strength of evidence was high. We

found no evidence of subgroup heterogeneity between studies of pramipexole (k=1), ropinirole (k =3) or rotigotine (k=3).

GABA-analogs

Efficacy of anticonvulsant drugs was evaluated in four randomized, double-blind, placebo-controlled studies (n = 441) (Tables 8 and 9). All four studies involved Gamma-aminobutyric acid GABA analogs (gabapentin, two trials; pregabalin, two trials). Trials were short (three 6-week trials and one 12-week trial). The mean age of study participants was 51 years. Women constituted 62 percent (range of means 59 to 66) of all participants randomized. In the two studies that reported race, 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 = 23). Mean RLS disease duration was 12 years. All four trials reported change in RLS symptom severity and impact as assessed by IRLS scale score (mean change from baseline) and CGI score. Two studies used dose titration (pregabalin beginning at 150 mg/day and titrating to 450 mg/day; gabapentin 600 to 2400 mg/day based on symptom response). A randomized trial by Kushida[35] used a fixed dose (1200 mg/day) of gabapentin, and a multiarm trial of pregabalin versus placebo by Allen[32] assessed five different fixed doses that ranged from 50 mg per day to 450 mg per day.

IRLS responders (≥50 percent score reduction) (Figure 9)**.** Two trials (low risk of bias) evaluated IRLS responders. Pregabalin compared to placebo significantly increased the proportion of IRLS responders (RR = 2.13; [95 percent CI, 1.36 to 3.34]). The absolute effect in terms of responders per 100 patients was 37 more (95 percent CI, 12 more to 76 more). The strength of evidence was high. There was no clear evidence of dose effect based on IRLS responders or IRLS total scores in the study by Allen.[32] A total of 208 subjects were enrolled across study arms and doses. While effect sizes increased with higher doses, confidence intervals were wide and overlapped across doses. Strength of evidence was high (Appendix D).

Responders on clinician and patient-rated global impression scale (Figures 10 and 11). The proportion of patients who reported improved or very much improved on the CGI was not significantly greater for the gabapentin treatment group versus placebo (RR=1.52; [95 percent CI, 0.89 to 2.58], I^2 = 83 percent). The strength of evidence was low. Gabapentin or pregabalin reduced symptom severity compared to placebo.

IRLS-mean change from baseline (Appendix D). Two studies (one each of pregabalin and gabapentin) found that GABA-analogs improved mean change in IRLS scores from baseline more than placebo (WMD = -4.51; [95 percent CI, -6.60 to -2.42]). We identified no heterogeneity between studies. Similar effects were seen in two other studies (one each of pregabalin and gabapentin) that reported end-of-study IRLS results (WMD =-6.56; [95 percent CI, -9.27 to -3.86]). There was some evidence of heterogeneity between studies, with the effect of pregabalin versus placebo (WMD = -4.35) being less than that in the crossover study of gabapentin (WMD = -8.30), I^2 = 53.0 percent, p = 0.14). The strength of evidence was moderate.

RLS remitters. One GABA analog trial reported the number of patients who achieved an IRLS score of zero points (Garcia-Borreguero 2010 ref). There were nine remitters (30 percent) in the pregabalin group compared with four (14 percent) in the placebo group, a difference that was not statistically significant (RR = 2.10; [95 percent CI, 0.73 to 6.06]).

RLS quality of life. One fixed-dose study of pregabalin found no statistically significant improvement in the RLS-QoL with any dose versus placebo over a 6-week period (k = 1, n = 122).[32]

Patient-reported sleep quality: All four studies provided information on self-rated sleep. All demonstrated a statistically significant improvement of GABA analogs versus placebo. However, variation in scales used and reporting methods precluded pooling, and in some cases, precluded identifying the magnitude of effect. Three studies used the Medical Outcomes Scale, either the full nine-item MOS-SPI-II scale or MOS-sleep adequacy,[34, 35, 73] and two used the Pittsburgh Sleep Quality Index.[33, 35] Self-rated daytime sleepiness using the Epworth Sleepiness Scale was not significantly different in one study reporting this outcome.[35]

Long-term tolerability and durability

Long-term durability and sustainability. Data from 18 observational studies and open label extensions of RCTs indicated that pharmacological treatment durability and sustainability, as measured by withdrawal from treatment and reasons for withdrawal, was fair to poor (Table 10). Studies reported on gabapentin, "multiple opioids," methadone, levodopa, and the dopamine agonist pramipexole, ropinirole and rotigotine. Withdrawals and reasons for withdrawals varied widely across examined drugs and durations. Study design, participant and RLS characteristics, and methods for ascertaining withdrawals and reasons for withdrawal varied. Withdrawal from treatment at 1 year or more ranged from 13 to 57 percent. Reasons for withdrawal were lack of efficacy (6 to 32 percent), and adverse events including augmentation (7 to 62 percent). Augmentation is believed not to occur with gabapentin or opioids.

Nonpharmacological therapies

Three small, short-term studies assessed nonpharmacological therapies in adults with moderate to severe RLS (Table 11, Appendix C, and Appendix D). A good quality RCT of pneumatic compression devices worn for at least 1 hour each day for 4 weeks starting prior to the time when symptoms typically began found better end-of-study (4 weeks) IRLS symptom scale scores (8.4 +/-3.4 versus 14.1 +/- 3.9; p = 0.006), dimensions of the RLS quality of life instrument (P<0.05 for all four dimensions), and daytime somnolence measures as assessed by the Epworth Sleepiness Scale (6.5 +/- 4.0 versus 10.6 +/- 3.8; p = 0.04) and complete resolution of symptoms (8 [38.1 percent] versus 0 [0 percent]; p = 0.007) more than sham devices (moderate quality of evidence). Enrollees had moderately severe RLS (mean baseline IRLS score = 19.6) that was on average 4 years in duration. Nearly two thirds of subjects were taking current medications for RLS (mostly pramipexole, ropinirole, or iron). Pneumatic compression devices were programmed to inflate the leg wraps for 5 seconds every minute. The only difference between intervention and sham devices was that the therapeutic devices generated 40 cm H_20 of air pressure with each inflation cycle, while sham devices generated a 3 to 4 cm H_20 rise in pressure. No subjects initiated new medical therapy for RLS or increased RLS medications during the study. None of the patients using placebo devices decreased or discontinued medical therapy, while five (23.3) individuals using therapeutic devices decreased or discontinued medical therapy.

In one fair quality study, treadmill walking and lower body resistance exercise performed three times weekly for 12 weeks improved IRLS scale scores (WMD = -9.4 [95 percent CI, -13.9

to -4.9]) compared to usual care (low quality of evidence). However, the authors reported results for only for 28 completers from 41 subjects enrolled.

A fair quality RCT of the botanical preparation valerian at 800 mg daily for 8 weeks did not improve IRLS symptom scale scores (p = 0.69), Pittsburgh Sleep Quality Index scores (p = 0.94) or Epworth Sleepiness Scale scores (0.64) more than placebo among 48 adults with severe RLS symptoms (mean IRLS scores = 23.5) occurring at least three times per week (low quality of evidence).

Comparative Effectiveness of RLS treatments and Dose Response

As the intent of this report was to conduct a comparative effectiveness review, we describe below the single study that directly compared two active interventions. We also report whether effectiveness or harms varies by drug dose. We described above subgroup findings of effectiveness and harms across pharmacologic interventions from placebo controlled trials by assessing whether there was evidence of statistically significant heterogeneity. However, we urge caution for drawing conclusions about comparative effectiveness and harms based on these indirect subgroup comparisons.

One 30-week study[15] (n=361) found that the dopamine agonist cabergoline improved IRLS symptom scale scores (WMD = -6.80; [95 percent CI, -9.02 to -4.58]) and RLS quality of life more than Levodopa (WMD = -7.10; [95 percent CI, -9.94 to -4.26]) in white adults with severe RLS (IRLS scale score = 25.7) (Appendix C and D). The quality of evidence was moderate.

We assessed whether the effects of dopamine agonists varied by dose based on reported outcomes from multiarmed fixed-dose trials. Most trials used dose titration at the discretion of the clinician based on symptom response and adverse effects, and did not report the mean or median doses used or outcomes according to dose. As previously noted (in the section describing specific outcomes), 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 GABA agonists.

For dopamine agonist and the outcome of IRLS responders, two studies of rotigotine assessed the effect of doses ranging from 0.5 mg per day to 3.0 mg per day (Appendix D). In the study by Hening,[19] risk ratios increased from 1.28 to 1.79 versus placebo for doses of 0.5 mg to 3.0 mg per day, but 95 percent confidence intervals were wide and overlapped across doses used. Results versus placebo were statistically significant for all doses except the 0.5 mg per day dose (RR = 1.28; [95 percent CI, 0.92 to 1.78]). The study by Trenkwalder[28] examined doses of 1.0, 2.0 and 3.0 mg/day. The effects were large and statistically significant at all studied doses. Risk ratios versus placebo ranged from 2.04 for the 1.0 mg/day dose to 2.18 for the 3.0 mg/day dose.

Three fixed-dose studies (one study of pramipexole and two of rotigotine) used different doses in separate arms and reported the proportion of IRLS scale scores at different doses of dopamine agonists. Doses of pramipexole ranged from 0.25 mg/day to 0.75 mg/day. In the two studies of rotigotine, doses ranged from 0.5 mg/day to 3.0 mg/day. While mean differences in IRLS scale scores increased slightly with higher doses, the absolute effect was less than 4 points and the confidence intervals around the estimates for doses overlapped (Appendix D).

For GABA-analogs, we found no clear evidence of dose effect based on IRLS responders or IRLS total scores in the study by Allen[32] evaluating pregabalin. A total of 208 subjects were enrolled across study arms and doses. Doses of pregabalin ranged from 50 to 450 mg/day. While

effect sizes increased with higher doses, confidence intervals were wide and overlapped across doses (Appendix D).

Key Question 2

What are the harms from RLS treatments?

d. What are the harms from RLS treatments when compared to placebo or no treatment?
e. What are the harms from RLS treatments when compared to other active treatments?
f. What are the long-term harms from treatment?

Key Points

- Study withdrawals (due to any reason) from RCTs were slightly less common in patients randomized to dopaminergic agents than to placebo (moderate strength of evidence).
- Study withdrawals due to adverse effects were more common (though not statistically so) with dopamine agonist treatment than placebo (low strength of evidence). Differences were primarily due to an increase in withdrawals related to adverse effects reported in three trials of transdermal rotigotine.
- The percentage of patients reporting one or more adverse effects was greater with dopamine agonists than with placebo (high strength of evidence).
- Short-term adverse effects from treatment with dopamine agonists compared to placebo were nausea, vomiting, and somnolence (high strength of evidence for all these outcomes).
- Application site reactions were much more common with transdermal rotigotine than with placebo (high strength of evidence).
- Some indirect evidence from placebo-controlled trials suggests that fatigue may be more common with ropinirole than with pramipexole or rotigotine (moderate strength of evidence).
- 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 pharmacologic 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 controlled trials: any study withdrawal, (Figures 12-15) study withdrawal due to adverse effects, and percentage of patients reporting at least one adverse effect (Appendix E). Patients were less likely to withdraw from dopamine agonist treatment than from placebo treatment (21 versus 23 percent; RR = 0.82; [95 percent CI, 0.68 to 1.00], k=14) (moderate strength of evidence). Study withdrawals due to adverse effects were more common (though not statistically so) with dopamine agonist treatment (10 versus 6 percent; RR = 1.36; [95 percent CI, 0.98 to 1.87], k=14) (low strength of evidence). More patients experienced at least one adverse effect with dopamine agonist than with placebo (RR = 1.17; [95 percent CI, 1.10 to 1.25], k=14) (high strength of evidence) (Figure 16). Results did not significantly vary compared to placebo in studies of pramipexole, ropinirole or rotigotine. We also assessed specific short-term adverse effects

(Appendix E). We observed more short-term adverse effects with dopamine agonists than with placebo, as follows: nausea (22 versus 7 percent, RR 3.42 [95 percent CI, 2.56 to 4.56], k=13), vomiting (11 versus 2 percent, RR 4.84 [95 percent CI, 2.77 to 8.47], k=5) and somnolence (12 versus 6 percent, RR 2.04; [95 percent CI, 1.50 to 2.76], k=8) (high strength of evidence for these outcomes). Fatigue was numerically but not statistically significantly greater (12 versus 6 percent, RR 1.86; [95 percent CI, 0.96 to 3.62], k=7) (moderate strength of evidence). Application site reactions were much more common with transdermal rotigotine than with placebo, 33 versus 7 percent, respectively (RR 8.20; [95 percent CI, 2.53 to 26.57], k=3) (high strength of evidence).

