Effective Health Care Program

Comparative Effectiveness Review
Number 86

Treatment for Restless Legs Syndrome

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Comparative Effectiveness Review

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Treatment for Restless Legs Syndrome

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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 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 are essential to the Effective Health Care Program. Please visit the Web site (www.effectivehealthcare.ahrq.gov) to see draft research questions and reports or to join an email 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 email to epc@ahrq.hhs.gov.

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Treatment 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 pharmacologic and nonpharmacologic treatments for RLS.

Data sources. We searched bibliographic databases MEDLINE (via OVID), Embase, and Natural Standards through June 2012.

Review methods. Eligible efficacy studies included randomized controlled trials (RCTs) of individuals with RLS published in English that lasted at least 4 weeks and compared pharmacologic and/or nonpharmacologic treatments with placebo or active treatment. 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) treatment adverse effects and withdrawals.

Results. Of the 53 studies included, one active comparator and 33 placebo-controlled RCTs provided efficacy and harms data, and 18 observational studies assessed long-term harms and adherence. RCTs were typically small and of short duration, and enrolled adult subjects with severe primary RLS of long duration. Placebo-controlled RCTs (18 trials) demonstrated that dopamine agonists (pramipexole, rotigotine, ropinirole, and cabergoline) increased the percentage of subjects who had a clinically important response defined as $\geq$50 percent reduction from baseline in mean International RLS symptom scale scores (IRLS responders) (risk ratio [RR]=1.60; [95% confidence interval [CI]: 1.38 to 1.86], k=7), improved RLS symptom scores, 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=-0.37; [95% CI: -0.48 to -0.27], k=9). Dopamine agonists resulted in more patients who experienced at least one adverse event (high-strength evidence for all outcomes). Long-term augmentation (drug-induced worsening of symptoms) and treatment withdrawal were common. Alpha-2-delta ligands (gabapentin enacarbil, gabapentin, and pregabalin) increased the number of IRLS responders (RR=1.66; [95% CI: 1.33 to 2.09], k=3, high strength of evidence) and mean change in IRLS symptom scores (k=3, high strength of evidence). Intravenous ferric carboxymaltose reduced IRLS symptom scale scores versus placebo (k=1, moderate strength of evidence). Four studies assessed nonpharmacologic interventions. Compression stockings but not the botanical extract valerian improved IRLS symptom scale 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 (low-strength evidence). Near-infrared light treatment improved IRLS symptom scores more than sham (low-strength evidence). Two trials compared active treatments. In one small crossover trial, pramipexole and levodopa/benserazide resulted in similar improvements in IRLS scores (low-strength evidence). Cabergoline improved IRLS scores and resulted in less augmentation than levodopa (moderate-strength evidence). Iron improved symptoms in adults with iron deficiency (k=2) (low-strength evidence). No studies enrolled pregnant women,

children, or those with end-stage renal disease. Withdrawal from mostly dopamine agonist and levodopa treatment at 1 year or more ranged from 13 to 57 percent. Treatment withdrawals were due to lack of efficacy (6% to 37%) as well as augmentation and other adverse events.

Conclusion. Compared to placebo, dopamine agonists and alpha-2-delta ligands reduce RLS symptoms and improve patient-reported sleep outcomes and disease-specific quality of life. Adverse effects of pharmacologic therapies and long-term treatment withdrawals due to adverse effects or lack of efficacy are common. Long-term effectiveness as well as applicability for adults with milder or less frequent RLS symptoms, individuals with secondary RLS, and children is unknown.

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Executive Summary

Introduction

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

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

RLS varies in symptom severity and frequency. Mild RLS may cause minor annoyance, but severe RLS can interfere with work, social activities, function, and emotional well-being. RLS-induced 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 1.5 percent to 7.4 percent in adults.[4] The variation reflects different approaches to diagnosing RLS and defining its frequency and severity, and the fact that many RLS questionnaires do not account for individuals who have conditions with similar symptoms. A telephone survey of U.S. adults who answered questions about RLS defined as "symptoms occurring at least twice weekly with moderate to severe impact" found prevalence to be 1.5 percent.[2]

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

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

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

(pramipexole, ropinirole, and rotigotine) and one calcium channel (alpha-2-delta) ligands (gabapentin enacarbil) are FDA approved for treatment of moderate to severe RLS.

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

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

Scope and Key Questions

Scope of the Review

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

Key Questions

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

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

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

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

a. What are the harms from RLS treatments when compared with placebo or no treatment?
b. What are the harms from RLS treatments when compared with other active treatments?
c. What are the long-term harms from treatment?