Comparative harms

One good quality 30-week randomized trial reported that compared to levodopa, cabergoline resulted in less augmentation and less augmentation leading to withdrawal (Appendix E). The drugs did not differ with regard to "any study withdrawals." Carbergoline 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.

We observed some subgroup differences across types of dopamine agonist in certain adverse events (Appendix D and E). We caution about making direct comparisons, however, because these are based on subgroup differences observed in placebo-controlled trials, not direct comparisons between drugs. Study and patient characteristics may account for some or all of the between-study differences or lack of differences that we observed. Withdrawals due to site application reaction were unique to transdermal rotigotine; all other studied pharmacological agents are taken orally. The increase in site application reaction was the main factor leading to a greater number of study withdrawals in studies of rotigotine compared to studies of pramipexole or ropinirole (I^2 = 74 percent, p = 0.02). Compared to placebo, fatigue was more common in the single study of ropinirole that reported this outcome than in studies of pramipexole (k = 4) or rotigotine (k=2) (I^2 = 92.6 percent, p<0.00001).

We assessed whether harms varied according to different drug doses based on findings from fixed-dose studies that assessed different doses (Appendix D). Compared to placebo, the relative risk of site reaction (k=3) was similar across doses of rotigotine, ranging from 0.5 to 3.0 mg/day. The relative risk of nausea, fatigue, and somnolence for rotigotine, pramipexole, and ropinirole versus placebo also did not vary significantly by dose, but the numbers of patients and events in each dose subgroup were small, and confidence intervals were wide and overlapped.

Long-term harms and withdrawal from treatment

We used data from 18 observational studies including open-label extensions of RCTS that reported at least 6 months of followup to assess the percentage individuals withdrawing from pharmacological treatments and reasons for withdrawal (lack of efficacy, adverse events, augmentation, other) (Table 10). 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 percent). Withdrawals in studies of gabapentin, and the dopamine agonist were typically greater than 20 percent. Reasons for withdrawal were adverse events (including augmentation) in about one-half of individuals, and lack of efficacy in 20 to 30 percent.

Augmentation was reported in 15 studies, all of which involved dopamine agonists or levodopa. In general, augmentation was common across dopaminergic or dopamine agonist drugs. Two small studies of levodopa reported that augmentation occurred in 35 to 60 percent of individuals at 6 to 12 months duration. Six studies of pramipexole with followup duration of 6 months to 10 years reported augmentation in 7 percent to 33 percent of individuals. Augmentation was reported in 10 and 23 percent of individuals treated with rotigotine at 1 and 5 years of followup. A single study of ropinirole with 1 year followup reported that only 2.3 percent of individuals experienced augmentation. It is not clear why period prevalence estimates varied widely across drugs or time periods.

Additional information on harms of individual drugs used for RLS treatment was obtained by searching the FDA website. We searched for: 1) any drug that has FDA approval for primary RLS treatment; 2) any drug studied in RCTs of individuals with primary RLS; 3) all drugs with long-term harms and withdrawal from treatment data from our review of 18 observational studies or longer-term extensions of RCTs in patients with primary RLS that met our eligibility criteria and were included above; 4) recommended for treatment of primary RLS in treatment algorithms (Table 10). These included drugs in the classes: dopaminergic agents, anticonvulsants (GABA-analogs), sedative-hypnotics and opioids. The FDA described adverse effects and warnings are derived from individuals using these medications that may not have RLS. Thus it is not possible to know if these adverse effects occur and to what frequency/severity among individuals with RLS.

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?

- No RCTs examined the effect of patient or RLS characteristics on benefits and harms of treatments for primary RLS.
- No RCTs enrolled children or 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 of evidence that iron may improve IRLS symptom scale scores and possibly the percentage of adults considered IRLS responders.

We found almost no evidence addressing the effect of patient characteristics on benefits and harms of treatments for RLS. While studies generally provided baseline age, race, disease severity, and primary and secondary RLS etiologies, results were not stratified by these characteristics. No study evaluated patients exclusively based on gender, race, age, 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 whom had been treated previously, and whose symptoms were frequent and high-moderate to severe.

Two small good quality RCTs evaluated iron therapy[54, 55] (one intravenous and one oral) in patients with RLS secondary to iron deficiency (Table 12, Appendix C Table 4). One 12-week trial of 18 subjects[55] found that compared to placebo, iron reduced IRLS scale scores by 9.16 points (95 percent CI,-15.2 to -3.1). Another trial of intravenous iron sucrose[54] administered five times over 3 months in 60 subjects found no difference versus placebo at 12 months in mean change in IRLS scale scores (p = 0.47). 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 percent CI, 1.07 to 3.18]). By 12 months, 21 of 31 subjects (68 percent) in the placebo group and nine of 29 (31 percent) in the iron group withdrew. Of these, 19 and five respectively withdrew due to lack of efficacy. The strength of evidence for these outcomes was low.

No studies assessed treatments in pregnant or recently postpartum 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. Studies typically excluded patients with psychiatric or other serious comorbid conditions including renal or liver disease and pregnant women or those contemplating becoming pregnant.

Study Quality/Risk of Bias and Applicability

Nearly all of the pharmacologic trials (dopamine agonist, anticonvulsants, and iron therapies) but only one of three nonpharmacological trials were considered of good quality or having a low risk of bias. 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 GABA analogs conducted in a highly selected population of adults with high-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 the comparative effectiveness and harms of commonly used treatments, or the effect of patient or RLS characteristics on outcomes.

Table 4. Outcomes evaluated in placebo studies of dopamine agonists

Study	IRLS total score: Mean change from baseline	IRLS Responders (≥50% score reduction)	IRLS Remitters (IRLS Score=0)	Clinical Global Impression: Responders (much improved)	Patient Global Impression: Responders (much improved)	MOS Patient-reported sleep quality scale	RLS Quality of life	Augmentation
Högl, 2011[20]	✓	NR	NR	✓	✓	NR	NR	✓
Montagna, 2011[22]	✓	✓	NR	✓	✓	NR	✓	NR
Hening, 2010[19]	✓	✓	✓	✓	NR	✓	✓	✓
Oertel, 2010[25]	✓	✓	✓	✓	NR	✓	✓	NR
Ferini-Stambi, 2008[18]	✓	NR	NR	✓	✓	✓	✓	NR
Kushida, 2008[21]	✓	NR	NR	✓	✓	✓	NR	NR
Trenkwalder, 2008[28]	✓	✓	NR	✓	NR	✓	✓	NR
Oertel, 2007[26]	✓	✓	NR	✓	✓	NR	NR	NR
Bogan, 2006[17]	✓	NR	NR	✓	NR	✓	✓	✓
Montplaisir, 2006[45]	NR	NR	NR	✓	NR	NR	NR	NR
Winkelman, 2006[31]	✓	✓	NR	✓	✓	NR	✓	NR
Adler,*2004[16]	NR	NR	✓	NR	NR	NR	NR	NR
Trenkwalder, 2004[29]	✓	NR	NR	✓	NR	✓	NR	NR
Walters, 2004[30]	✓	NR	NR	✓	NR	✓	NR	NR
Totals	**12**	**6**	**3**	**13**	**6**	**8**	**7**	**3**

NR= not reported

Table 5. Study duration and baseline characteristics of patients (means and range) in studies of dopamine agonists

Dopamine agonist type (# studies)	Trial duration (double-blind phase), weeks	Number of patients evaluated	Age, years	Women, %	RLS duration, years	Baseline IRLS* score	Previous RLS therapy, %
Pramipexole (5)[18, 20, 22, 26, 31]	13.4 (6 to 26)	1794 (331 to 404)	55.2 (51.4 to 56.9)	65 (60 to 70)	4.9 (3.4 to 5.7)	24.5 (23.5 to 25.9)	26.0 (21.8 to 30.8)
Ropinirole (6)[16, 17, 21, 29, 30, 45]	11.9 (8 to 12)	1430 (22 to 381)	53.3 (50.9 to 60)	61 (55 to 73)	19.1 (16.8 to 22.8; *5 trials***)	24.3 (22 to 26)	44.3 (40.9 to 44.6; *2 trials***)
Rotigotine (3)[19, 25, 28]	26.1 (7 to 29)	1030 (67 to 505)	55.2 (52.4 to 59.4)	67 (60 to 74)	2.1 (2.1 to 2.2; *2 trials***)	25.6 (23.3 to 28.1)	53.3 (35.8 to 72)
Overall (n=14)	16 (6 to 29)	4254 (22 to 505)	54.6 (50.9 to 60)	64 (55 to 74)	8.8 (2.1 to 22.8; *12 trials***)	24.7 (22 to 28.1)	36.7 (21.8 to 72; *10 trials***)

* IRLS = International Restless Legs Scale: Scoring criteria are: Mild (score 1-10); Moderate (score 11-20); Severe (score 21-30); Very severe (score 31-40).
** Number of studies reporting (not all trials may have reported this variable).

Table 6. Overall strength of evidence for individual outcomes in 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	6	2085	RR 1.61 [1.35 to 1.92]	low	direct	precise	consistent	High
	pramipexole	3	1079	RR 1.46 [1.22 to 1.74]	low	direct	precise	consistent	High
	rotigotine	3	1006	RR 1.83 [1.41 to 2.38]	low	direct	precise	consistent	High
IRLS total score: Mean change from baseline	All trials vs. placebo	12	3347	WMD -4.47 [-5.41 to -3.52]	low	direct	precise	consistent	High
	pramipexole	5	1578	WMD -4.76 [-6.24 to -3.28]	low	direct	precise	consistent	High
	ropinirole	4	1286	WMD -3.29 [-4.31 to -2.27]	low	direct	precise	consistent	High
	rotigotine	3	483	WMD -6.07 [-8.33 to -3.81]	low	direct	precise	consistent	High
	Cabergoline vs. levodopa	1	361	WMD -6.80 [-9.02 to -4.58]	low	direct	precise	unknown	Moderate
Clinical Global Impression responders: (much-very much improved)	All trials vs. placebo	13	4074	RR 1.46 [1.35 to 1.58]	low	direct	precise	consistent	High
	pramipexole	5	1747	RR 1.61 [1.40 to 1.86]	low	direct	precise	consistent	High
	ropinirole	5	1377	RR 1.37 [1.25 to 1.50]	low	direct	precise	consistent	High
	rotigotine	3	950	RR 1.35 [1.16 to 1.57]	low	direct	precise	consistent	High
Patient Global Impression responders: (much-very much improved)	All trials vs. placebo	6	2069	RR 1.66 [1.45 to 1.90]	low	direct	precise	consistent	High
	pramipexole	5	1712	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	7	1779	SMD -0.40 [-0.52 to -0.29]	low	direct	precise	consistent	High
	pramipexole	3	912	SMD -0.43 [-0.61 to -0.25]	low	direct	precise	consistent	High
	ropinirole	1	377	SMD -0.31 [-0.51 to -0.11]	low	direct	precise	unknown	Moderate
	rotigotine	3	483	SMD -0.42 [-0.52 to -0.29]	low	direct	precise	inconsistent	Moderate
	Cabergoline vs. levodopa	1	361	SMD -0.50 [-0.72 to -0.30]	low	direct	precise	unknown	Moderate
Self-rated sleep MOS-SPI-II	All trials vs. placebo	8	2052	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	1237	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
Patients with ≥ 1 adverse event	All trials vs. placebo	14	4248	RR 1.17 [1.10 to 1.25]	low	direct	precise	consistent	High
	pramipexole	5	1790	RR 1.16 [1.04 to 1.29]	low	direct	precise	inconsistent	Moderate
	ropinirole	6	1429	RR 1.18 [1.09 to 1.27]	low	direct	precise	consistent	High

	rotigotine	3	1029	RR 1.23 [0.93 to 2.38]	low	direct	imprecise	consistent	Moderate
	Cabergoline vs. levodopa	1	361	RR 1.07 [0.97 to 1.19]	low	direct	precise	unknown	Moderate
Any study withdrawal	All trials vs. placebo	14	4253	RR 0.82 [0.68 to 1.00]	low	direct	precise	inconsistent	Moderate
	pramipexole	5	1792	RR 0.71 [0.50 to 1.01]	low	direct	imprecise	inconsistent	Low
	ropinirole	6	1432	RR 0.91 [0.72 to 1.14]	low	direct	imprecise	consistent	Moderate
	rotigotine	3	1029	RR 0.92 [0.56 to 1.50]	low	direct	imprecise	inconsistent	Low
	Cabergoline vs. levodopa	1	361	RR 0.92 [0.72 to 1.16]	low	direct	imprecise	unknown	Low
Study withdrawals due to an adverse event	All trials vs. placebo	14	4252	RR 1.36 [0.98 to 1.87]	low	direct	imprecise	inconsistent	Low
	pramipexole	5	1791	RR 0.97 [0.69 to 1.35]	low	direct	imprecise	consistent	Moderate
	ropinirole	6	1432	RR 1.41 [0.89 to 2.22]	low	direct	imprecise	consistent	Moderate
	rotigotine	3	1029	RR 2.85 [1.40 to 5.80]	low	direct	precise	consistent	High
	Cabergoline vs. levodopa	1	361	RR 1.50 [0.95 to 2.37]	low	direct	imprecise	inconsistent	Low
Nausea	All trials vs. placebo	13	3879	RR 3.42 [2.56 to 4.56]	low	direct	precise	consistent	High
	pramipexole	4	1421	RR 2.63 [1.78 to 3.90]	low	direct	precise	consistent	High
	ropinirole	6	1429	RR 4.36 [2.75 to 6.91]	low	direct	precise	consistent	High
	rotigotine	3	1029	RR 2.79 [1.34 to 5.79]	low	direct	precise	consistent	High
Vomiting	Ropinirole	5	1377	RR 4.84 [2.77 to 8.47]	low	direct	precise	consistent	High
Somnolence	All trials vs. placebo	8	2314	RR 2.04 [1.50 to 2.76]	low	direct	precise	consistent	High
	pramipexole	2	673	RR 1.65 [0.85 to 3.23]	low	direct	imprecise	consistent	Moderate
	ropinirole	4	1070	RR 2.29 [1.56 to 3.36]	low	direct	precise	consistent	High
	rotigotine	2	571	RR 1.73 [0.84 to 3.57]	low	direct	imprecise	consistent	Moderate
Application site reactions	Rotigotine	3	1029	RR 8.20 [2.53 to 26.57]	low	direct	precise	consistent	High

MOS-SPI-II = Medical Outcomes Scale- Sleep Problems Index II; RR = relative risk; SMD = standardized mean difference; WMD = weighted mean difference (a negative SMD and WMD indicates that the active treatment is more effective then placebo)

Figure 3. Efficacy outcomes for treatment with dopamine agonists: proportion of study participants who reported greater than 50% reduction in mean IRLS score from baseline.

Study or Subgroup	Dopamine agonists Events	Total	Placebo Events	Total	Weight	Risk Ratio M-H, Random, 95% CI
1.3.1 Pramipexole studies						
Montagna 2011	154	203	114	199	26.3%	1.32 [1.15, 1.53]
Oertel 2007	117	224	33	114	15.7%	1.80 [1.32, 2.47]
Winkelman 2006	157	254	36	85	18.4%	1.46 [1.12, 1.90]
Subtotal (95% CI)		**681**		**398**	**60.4%**	**1.46 [1.22, 1.74]**
Total events	428		183			
Heterogeneity: Tau² = 0.01; Chi² = 3.51, df = 2 (P = 0.17); I² = 43%						
Test for overall effect: Z = 4.19 (P < 0.0001)						
1.3.2 Rotigotine studies						
Hening 2010	224	394	37	99	18.2%	1.52 [1.16, 1.99]
Oertel 2010	35	46	7	20	6.4%	2.17 [1.17, 4.04]
Trenkwalder 2008	183	333	29	114	15.0%	2.16 [1.55, 3.00]
Subtotal (95% CI)		**773**		**233**	**39.6%**	**1.83 [1.41, 2.38]**
Total events	442		73			
Heterogeneity: Tau² = 0.02; Chi² = 3.07, df = 2 (P = 0.22); I² = 35%						
Test for overall effect: Z = 4.53 (P < 0.00001)						
Total (95% CI)		**1454**		**631**	**100.0%**	**1.61 [1.35, 1.92]**
Total events	870		256			
Heterogeneity: Tau² = 0.02; Chi² = 11.57, df = 5 (P = 0.04); I² = 57%						
Test for overall effect: Z = 5.36 (P < 0.00001)						
Test for subgroup differences: Chi² = 2.03, df = 1 (P = 0.15), I² = 50.8%						

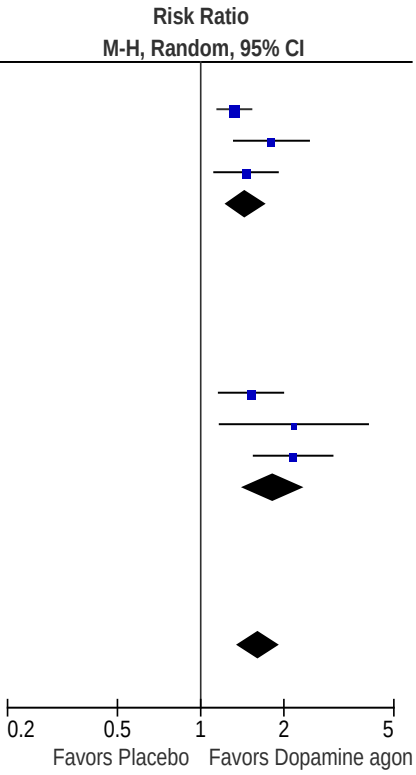


Table 7. IRLS Responders (≥50% score reduction): Absolute effect per 100 patients

Study	Number of studies	Dopamine Agonist % (n/N)	Placebo % (n/N)	RR [95% CI]	Absolute effect [95% CI]
Pramipexole	3	62.8 (428/681)	46.0 (183/398)	1.46 [1.22 to 1.74]	21 more per 100 [10 more to 34 more]
Rotigotine	3	57.2 (442/773)	31.3 (73/233)	1.83 [1.41 to 2.38]	26 more per 100 [13 more to 43 more]
All studies	6	59.8 (870/1454)	40.6 (256/631)	1.61 [1.35 to 1.92]	25 more per 100 [14 more to 37 more]

CI = confidence intervals

Figure 4. Efficacy outcomes for treatment with dopamine agonists: proportion of study participants who reported improved or much improved on clinician rated global impressions scale (CGI)

Study or Subgroup	Dopamine agonists Events	Total	Placebo Events	Total	Weight	Risk Ratio M-H, Random, 95% CI
1.6.1 Pramipexole studies						
Ferini-Strambi 2008	118	178	72	179	8.5%	1.65 [1.34, 2.03]
Högl 2011	111	162	80	159	9.6%	1.36 [1.13, 1.64]
Montagna 2011	140	202	72	195	8.6%	1.88 [1.53, 2.30]
Oertel 2007	141	224	37	114	5.6%	1.94 [1.46, 2.57]
Winkelman 2006	180	250	43	84	7.8%	1.41 [1.13, 1.76]
Subtotal (95% CI)		**1016**		**731**	**40.0%**	**1.61 [1.40, 1.86]**
Total events	690		304			
Heterogeneity: Tau² = 0.01; Chi² = 8.49, df = 4 (P = 0.08); I² = 53%						
Test for overall effect: Z = 6.60 (P < 0.00001)						
1.6.2 Ropinirole studies						
Bogan 2006	137	187	109	193	11.9%	1.30 [1.12, 1.51]
Kushida 2008	124	175	92	184	10.4%	1.42 [1.19, 1.68]
Montplaisir 2006	31	45	21	45	3.7%	1.48 [1.02, 2.13]
Trenkwalder 2004	78	146	56	137	6.6%	1.31 [1.02, 1.68]
Walters 2004	78	131	53	134	6.6%	1.51 [1.17, 1.94]
Subtotal (95% CI)		**684**		**693**	**39.1%**	**1.37 [1.25, 1.50]**
Total events	448		331			
Heterogeneity: Tau² = 0.00; Chi² = 1.48, df = 4 (P = 0.83); I² = 0%						
Test for overall effect: Z = 6.65 (P < 0.00001)						
1.6.3 Rotigotine studies						
Hening 2010	264	380	56	98	9.7%	1.22 [1.01, 1.46]
Oertel 2010	37	44	12	20	3.5%	1.40 [0.96, 2.05]
Trenkwalder 2008	213	307	46	101	7.6%	1.52 [1.22, 1.91]
Subtotal (95% CI)		**731**		**219**	**20.9%**	**1.35 [1.16, 1.57]**
Total events	514		114			
Heterogeneity: Tau² = 0.00; Chi² = 2.40, df = 2 (P = 0.30); I² = 17%						
Test for overall effect: Z = 3.86 (P = 0.0001)						
Total (95% CI)		**2431**		**1643**	**100.0%**	**1.46 [1.35, 1.58]**
Total events	1652		749			
Heterogeneity: Tau² = 0.01; Chi² = 19.08, df = 12 (P = 0.09); I² = 37%						
Test for overall effect: Z = 9.57 (P < 0.00001)						
Test for subgroup differences: Chi² = 4.09, df = 2 (P = 0.13), I² = 51.1%						

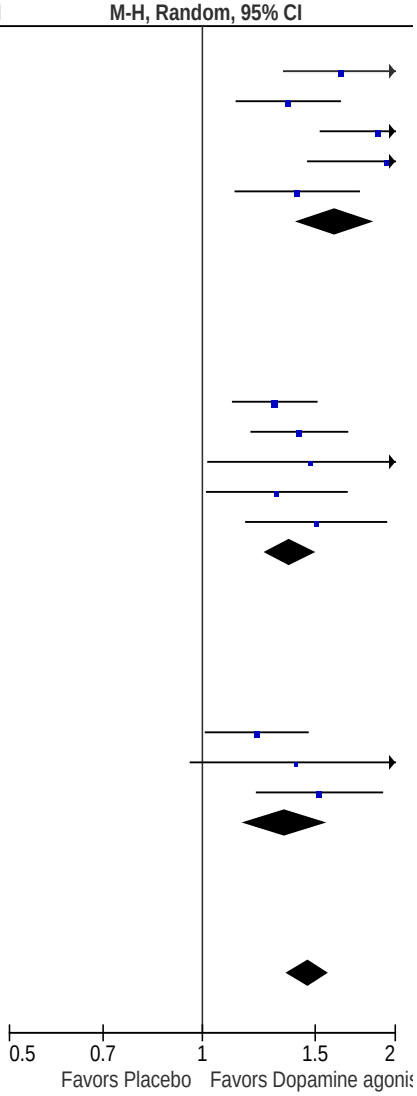


Figure 5. Efficacy outcomes for treatment with dopamine agonists: proportion of study participants who reported improved or much improved on patient rated global impressions scale (PGI)

Study or Subgroup	Dopamine agonists Events	Dopamine agonists Total	Placebo Events	Placebo Total	Weight	Risk Ratio M-H, Random, 95% CI
1.6.1 Pramipexole studies						
Ferini-Strambi 2008	112	178	68	179	18.8%	1.66 [1.33, 2.06]
Högl 2011	101	162	70	159	19.3%	1.42 [1.15, 1.75]
Montagna 2011	112	178	68	179	18.8%	1.66 [1.33, 2.06]
Oertel 2007	138	224	36	114	13.7%	1.95 [1.46, 2.61]
Winkelman 2006	108	254	12	85	5.2%	3.01 [1.75, 5.19]
Subtotal (95% CI)		**996**		**716**	**75.7%**	**1.72 [1.45, 2.05]**
Total events	571		254			
Heterogeneity: Tau² = 0.02; Chi² = 8.45, df = 4 (P = 0.08); I² = 53%						
Test for overall effect: Z = 6.21 (P < 0.00001)						
1.6.2 Ropinirole studies						
Kushida 2008	136	174	94	183	24.3%	1.52 [1.29, 1.79]
Subtotal (95% CI)		**174**		**183**	**24.3%**	**1.52 [1.29, 1.79]**
Total events	136		94			
Heterogeneity: Not applicable						
Test for overall effect: Z = 5.10 (P < 0.00001)						
Total (95% CI)		**1170**		**899**	**100.0%**	**1.66 [1.45, 1.90]**
Total events	707		348			
Heterogeneity: Tau² = 0.01; Chi² = 9.45, df = 5 (P = 0.09); I² = 47%						
Test for overall effect: Z = 7.41 (P < 0.00001)						
Test for subgroup differences: Chi² = 1.07, df = 1 (P = 0.30), I² = 6.5%						

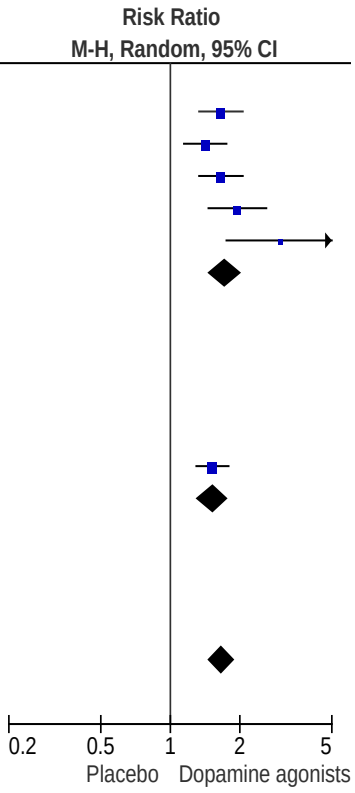


Figure 6. Efficacy outcomes for treatment with dopamine agonists: mean change in IRLS scale score from baseline

Study or Subgroup	Dopamine agonists Mean	SD	Total	Placebo Mean	SD	Total	Weight	Mean Difference IV, Random, 95% CI
1.1.1 Pramipexole studies (0.5 mg for fixed-dose/dose finding trials)								
Ferini-Strambi 2008	-13.4	9.3	178	-9.6	9.4	179	9.9%	-3.80 [-5.74, -1.86]
Högl 2011	-13.7	10.3	162	-11.1	10.1	159	8.7%	-2.60 [-4.83, -0.37]
Montagna 2011	-14.2	9.9	202	-8.1	9.8	196	9.9%	-6.10 [-8.04, -4.16]
Oertel 2007	-12.3	9	224	-5.7	9.6	114	9.1%	-6.60 [-8.72, -4.48]
Winkelman 2006	-13.8	8.9	79	-9.3	9.2	85	6.9%	-4.50 [-7.27, -1.73]
Subtotal (95% CI)			**845**			**733**	**44.5%**	**-4.76 [-6.24, -3.28]**
Heterogeneity: Tau² = 1.61; Chi² = 9.30, df = 4 (P = 0.05); I² = 57%								
Test for overall effect: Z = 6.30 (P < 0.00001)								
1.1.2 Ropinerole studies								
Bogan 2006	-13.5	8.2	186	-9.8	8.3	191	11.1%	-3.70 [-5.37, -2.03]
Kushida 2008	-15.11	13.2	175	-11	13.6	184	6.9%	-4.11 [-6.88, -1.34]
Trenkwalder 2004	-11	8.7	146	-8	8.7	138	9.5%	-3.00 [-5.02, -0.98]
Walters 2004	-11.2	8.7	131	-8.7	8.7	135	9.2%	-2.50 [-4.59, -0.41]
Subtotal (95% CI)			**638**			**648**	**36.7%**	**-3.29 [-4.31, -2.27]**
Heterogeneity: Tau² = 0.00; Chi² = 1.20, df = 3 (P = 0.75); I² = 0%								
Test for overall effect: Z = 6.33 (P < 0.00001)								
1.1.3 Rotigotine studies (2 mg for fixed-dose/dose finding trials)								
Hening 2010	-13.4	9.2	95	-9	7.7	99	8.1%	-4.40 [-6.79, -2.01]
Oertel 2010	-16.5	9.3	46	-9.9	9.9	20	2.9%	-6.60 [-11.70, -1.50]
Trenkwalder 2008	-16.2	9.4	109	-8.6	9.6	114	7.8%	-7.60 [-10.09, -5.11]
Subtotal (95% CI)			**250**			**233**	**18.8%**	**-6.07 [-8.33, -3.81]**
Heterogeneity: Tau² = 1.61; Chi² = 3.35, df = 2 (P = 0.19); I² = 40%								
Test for overall effect: Z = 5.26 (P < 0.00001)								
Total (95% CI)			**1733**			**1614**	**100.0%**	**-4.47 [-5.41, -3.52]**
Heterogeneity: Tau² = 1.40; Chi² = 22.74, df = 11 (P = 0.02); I² = 52%								
Test for overall effect: Z = 9.22 (P < 0.00001)								
Test for subgroup differences: Chi² = 6.06, df = 2 (P = 0.05), I² = 67.0%								

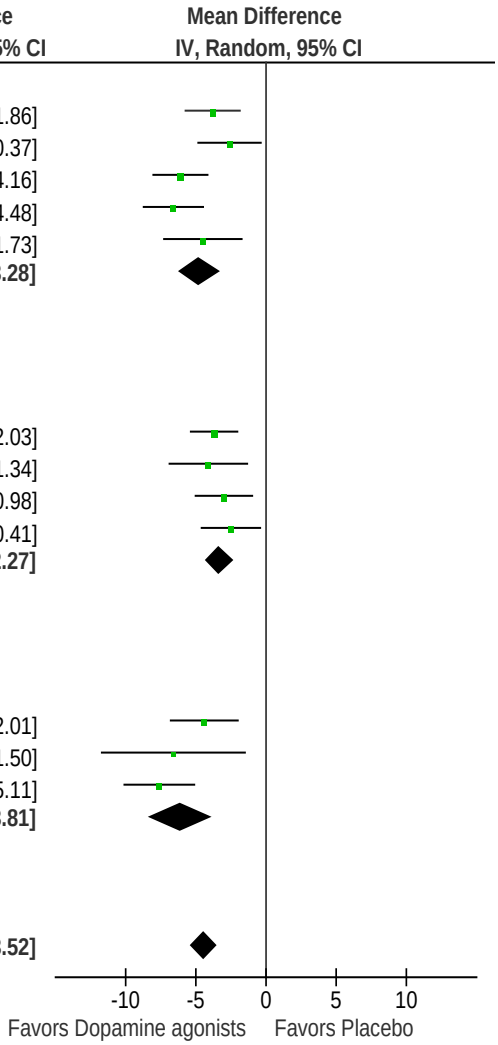


Figure 7. Efficacy outcomes for treatment with dopamine agonists: change in RLS-specific quality of life

Study or Subgroup	Dopamine agonists Mean	SD	Total	Placebo Mean	SD	Total	Weight	Std. Mean Difference IV, Random, 95% CI
1.19.1 Pramipexole studies (0.5 mg for fixed-dose/dose finding trials)								
Ferini-Strambi 2008	-18.3	18.8	178	-13.4	17.3	178	19.0%	-0.27 [-0.48, -0.06]
Montagna 2011	-21.2	19.1	200	-12.3	17.4	192	19.9%	-0.49 [-0.69, -0.28]
Winkelman 2006	-21.3	13.3	79	-13.5	12.9	85	10.8%	-0.59 [-0.91, -0.28]
Subtotal (95% CI)			**457**			**455**	**49.7%**	**-0.43 [-0.61, -0.25]**
Heterogeneity: Tau² = 0.01; Chi² = 3.55, df = 2 (P = 0.17); I² = 44%								
Test for overall effect: Z = 4.67 (P < 0.00001)								
1.19.2 Ropinerole studies								
Bogan 2006	-16.9	14.6	186	-12.4	14.4	191	19.6%	-0.31 [-0.51, -0.11]
Subtotal (95% CI)			**186**			**191**	**19.6%**	**-0.31 [-0.51, -0.11]**
Heterogeneity: Not applicable								
Test for overall effect: Z = 2.99 (P = 0.003)								
1.19.3 Rotigotine studies (2 mg for fixed-dose/dose finding trials)								
Hening 2010	-13.5	12.1	95	-10.7	11.5	99	12.7%	-0.24 [-0.52, 0.05]
Oertel 2010	-15.5	14.5	46	-10.3	14.5	20	4.5%	-0.35 [-0.88, 0.17]
Trenkwalder 2008	-15.7	12.8	109	-7.3	13.5	114	13.6%	-0.64 [-0.91, -0.37]
Subtotal (95% CI)			**250**			**233**	**30.7%**	**-0.42 [-0.70, -0.14]**
Heterogeneity: Tau² = 0.03; Chi² = 4.13, df = 2 (P = 0.13); I² = 52%								
Test for overall effect: Z = 2.96 (P = 0.003)								
Total (95% CI)			**893**			**879**	**100.0%**	**-0.40 [-0.52, -0.29]**
Heterogeneity: Tau² = 0.01; Chi² = 8.66, df = 6 (P = 0.19); I² = 31%								
Test for overall effect: Z = 6.77 (P < 0.00001)								
Test for subgroup differences: Chi² = 0.83, df = 2 (P = 0.66), I² = 0%								

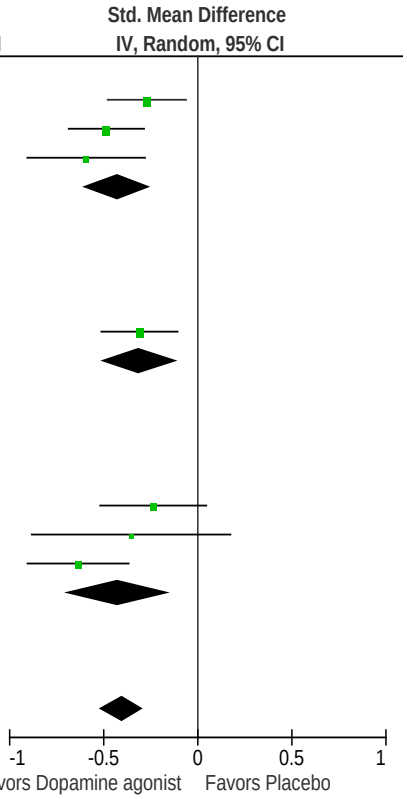


Figure 8. Efficacy outcomes for treatment with dopamine agonists: change in sleep (MOS) scores

Study or Subgroup	Dopamine agonists Mean	SD	Total	Placebo Mean	SD	Total	Weight	Std. Mean Difference IV, Random, 95% CI
1.24.1 Pramipexole studies								
Ferini-Strambi 2008	19.5	19.2	178	12.9	17.8	178	17.5%	0.36 [0.15, 0.57]
Subtotal (95% CI)			**178**			**178**	**17.5%**	**0.36 [0.15, 0.57]**
Heterogeneity: Not applicable								
Test for overall effect: Z = 3.33 (P = 0.0009)								
1.24.2 Ropinerole studies								
Bogan 2006	22.8	18	176	14.6	18	182	17.4%	0.45 [0.24, 0.66]
Kushida 2008	22.4	23.5	174	16.8	22.4	183	17.7%	0.24 [0.04, 0.45]
Trenkwalder 2004	14.8	22	140	9	18.2	130	13.3%	0.29 [0.05, 0.53]
Walters 2004	16.5	20	123	7	18.1	129	12.2%	0.50 [0.25, 0.75]
Subtotal (95% CI)			**613**			**624**	**60.6%**	**0.37 [0.24, 0.49]**
Heterogeneity: Tau² = 0.00; Chi² = 3.49, df = 3 (P = 0.32); I² = 14%								
Test for overall effect: Z = 5.88 (P < 0.00001)								
1.24.3 Rotigotine studies (2 mg for fixed-dose/dose finding trials)								
Hening 2010	21.5	20	95	14.8	18.1	99	9.5%	0.35 [0.07, 0.63]
Oertel 2010	20.5	21.4	46	14.1	21	21	2.8%	0.30 [-0.22, 0.82]
Trenkwalder 2008	20.1	20.5	99	10	16.7	99	9.5%	0.54 [0.25, 0.82]
Subtotal (95% CI)			**240**			**219**	**21.9%**	**0.43 [0.24, 0.61]**
Heterogeneity: Tau² = 0.00; Chi² = 1.11, df = 2 (P = 0.57); I² = 0%								
Test for overall effect: Z = 4.45 (P < 0.00001)								
Total (95% CI)			**1031**			**1021**	**100.0%**	**0.38 [0.29, 0.46]**
Heterogeneity: Tau² = 0.00; Chi² = 4.95, df = 7 (P = 0.67); I² = 0%								
Test for overall effect: Z = 8.42 (P < 0.00001)								
Test for subgroup differences: Chi² = 0.33, df = 2 (P = 0.85), I² = 0%								

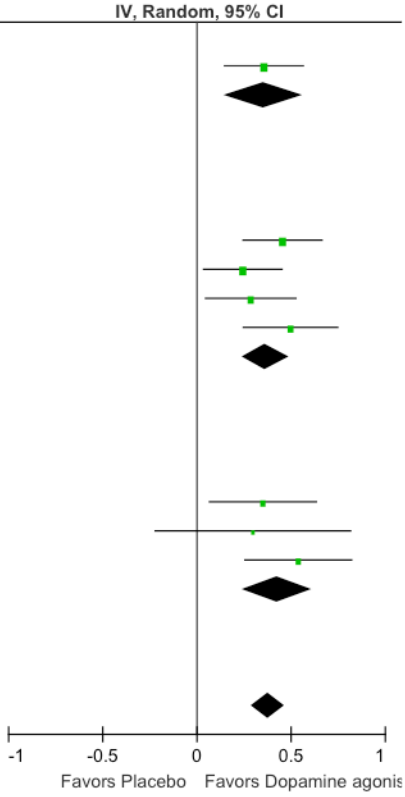


Table 8: Summary of study baseline characteristics for GABA analogs drug trials

Characteristic	Mean (range) *Unless otherwise note*	Number of trials reporting
Total number of patients evaluated	441 (24 to 222)	4
Age of subjects, years	51.1 (50.5 to 55.0)	4
Women, %	62 (59 to 66)	4
Race/ethnicity, white %	95 (92 to 97)	2 [a,c]
RLS disease duration, years	12.1 (7.7 to 51.2)	3 [a,b,d]
Baseline IRLS total score (range 0 to 40)	23.0 (20 to 24.8)	4
Patients with severe disease, % (number of patients)	8 (17)	1 [c]
Previous RLS therapy, % (number of patients)	31.7 (70)	1 [c]
Trials evaluating pregabalin, % (number of patients)	44 (195)	2 [a,b]
Trials evaluating gabapentin, % (number of patients)		2 [c,d]
Crossover trials, % (number of patients)	11 (24)	1 [d]

IRLS = International Restless Legs Scale
a=Allen 2010; b= Garcia-Borreguero 2010; c= Kushida 2009; d=Garcia-Borreguero 2002

Table 9. Overall strength of evidence for individual outcomes in studies of GABA analogs

Outcome	Number of trials	n	Summary statistics, [95% CI]	Risk of bias	Directness	Precision	Consistency	Evidence rating
IRLS Responders (≥50% score reduction)	2	182	RR 2.03 [1.33 to 3.11]	low	direct	precise	consistent	High
IRLS total score: Mean change from baseline	2	264	WMD -4.51 [-6.60 to -2.42]	moderate	direct	precise	consistent	Moderate
IRLS total score: Mean score at endpoint	2	102	WMD -6.56 [-9.27 to -3.86]	moderate	direct	precise	consistent	Moderate
Clinical Global Impression: Responders (much improved)	2	341	RR 1.52 [0.89 to 2.58]	moderate	direct	imprecise	inconsistent	Low
Self-rated sleep MOS-SPI-II	1	47	SMD 0.29 [-0.29 to 0.86]	low	direct	imprecise	unknown	Low
Patients with ≥ 1 adverse event	3	417	RR 1.38 [0.90 to 2.12]	low	direct	imprecise	inconsistent	Low
Any study withdrawal	3	417	RR 0.81 [0.49 to 1.34]	low	direct	imprecise	consistent	Moderate
Study withdrawals due to an adverse event	3	417	RR 3.18 [1.17 to 8.66]	low	direct	precise	consistent	High

MOS-SPI-II = Medical Outcomes Scale- Sleep Problems Index II; RR = relative risk; WMD = weighted mean difference

Figure 9. IRLS Responders GABA analogs (≥50% scale score reduction)

Study or Subgroup	GABA analog Events	GABA analog Total	Placebo Events	Placebo Total	Weight	Risk Ratio M-H, Random, 95% CI
2.3.1 Pregabalin						
Allen 2010	61	103	5	21	29.7%	2.49 [1.14, 5.44]
Garcia-Borreguero 2010	22	30	11	28	70.3%	1.87 [1.12, 3.10]
Subtotal (95% CI)		**133**		**49**	**100.0%**	**2.03 [1.33, 3.11]**
Total events	83		16			
Heterogeneity: Tau² = 0.00; Chi² = 0.41, df = 1 (P = 0.52); I² = 0%						
Test for overall effect: Z = 3.26 (P = 0.001)						
Total (95% CI)		**133**		**49**	**100.0%**	**2.03 [1.33, 3.11]**
Total events	83		16			
Heterogeneity: Tau² = 0.00; Chi² = 0.41, df = 1 (P = 0.52); I² = 0%						
Test for overall effect: Z = 3.26 (P = 0.001)						
Test for subgroup differences: Not applicable						

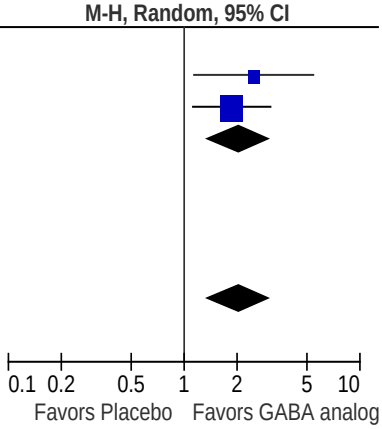


Figure 10: Efficacy outcomes for treatment with GABA analogs: proportion of patients who reported improved or much improved on the clinician rated global impressions scale (CGI)

Study or Subgroup	GABA analog Events	GABA analog Total	Placebo Events	Placebo Total	Weight	Risk Ratio M-H, Random, 95% CI
2.6.1 Pregabalin						
Allen 2010	73	103	13	21	47.3%	1.14 [0.80, 1.64]
Subtotal (95% CI)		**103**		**21**	**47.3%**	**1.14 [0.80, 1.64]**
Total events	73		13			
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.74 (P = 0.46)						
2.6.2 Gabapentin						
Kushida 2009	83	109	42	108	52.7%	1.96 [1.51, 2.54]
Subtotal (95% CI)		**109**		**108**	**52.7%**	**1.96 [1.51, 2.54]**
Total events	83		42			
Heterogeneity: Not applicable						
Test for overall effect: Z = 5.09 (P < 0.00001)						
Total (95% CI)		**212**		**129**	**100.0%**	**1.52 [0.89, 2.58]**
Total events	156		55			
Heterogeneity: Tau² = 0.12; Chi² = 5.77, df = 1 (P = 0.02); I² = 83%						
Test for overall effect: Z = 1.55 (P = 0.12)						
Test for subgroup differences: Chi² = 5.68, df = 1 (P = 0.02), I² = 82.4%						

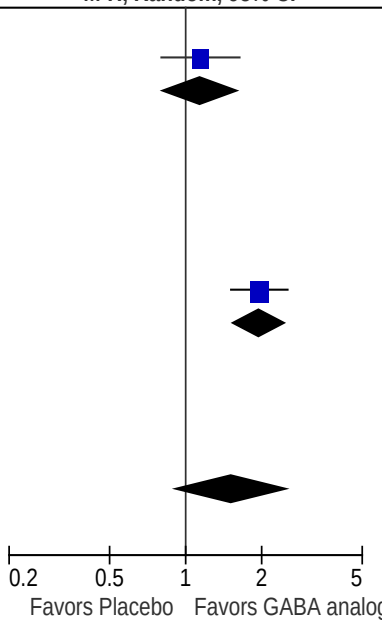


Table 10. Long-term harms with pharmacologic treatment: Augmentation

Class of Drugs	Drug	Study (year)	Design	Duration (years)	Augmentation	Withdrawal from treatment	Reason for withdrawal (% of all withdrawals)	Adverse Events
Anticonvulsant drug	**Gabapentin**	Ellenbogen, 2011[38]	Open-label extension to RCT	1	NA	37% (187/573)	Lack of efficacy (5.8%); Adverse events (34.2%); Other reasons (38%)	Somnolence, dizziness, headache, fatigue, nausea, condition aggravated, nasopharyngitis, upper respiratory tract infection,
Opioids	**Mulitple opioids [tilidine, dihydrocodeine, oxycodonoe, propoxyphene, methadone]**	Walters, 2001[52]	Retrospective	3.8 (mean, range 1 wk to 23 years)	NA	44% (16/36)	Lack of efficacy (44%) Adverse events (50%) Addiction and tolerance (6%)	Sleep apnea, daytime fatigue, migraine headache, grogginess, paradoxical hyperalerting response, constipation
	Methadone	Silver, 2011[50]	Retrospective	10	NA	15% (11/76) during the first year and 0% subsequently	Lack of efficacy Adverse events	Specific adverse events not reported
	Methadone	Ondo, 2005[74]	Prospective	1.9 (mean)	NA	37% (10/27)	Lack of efficacy (25%) Adverse events (62%)	Constipation, fatigue, insomnia, sedation, rash, decreased libido, confusion, hypertension
Dopaminergic drug	**Levodopa**	Högl, 2011[20]	Prospective	0.5	60% (36/60)	42% (25/60)	Lack of efficacy (28%) Adverse events (12%) Augmentation (28%) Other reasons (32%)	Fatigue, nausea, headache, condition aggravated, somnolence, nasopharyngitis, muscle spasms, arthralgia
	Levodopa	Trenkwalder, 2003[51]	Open label extension of RCT	1	34.8% (8/23)	56% (13/23)	Lack of efficacy (7%); Adverse events(7%); Augmentation (62%); Other reasons (23%);	Worsening of RLS symptoms, dry mouth, itching, persistent diarrhea
Dopamine Agonists	**Pramipexole**	Inoue, 2010[44]	Open label extension of RCT	1	4.3% (6/141)	12.8% (18/141)	Adverse events (44%) Other reasons (56%)	Nasopharyngitis, somnolence, headache, nausea, vomiting
	Pramipexole	Silber, 2003[49]	Retrospective	1.2 (mean)	33% (16/49)	25% (15/60)	Lack of efficacy (27%); Adverse events (67%) Augmentation (6%) ;	Insomnia, nausea or dyspepsia, postural light headedness

Class of Drugs	Drug	Study (year)	Design	Duration (years)	Augmentation	Withdrawal from treatment	Reason for withdrawal (% of all withdrawals)	Adverse Events
	Pramipexole	Silver, 2011[50]	Retrospective	10 years	7%	17% during the first year and 9±3.9% during subsequent years	Lack of efficacy Adverse events Augmentation (7%)	Nausea, sleepiness, insomnia
	Pramipexole	Ferini-Strambi, 2002[39]	Open,label case series	0.5	8.3% (5/60)	NR	NR	Nausea, excessive daytime sleepiness, sedation
	Pramipexole	Montplaisir, 2006[45]	Retrospective	2.5 (mean)	33% (65/195)	22% (43/195)	Lack of efficacy (28%) Adverse events (47%) Other reasons (25%)	Dizziness, nausea, sleepiness, insomnia
	Pramipexole	Winkelman, 2004[53]	Retrospective	1.8	32% (19/59)	NR	NR	NR
	Ropinirole	Garcia-Borreguero, 2007[41]	Open label extension of RCT	1	2.3% (7/309)	19% (59/310)	Lack of efficacy (19%) Adverse events (44%)	Nausea, headache, arthralgia, nasopharyngitis, dizziness, back pain, vomiting, aggravation of symptoms, fatigue, somnolence
	Rotigotine	Oertel, 2011[46]	Open label extension of RCT	5	23% (69/295)	57% (169/295)	Lack of efficacy (18%) Adverse events (53%) Other reasons (29%)	Application site reactions, insomnia, depression, nausea, fatigue, headache, dizziness, pulmonary fibrosis, obsessive compulsive disorder, sleep attack or sudden onset of sleep, syncope, nausea, sleep apnea
	Rotigotine	Benes, 2009[37]	Retrospective	1	9.7 % (60/620)	NR	NR	NR
	Multiple dopamine agonists [pramipexole; ropinirole; pergolide]	Ondo, 2004[47]	Retrospecitive	3.2 (mean, SD=1.7)	22% (18/83)	19% (10/52)	Lack of efficacy (20%) Adverse events (20%) Augmentation (10%) Other reasons (50%)	Daytime sleepiness, nausea, peripheral edema, dizziness, light-headedness, gastrointestinal upset, constipation, headache, itchiness, rash.

Class of Drugs	Drug	Study (year)	Design	Duration (years)	Augmentation	Withdrawal from treatment	Reason for withdrawal (% of all withdrawals)	Adverse Events
	Multiple dopaminergic drugs (levodopa, pramipexole, ropinirole, rotigotine). *Results not reported for individual drug*	Godau, 2010[42]	Prospective	1	24% (14/60)	NR	NR	Sleepiness, nausea, dizziness, headache, vivid dreams, leg oedema, erectile dysfunction
	Multiple dopaminergic drugs	Frauscher, 2009[40]	Prospective	1.5	11% (13/118)	NR	NR	NR
	Multiple dopaminergic drugs (ropinirole, pramipexole, levodopa)	Allen, 2011[36]	Cross-sectional	2.7 (mean)	20% (53/266)	NR	NR	NR

Table 11. Strength of evidence for the non-pharmacologic trials

Intervention	Outcome	Number of trials	n	Summary statistics, [95% CI]	Risk of bias	Directness	Precision	Consistency	Evidence rating
Valerian (botanical)[14]	IRLS total score: Mean change from baseline	1	37	WMD 1.30 [-5.08 to 7.68]	moderate	direct	imprecise	unknown	Low
Exercise[13]	IRLS total score: Mean score at endpoint	1	28	WMD -9.40 [-13.86 to -4.94]	moderate	direct	precise	unknown	Low
Compression device[12]	IRLS total score: Mean score at endpoint	1	35	MD -5.70 [-8.21 to -3.19]	low	direct	precise	unknown	moderate

IV = intravenous; WMD = weighted mean difference; MD = mean difference.

Figure 11. Short-term harms of treatment with dopamine agonists: any study withdrawal

Study or Subgroup	Dopamine agonists Events	Total	Placebo Events	Total	Weight	Risk Ratio M-H, Random, 95% CI
1.8.1 Pramipexole studies						
Ferini-Strambi 2008	27	182	52	187	8.8%	0.53 [0.35, 0.81]
Högl 2011	35	166	60	163	10.0%	0.57 [0.40, 0.82]
Montagna 2011	26	203	41	201	8.2%	0.63 [0.40, 0.99]
Oertel 2007	12	230	8	115	3.7%	0.75 [0.32, 1.78]
Winkelman 2006	53	259	11	86	6.1%	1.60 [0.88, 2.92]
Subtotal (95% CI)		**1040**		**752**	**36.8%**	**0.71 [0.50, 1.01]**
Total events	153		172			
Heterogeneity: Tau² = 0.09; Chi² = 10.11, df = 4 (P = 0.04); I² = 60%						
Test for overall effect: Z = 1.91 (P = 0.06)						
1.8.2 Ropinirole studies						
Adler 2004	2	22	1	22	0.7%	2.00 [0.20, 20.49]
Bogan 2006	23	187	26	194	7.1%	0.92 [0.54, 1.55]
Kushida 2008	25	176	27	186	7.4%	0.98 [0.59, 1.62]
Montplaisir 2006	15	45	28	47	7.8%	0.56 [0.35, 0.90]
Trenkwalder 2004	35	147	30	139	8.6%	1.10 [0.72, 1.69]
Walters 2004	29	131	29	136	8.2%	1.04 [0.66, 1.64]
Subtotal (95% CI)		**708**		**724**	**39.8%**	**0.91 [0.72, 1.14]**
Total events	129		141			
Heterogeneity: Tau² = 0.01; Chi² = 5.68, df = 5 (P = 0.34); I² = 12%						
Test for overall effect: Z = 0.82 (P = 0.41)						
1.8.3 Rotigotine studies						
Hening 2010	152	404	33	100	10.9%	1.14 [0.84, 1.55]
Oertel 2010	5	46	1	21	0.8%	2.28 [0.28, 18.35]
Trenkwalder 2008	96	341	49	117	11.6%	0.67 [0.51, 0.88]
Subtotal (95% CI)		**791**		**238**	**23.3%**	**0.92 [0.56, 1.50]**
Total events	253		83			
Heterogeneity: Tau² = 0.11; Chi² = 7.33, df = 2 (P = 0.03); I² = 73%						
Test for overall effect: Z = 0.35 (P = 0.73)						
Total (95% CI)		**2539**		**1714**	**100.0%**	**0.82 [0.68, 1.00]**
Total events	535		396			
Heterogeneity: Tau² = 0.06; Chi² = 28.02, df = 13 (P = 0.009); I² = 54%						
Test for overall effect: Z = 1.98 (P = 0.05)						
Test for subgroup differences: Chi² = 1.44, df = 2 (P = 0.49), I² = 0%						

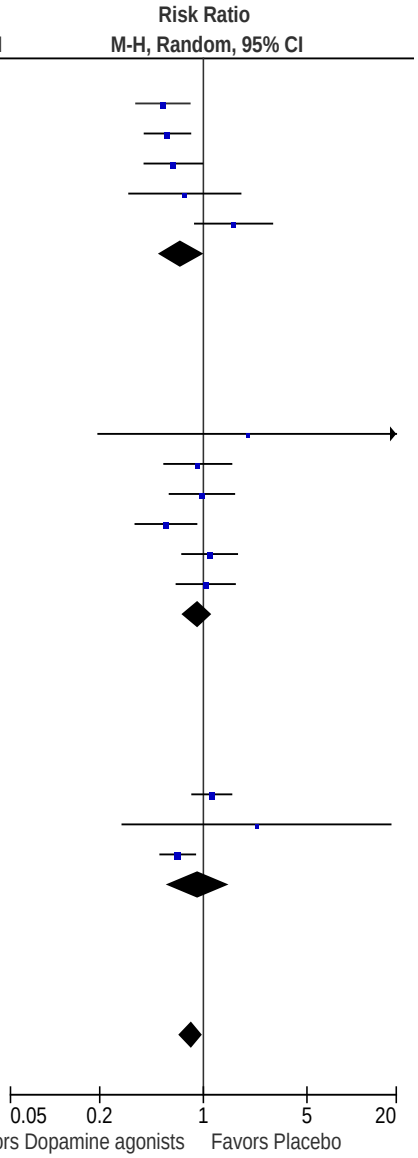


Figure 12. Short-term harms of treatment with dopamine agonists: study withdrawals due to adverse events

Study or Subgroup	Dopamine agonists Events	Dopamine agonists Total	Placebo Events	Placebo Total	Weight	Risk Ratio M-H, Random, 95% CI
1.9.1 Pramipexole studies						
Ferini-Strambi 2008	17	182	16	187	11.5%	1.09 [0.57, 2.09]
Högl 2011	19	166	23	163	12.9%	0.81 [0.46, 1.43]
Montagna 2011	9	203	11	201	8.5%	0.81 [0.34, 1.91]
Oertel 2007	6	230	5	115	5.7%	0.60 [0.19, 1.92]
Winkelman 2006	32	258	6	86	8.8%	1.78 [0.77, 4.11]
Subtotal (95% CI)		**1039**		**752**	**47.5%**	**0.97 [0.69, 1.35]**
Total events	83		61			
Heterogeneity: Tau² = 0.00; Chi² = 3.36, df = 4 (P = 0.50); I² = 0%						
Test for overall effect: Z = 0.18 (P = 0.85)						
1.9.2 Ropinirole studies						
Adler 2004	1	22	1	22	1.3%	1.00 [0.07, 15.00]
Bogan 2006	7	187	9	194	7.4%	0.81 [0.31, 2.12]
Kushida 2008	8	176	6	186	6.7%	1.41 [0.50, 3.98]
Montplaisir 2006	1	45	0	47	1.0%	3.13 [0.13, 74.90]
Trenkwalder 2004	16	147	6	139	8.0%	2.52 [1.02, 6.26]
Walters 2004	11	131	9	136	8.7%	1.27 [0.54, 2.96]
Subtotal (95% CI)		**708**		**724**	**33.0%**	**1.41 [0.89, 2.22]**
Total events	44		31			
Heterogeneity: Tau² = 0.00; Chi² = 3.22, df = 5 (P = 0.67); I² = 0%						
Test for overall effect: Z = 1.47 (P = 0.14)						
1.9.3 Rotigotine studies						
Hening 2010	82	404	4	100	7.2%	5.07 [1.91, 13.51]
Oertel 2010	2	46	1	21	1.7%	0.91 [0.09, 9.52]
Trenkwalder 2008	54	341	8	117	10.5%	2.32 [1.14, 4.72]
Subtotal (95% CI)		**791**		**238**	**19.5%**	**2.85 [1.40, 5.80]**
Total events	138		13			
Heterogeneity: Tau² = 0.11; Chi² = 2.67, df = 2 (P = 0.26); I² = 25%						
Test for overall effect: Z = 2.90 (P = 0.004)						
Total (95% CI)		**2538**		**1714**	**100.0%**	**1.36 [0.98, 1.87]**
Total events	265		105			
Heterogeneity: Tau² = 0.13; Chi² = 20.42, df = 13 (P = 0.09); I² = 36%						
Test for overall effect: Z = 1.84 (P = 0.07)						
Test for subgroup differences: Chi² = 7.69, df = 2 (P = 0.02), I² = 74.0%						

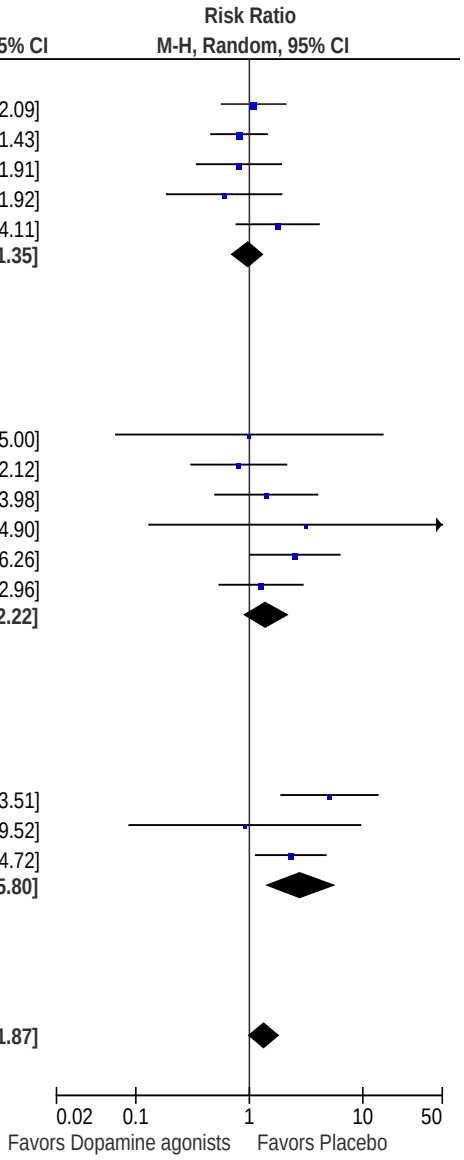


Figure 13. Short-term harms of treatment with GABA analogs: any study withdrawals

Study or Subgroup	GABA analog Events	GABA analog Total	Placebo Events	Placebo Total	Weight	Risk Ratio M-H, Random, 95% CI
2.7.1 Pregabalin						
Allen 2010	14	114	2	23	12.6%	1.41 [0.34, 5.80]
Garcia-Borreguero 2010	6	30	9	28	31.2%	0.62 [0.25, 1.52]
Subtotal (95% CI)		**144**		**51**	**43.8%**	**0.79 [0.37, 1.68]**
Total events	20		11			
Heterogeneity: Tau² = 0.00; Chi² = 0.94, df = 1 (P = 0.33); I² = 0%						
Test for overall effect: Z = 0.62 (P = 0.53)						
2.7.2 Gabapentin						
Kushida 2009	14	114	16	108	56.2%	0.83 [0.43, 1.62]
Subtotal (95% CI)		**114**		**108**	**56.2%**	**0.83 [0.43, 1.62]**
Total events	14		16			
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.55 (P = 0.58)						
Total (95% CI)		**258**		**159**	**100.0%**	**0.81 [0.49, 1.34]**
Total events	34		27			
Heterogeneity: Tau² = 0.00; Chi² = 0.94, df = 2 (P = 0.62); I² = 0%						
Test for overall effect: Z = 0.82 (P = 0.41)						
Test for subgroup differences: Chi² = 0.01, df = 1 (P = 0.92), I² = 0%						

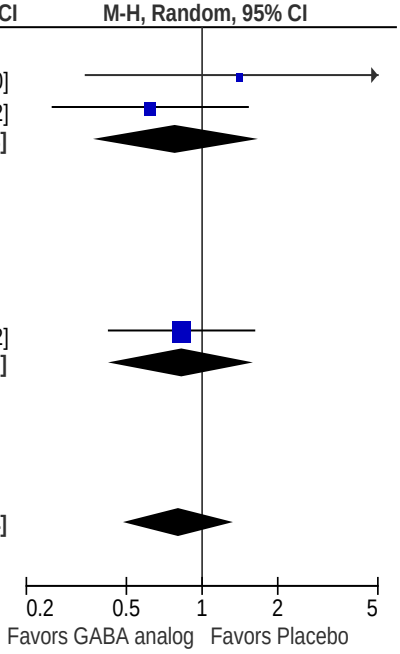


Figure 14. Short-term harms of treatment with GABA analogs: study withdrawals due to adverse events

Study or Subgroup	GABA analog Events	GABA analog Total	Placebo Events	Placebo Total	Weight	Risk Ratio M-H, Random, 95% CI
2.8.1 Pregabalin						
Allen 2010	10	114	1	23	24.9%	2.02 [0.27, 15.00]
Garcia-Borreguero 2010	4	30	0	28	12.1%	8.42 [0.47, 149.62]
Subtotal (95% CI)		**144**		**51**	**37.1%**	**3.22 [0.62, 16.69]**
Total events	14		1			
Heterogeneity: Tau² = 0.00; Chi² = 0.65, df = 1 (P = 0.42); I² = 0%						
Test for overall effect: Z = 1.39 (P = 0.16)						
2.8.3 Gabapentin						
Kushida 2009	10	114	3	108	62.9%	3.16 [0.89, 11.17]
Subtotal (95% CI)		**114**		**108**	**62.9%**	**3.16 [0.89, 11.17]**
Total events	10		3			
Heterogeneity: Not applicable						
Test for overall effect: Z = 1.78 (P = 0.07)						
Total (95% CI)		**258**		**159**	**100.0%**	**3.18 [1.17, 8.66]**
Total events	24		4			
Heterogeneity: Tau² = 0.00; Chi² = 0.64, df = 2 (P = 0.72); I² = 0%						
Test for overall effect: Z = 2.26 (P = 0.02)						
Test for subgroup differences: Chi² = 0.00, df = 1 (P = 0.99), I² = 0%						

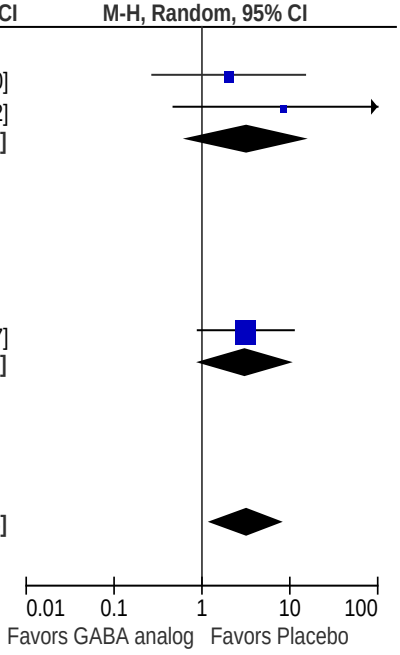


Figure 15. Patients with ≥1 adverse effect, dopamine agonist trials

Study or Subgroup	Dopamine agonists Events	Total	Placebo Events	Total	Weight	Risk Ratio M-H, Random, 95% CI
1.10.1 Pramipexole studies						
Ferini-Strambi 2008	106	182	86	187	6.2%	1.27 [1.04, 1.54]
Högl 2011	120	166	106	163	8.5%	1.11 [0.96, 1.29]
Montagna 2011	124	203	103	200	7.2%	1.19 [1.00, 1.41]
Oertel 2007	150	230	55	115	5.7%	1.36 [1.10, 1.69]
Winkelman 2006	209	258	69	86	9.9%	1.01 [0.90, 1.14]
Subtotal (95% CI)		**1039**		**751**	**37.5%**	**1.16 [1.04, 1.29]**
Total events	709		419			
Heterogeneity: Tau² = 0.01; Chi² = 8.96, df = 4 (P = 0.06); I² = 55%						
Test for overall effect: Z = 2.61 (P = 0.009)						
1.10.2 Ropinirole studies						
Adler 2004	10	22	2	22	0.2%	5.00 [1.23, 20.24]
Bogan 2006	155	187	129	193	10.0%	1.24 [1.10, 1.40]
Kushida 2008	138	176	119	186	9.2%	1.23 [1.07, 1.40]
Montplaisir 2006	26	45	24	47	2.5%	1.13 [0.78, 1.65]
Trenkwalder 2004	120	146	103	138	9.8%	1.10 [0.97, 1.25]
Walters 2004	112	131	102	136	9.9%	1.14 [1.01, 1.29]
Subtotal (95% CI)		**707**		**722**	**41.6%**	**1.18 [1.09, 1.27]**
Total events	561		479			
Heterogeneity: Tau² = 0.00; Chi² = 6.90, df = 5 (P = 0.23); I² = 28%						
Test for overall effect: Z = 4.19 (P < 0.0001)						
1.10.3 Rotigotine studies						
Hening 2010	355	404	84	100	11.5%	1.05 [0.95, 1.15]
Oertel 2010	34	46	12	21	2.1%	1.29 [0.86, 1.95]
Trenkwalder 2008	265	341	64	117	7.2%	1.42 [1.19, 1.69]
Subtotal (95% CI)		**791**		**238**	**20.9%**	**1.23 [0.93, 1.61]**
Total events	654		160			
Heterogeneity: Tau² = 0.05; Chi² = 12.61, df = 2 (P = 0.002); I² = 84%						
Test for overall effect: Z = 1.46 (P = 0.14)						
Total (95% CI)		**2537**		**1711**	**100.0%**	**1.17 [1.10, 1.25]**
Total events	1924		1058			
Heterogeneity: Tau² = 0.01; Chi² = 28.05, df = 13 (P = 0.009); I² = 54%						
Test for overall effect: Z = 4.87 (P < 0.00001)						
Test for subgroup differences: Chi² = 0.16, df = 2 (P = 0.92), I² = 0%						

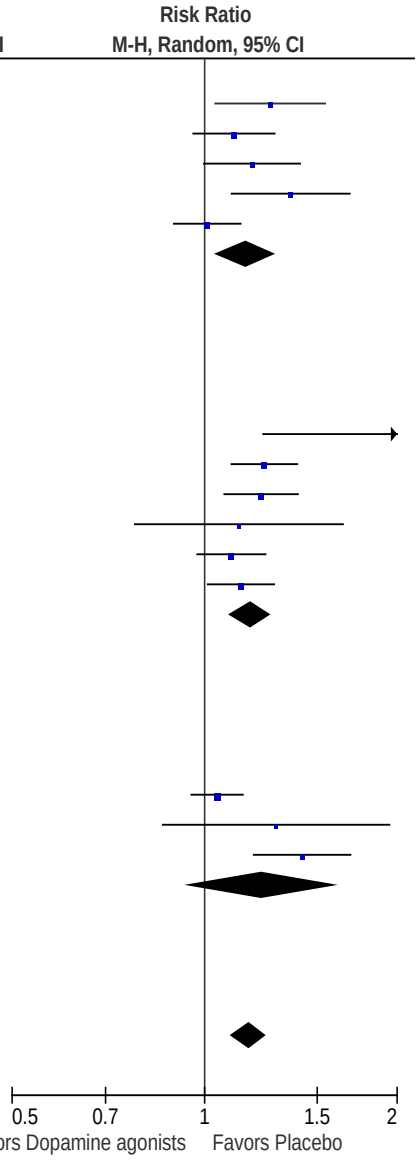


Table 12. Strength of evidence for Iron trials for the treatment of secondary RLS

Outcome	Number of trials	n	Summary statistics, [95% CI]	Risk of bias	Directness	Precision	Consistency	Evidence rating
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

RR = risk ratio; WMD = weighted mean difference.
* post-hoc analysis

Discussion

The main intent of this report was to conduct a comparative effectiveness review on treatments for restless leg syndrome. However, we identified only one randomized controlled trial that directly compared two treatment options. This single study assessed two drugs no longer widely used for this condition (cabergoline and levodopa). The included studies are insufficient to conduct reliable indirect comparisons from which to draw valid information about comparative benefits and harms. Thus, we could not make accurate conclusions about the comparative effectiveness and harms of treatments for RLS. We also assessed whether effectiveness and harms varied across drugs or doses based on evidence of subgroup heterogeneity. However, we caution about conclusions based on these comparisons, since any differences or lack of differences in findings could be due to variations in study populations or disease characteristics.

Results from small, placebo-controlled randomized trials of short duration do suggest however that dopamine agonists (ropinirole, pramipexole, and rotigotine) and anticonvulsant GABA analogs (gabapentin and pregabalin) reduce symptoms, increase the percentage of IRLS responders, and improve disease-specific quality of life and patient-reported sleep outcomes. 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. Applicability is limited to nonpregnant adults who have high-moderate to very severe RLS and no major comorbidities.

Randomized controlled trial evidence regarding treatments for restless legs syndrome is limited in quality and quantity. Applicability is largely unknown for long-term outcomes and for individuals who have mild to moderate RLS symptoms or who have RLS symptoms and are pregnant, recently postpartum, have iron deficiency or end-stage renal disease. All RCTs were short in duration and enrolled highly selected populations with symptoms that were very severe to high-moderate, frequent, and long-standing. Many enrollees had previously received RLS treatments and most were recruited from RLS clinics, not primary care, mental health or population based settings. These settings are where many individuals first present with symptoms suggestive of RLS and where clinicians diagnose and frequently initiate treatment or referrals. Randomized trials of pharmacological therapies consisted mainly of dopaminergic agents, while a few studies assessed GABA analogs. 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.[5] Few nonpharmacological therapies were assessed, and they were limited to a single small study each.

Exclusion criteria were many, and enrolled patients were typically recruited from RLS clinics not primary care settings. 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 disease, and few lasted longer than 6 months. Among studies that permitted enrollment of individuals with moderate symptoms, the symptom threshold for eligibility was typically at least “mid to high-moderate” and mean baseline RLS symptom scale scores were rated as severe. None of the enrolled individuals were under age 18, and the vast 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. Although symptom scales are widely used in research studies, their use in clinical settings is less clear and likely very limited. Furthermore, despite that RCT study subjects met consensus definitions of RLS, these criteria are not routinely used in clinical settings to diagnose, assess severity, or initiate therapy. Thus, the applicability of results from these RCTs to individuals seen in primary care settings is not established. Outcomes were not stratified by patient and RLS characteristics, and we could not determine whether findings vary by these factors.

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 GABA agonist pregabalin (k = 1). Because studies reported a large placebo response, we urge caution in using information from uncontrolled studies as the basis for recommending 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. Future randomized blinded controlled studies of dose effect and timing are needed. Future trials are also needed to directly compare benefits and harms of the current widely used dopaminergic agents (pramipexole, ropinirole, and rotigotine) and GABA analogs (gabapentin and pregabalin). Comparative effectiveness and harms for primary therapy should be further examined, along with algorithms intended to guide the use of a particular agent or changes in dose, timing, or type of intervention.

Few studies assessed individuals with secondary RLS, an evidence gap that needs to be closed. No studies enrolled pregnant women or those with postpartum RLS. Only two studies assessed the effect of iron therapy on RLS symptoms in adults with iron deficiency. These studies were small, short term, and had methodological flaws; however, they suggested that iron therapy may improve symptoms in these individuals. A single study[75] that did not meet our eligibility criteria because it did not use validated RLS symptom scale scores found no benefit with oral iron therapy in adults with RLS and normal iron stores. Another small short-term RCT[76] assessed intravenous iron versus placebo in patients on hemodialysis with normal iron stores. This study used unvalidated measures and found no benefit. The effectiveness of iron therapy for RLS is not clear and needs additional research. We identified one other study[77] 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. Because RLS is common in patients with end-stage renal disease, additional research is needed.

For individuals who are unable to initiate or tolerate dopaminergic agents, or for whom these drugs have failed, recommended treatments include off-label use of opioids, sedative hypnotics, and tramadol. None of these are FDA approved for treatment of RLS, and we found no eligible studies evaluating these agents. A single crossover study of 11 patients assessed oxycodone versus placebo and reported improvement in leg sensation, motor restlessness, and alertness[78].

The RCT evidence base for RLS treatments is mostly limited to short-term, placebo-controlled efficacy studies of dopamine agonists and anticonvulsant GABA analogs conducted in highly selected patient populations with longstanding, high moderate to very severe primary RLS. We found no data from randomized controlled trials on the comparative benefits or harms

of these drugs. Only two small studies[54, 55] of iron therapy addressed secondary RLS due to iron deficiency, providing low strength of evidence that iron replacement therapy may improve symptoms. Assessment of nonpharmacological interventions was limited to three trials, one on exercise,[13] one on compression stockings,[12] and one on the herb valerian.[14] These provided low strength evidence for a benefit with compression stockings and exercise but not with valerian.

No studies assessed the potential effects 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. No studies meeting our inclusion criteria assessed opioids, sedative hypnotics, or tramadol, all of which are recommended in treatment algorithms[5] and presumably used in clinical practice.

The long-term benefits, adherence, and harms as well as the comparative effectiveness and harms of commonly used and FDA-approved treatments are not well known. Future trials of other therapies are needed, because current evidence suggests that available options have limited short- and long-term effectiveness and frequently result adverse effects and treatment discontinuation.

Long-term studies reporting withdrawals due to loss of efficacy or side effects suggest that for many RLS patients, the benefits of pharmacological treatment are not sustained over time, and that available pharmacological interventions result in adverse effects and are often discontinued. Augmentation, a drug-induced exacerbation of the disease, can occur with long-term treatment with Levodopa and dopamine analog drugs.

Nonpharmacological interventions such as exercise and compression stockings were assessed in only one study each. While results suggested these interventions may improve symptoms, the studies were very small and short-term. The exercise therapy trial had a high dropout rate (30 percent). Further, the authors reported outcomes only for individuals who completed the study. Thus, their findings are limited in both quality and applicability. No RCTs examined other recommended nonpharmacological therapies such as psychotherapy or hot or cold baths.

Evaluating any treatment for RLS 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 scale scores 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, for whom a chronic, progressive disorder may require daily treatment for decades. Even nonpharmacological interventions and other treatments for those with milder symptoms are often long term. Yet, the evidence base 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 highly selected population of RLS patients must 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. 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 are likely to have milder symptoms or other conditions that mimic RLS (e.g., periodic leg movement disorders, nocturnal leg cramps, vascular or neurogenic claudication). They may have more comorbidities than subjects included in available RCTs.

In conclusion, RCT evidence for RLS treatments is mostly limited to short-term, placebo-controlled efficacy studies of dopamine agonists and GABA analogs conducted in a highly selected population of adults with high-moderate to very severe primary RLS of long duration. Compared to placebo, dopamine agonists and GABA analogs reduce symptoms, improve patient-reported sleep outcomes and disease-specific quality of life, and increase the percentage of individuals considered to have "responded to treatment." Both short- and long-term adverse effects and treatment withdrawals due to adverse effects or lack of efficacy are common. We found no high quality data on comparative effectiveness and harms of commonly used treatments or the effect of patient or RLS characteristics on outcomes. Applicability to adults with less frequent or less severe (mild to moderate) RLS symptoms, children, or those with secondary RLS is unknown.

Future Research Recommendations

Table 13 summarizes our main recommendations for future research based on the gaps identified in this review.

Table 13. Future Research Recommendations

Topical Issues	Specific Research Gaps	Recommendations
Limited evidence base	• Evidence base consists almost exclusively of pharmacological treatments and dopamine agonists in particular	• More studies of nonpharmacological treatments
	• Many classes of drugs used in clinical practice such as opioids and sedative hypnotics have not been evaluated in clinical trials	• Studies of classes of drugs other than dopamine agonists such as opioids and sedative hypnotics
	• We found no evidence for effectiveness of therapies in specific subgroups such as children, older adults with multimorbidities, or individuals with secondary RLS	• Studies of effectiveness of drugs in specific sub-groups such as children, older adults, and individuals with secondary RLS
Long-term durability of treatment benefits	• Long-term durability of treatment benefits remains an unaddressed concern	• Long-term studies that establish the time frame over which treatment benefits are sustained for different types of 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	• Studies that report effectiveness of treatments for various subgroups of patients such as those with different disease duration, patients *de novo* to treatment, and those for whom previous treatment failed
Augmentation	• Augmentation is a significant harm with long-term dopaminergic therapy and can lead to treatment discontinuation;	• 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

	yet, little is known about patient characteristics that may lead to augmentation	• 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 unclear whether the degree of benefit as established by symptom scale scores such as IRLS scale translates to meaningful improvement for patients • The clinical relevance of objective measures of assessment such as polysomnography is unclear	• Establish minimum important differences in scale scores that translate to clinically significant improvement for individual patients • Report outcomes such as proportions of patients with remission of symptoms (IRLS score=0), patient-reported sleep outcomes and quality of life • 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

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. 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.
4. García-Borreguero D, Egatz R, Winkelmann J, et al. Epidemiology of restless legs syndrome: The current status. Sleep medicine reviews. 2006 Jul;10(3):153-67.
5. 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.
6. Garcia-Borreguero D, Williams AM. Dopaminergic augmentation of restless legs syndrome. Sleep Med Rev. 2010 Oct;14(5):339-46. PMID 20219397.
7. 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.
8. Manconi M, Govoni V, De Vito A, et al. Restless legs syndrome and pregnancy. Neurology. 2004 Sep 28;63(6):1065-9. PMID 15452299.
9. Higgins JPT, Green S, eds. Cochrane handbook for systematic reviews of interventions: The Cochrane Collaboration; 2008.
10. 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.
11. Atkins D, Chang S, Gartlehner G, et al. Assessing the Applicability of Studies When Comparing Medical Interventions. Quality AHRQ; December 2010. http://www.effectivehealthcare.ahrq.gov/index.cfm/search-for-guides-reviews-and-reports/?pageaction=displayProduct&productID=603#2412.
12. 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.
13. 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. 2006 Sep-Oct;19(5):487-93. PMID 16951298.
14. 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.
15. 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 15;22(5):696-703. PMID 17274039.
16. Adler CH, Hauser RA, Sethi K, et al. Ropinirole for restless legs syndrome: a placebo-controlled crossover trial. Neurology. 2004. 62(8):1405-7. PMID 15111683.
17. 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.
18. 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.
19. 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.
20. 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.

21. 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.
22. 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. 2011.12(1):34-40. PMID 20965780.
23. 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.
24. 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.
25. 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.
26. 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.
27. 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.
28. 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.
29. 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.
30. 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.
31. 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.
32. 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.
33. 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.
34. 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.
35. 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.
36. 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.
37. 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.
38. 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.
39. Ferini-Strambi L. Restless legs syndrome augmentation and pramipexole treatment. Sleep Medicine. 2002 Nov;3 Suppl:S23-5. PMID 14592163.

40. 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.
41. 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.
42. 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.
43. 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.
44. 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.
45. 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.
46. 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.
47. 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.
48. Ondo WG, Lai D. Association between restless legs syndrome and essential tremor. Movement Disorders. 2006 Apr;21(4):515-8. PMID 16250022.
49. 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.
50. 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.
51. 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.
52. 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.
53. 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.
54. 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.
55. 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.
56. Ekbom K. Restless legs syndrome. Neurology. 1960 Sep 01;10:868-73.
57. Walters AS, Walters AS, Aldrich MS, et al. Toward a better definition of the restless legs syndrome. Movement disorders : official journal of the Movement Disorder Society. 1995 Sep;10(5):634-42.
58. 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 Apr 01. 108(4):101-19.
59. Happe S, Reese JP, Stiasny-Kolster K, et al. Assessing health-related quality of life in patients with restless legs syndrome. Sleep medicine. 2009 Apr;10(3):295-305.
60. Kohnen R, Allen RP, Benes H, et al. Assessment of restless legs syndrome—Methodological approaches for use in practice and clinical trials. Movement disorders : official journal of the Movement Disorder Society. 2007;22(S18):S485-S94.

61. Walters AS, LeBrocq C, Dhar A, et al. Validation of the International Restless Legs Syndrome Study Group rating scale for restless legs syndrome. Sleep medicine. 2003 Apr 01;4(2):121-32.
62. Banerjee D. The Epworth Sleepiness Scale. Occupational Medicine. 2007;57:232.
63. Allen RP, Kosinski M, Hill-Zabala CE, et al. Psychometric evaluation and tests of validity of the Medical Outcomes Study 12-item Sleep Scale (MOS sleep). Sleep Medicine. 2009 May;10(5):531-9. PMID 18805054.
64. Buysse DJ, Reynolds CF, 3rd, Monk TH, et al. The Pittsburgh Sleep Quality Index: a new instrument for psychiatric practice and research. Psychiatry Res. 1989 May;28(2):193-213. PMID 2748771.
65. García-Borreguero D, Kohnen R, Högl B, et al. Validation of the Augmentation Severity Rating Scale (ASRS): A multicentric, prospective study with levodopa on restless legs syndrome☆. Sleep medicine. 2007 Aug;8(5):455-63.
66. Hornyak M, Feige B, Riemann D, et al. Periodic leg movements in sleep and periodic limb movement disorder: Prevalence, clinical significance and treatment. Sleep medicine reviews. 2006 Jul;10(3):169-77.
67. García-Borreguero D, Stillman P, Benes H, et al. Algorithms for the diagnosis and treatment of restless legs syndrome in primary care. BMC neurology. 2011;11(1):28.
68. Liberati A, Altman DG, Tetzlaff J, et al. The PRISMA statement for reporting systematic reviews and meta-analyses of studies that evaluate health care interventions: explanation and elaboration. Journal of Clinical Epidemiology. 2009 Oct;62(10):e1-34. PMID 19631507.
69. Review Manager. 5.0 ed. Copenhagen: The Nordic Cochrane Centre, The Cochrane Collaboration; 2008.
70. Egger M, Davey Smith G, Schneider M, et al. Bias in meta-analysis detected by a simple, graphical test. BMJ. 1997 Sep 13;315(7109):629-34. PMID 9310563.
71. Hogl B, Garcia-Borreguero D, Sohr M, et al. Similar incidences of augmentation during 26 weeks of double-blind pramipexole treatment for restless legs syndrome in comparison to placebo. Neurology. 2009;72(11 (Suppl 3), A106).
72. Kushida CA, Walters AS, Becker P, et al. A randomized, double-blind, placebo-controlled, crossover study of XP13512/GSK1838262 in the treatment of patients with primary restless legs syndrome. Sleep. 2009 Feb;32(2):159-68. PMID 19238802.
73. Allen RP, Bharmal M, Calloway M. Prevalence and disease burden of primary restless legs syndrome: results of a general population survey in the United States. Movement Disorders. 2011 Jan;26(1):114-20. PMID 21322022.
74. Ondo WG. Methadone for refractory restless legs syndrome. Movement Disorders. 2005 Mar;20(3):345-8. PMID 15580610.
75. Davis BJ, Rajput A, Rajput ML, et al. A randomized, double-blind placebo-controlled trial of iron in restless legs syndrome. European Neurology. 2000;43(2):70-5. PMID 10686463.
76. Sloand JA, Shelly MA, Feigin A, et al. A double-blind, placebo-controlled trial of intravenous iron dextran therapy in patients with ESRD and restless legs syndrome. American Journal of Kidney Diseases. 2004 Apr;43(4):663-70. PMID 15042543.
77. Thorp ML, Morris CD, Bagby SP. A crossover study of gabapentin in treatment of restless legs syndrome among hemodialysis patients. American Journal of Kidney Diseases. 2001 Jul;38(1):104-8. PMID 11431189.
78. Walters AS, Wagner ML, Hening WA, et al. Successful treatment of the idiopathic restless legs syndrome in a randomized double-blind trial of oxycodone versus placebo. Sleep. 1993 Jun;16(4):327-32. PMID 8341893.

Acronyms and Abbreviations

AE	adverse effect
AHRQ	Agency for Healthcare Research and Quality
CER	comparative effectiveness review
CGI	clinician-assessed global impression
CI	confidence interval
ESRD	end-stage renal disease
FDA	Food and Drug Administration
GABA	Gamma-aminobutyric acid
ICTRP	International Controlled Trials Registry Platform
IRLS	International RLS symptom scale
MOS	Medical Outcomes Study Sleep Problem Index
NIH	National Institutes of Health
PGI	patient-assessed global impression
PLM	periodic limb movements
RCT	randomized controlled trials
RLS	Restless leg syndrome
RR	risk ratios
SMD	standardized mean difference
TEP	technical expert panel
WMD	weighted mean difference