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

Methods

Literature Search Strategy

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

Inclusion and Exclusion Criteria

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

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

Study Selection

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

exclusion reason at the full-text screening stage. The excluded articles and the reasons for exclusion are listed in Appendix B in the full report.

Data Extraction

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

- Study characteristics, including design (e.g. parallel or crossover, long-term extension studies), eligibility criteria, duration, setting, funding source, blinding, intention-to-treat analysis, reporting of dropouts/attrition
- Patient characteristics, including age, race, sex, comorbidities, RLS diagnostic criteria, previous RLS medication history, duration of RLS (time since diagnosis), baseline RLS symptom severity and frequency, iron, pregnancy, and end-stage renal disease status
- Intervention/comparator characteristics, including type, dosage, titration, and washout period (for crossover trials)
- Outcomes, including International Restless Legs Syndrome Study Group (IRLS) Rating Scale responders defined as "patients with ≥50 percent reduction in IRLS scale score" (our primary outcome), mean change in IRLS scale score from baseline, percentage of patients with complete remission, percentage of patients reporting "much improved" or "very much improved" on clinicianassessed global impressions (CGI) or patient assessed global impressions (PGI) scales, RLS quality of life, patient-reported sleep quality, number of individuals experiencing adverse effects, dropouts, dropouts due to adverse effects, treatment discontinuation due to adverse effects, specific adverse effects, and augmentation

Risk of Bias of Individual Studies

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

Data Synthesis

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

Strength of the Body of Evidence

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

Applicability

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

Results

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

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

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

Key Points

- RCT results were limited to short-term efficacy studies versus placebo or usual care (≤6 months).
- Compared with placebo, dopamine agonists (ropinirole, pramipexole, and rotigotine) increased the percentage of patients with a clinically important response (≥50% reduction in IRLS symptom scale scores or who were improved or much improved on patient or clinician-reported global impressions scale), reduced RLS symptoms, and improved disease-specific quality of life and patient-reported sleep outcomes (high-strength evidence).
- Alpha-2-delta ligands (gabapentin enacarbil, and pregabalin) increased the percentage of patients with a clinically important response (≥50% reduction in IRLS), improved clinician-reported global impressions (high-strength evidence), disease-specific quality of

life and other patient-reported sleep outcomes compared with placebo (low-strength evidence). Gabapentin enacarbil improved sleep adequacy based on the medical outcome scale (MOS)-sleep adequacy domain (high-strength evidence).

- We found no clear evidence of a dose effect for the outcomes of IRLS responders or mean change in IRLS scale scores for either dopamine agonists or alpha-2-delta ligands.
- There is limited indirect comparison evidence that the effect on clinically important response may vary somewhat by specific type of dopamine agonist or alpha-2-delta ligand.
- Intravenous ferric carboxymaltose slightly improved IRLS symptom scale scores and disease-specific quality of life compared to placebo[15] (moderate-strength evidence) and improved patient-reported sleep outcomes (low-strength evidence) in patients without iron deficiency.
- No eligible studies assessed opioids, sedative hypnotics, or tramadol, though these are used clinically for RLS treatment.
- One small crossover trial found no significant improvement in IRLS scores with dopamine agonist pramipexole treatment compared with dual release levodopa/benserazide therapy (low-strength evidence).[16] One study[17] found that the dopamine agonist cabergoline improved scores on the IRLS symptom scale and RLS quality of life scale more than levodopa (moderate-strength evidence).
- Four small RCTs[18-21] addressed nonpharmacologic interventions. Pneumatic compression devices[18] reduced IRLS symptom scale scores more than sham (moderate-strength evidence). Near-infrared light treatment improved IRLS symptom scores more than sham (low-strength evidence).[21] Strength training and treadmill walking[19] improved IRLS symptoms, but adherence was poor (low-strength evidence). The botanical extract valerian[20] was not effective (low-strength evidence).
- Applicability to broader populations may be limited because studies enrolled middle-aged adults who were not pregnant and primarily white and who had few comorbidities and RLS symptoms that were long term, frequent, and high-moderate to very severe.
- Observational studies and long-term open-label followup from RCTs of pharmacologic interventions found that treatment withdrawal due to lack of efficacy at 1 year or more ranged from 6 to 32 percent.

Dopamine Agonists

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

Only two placebo-controlled trials lasted 24 weeks or more,[26,34] and none exceeded 28 weeks. The mean age of participants was 55 years, and women constituted 65 percent (range 55

to 74) of randomized participants. The majority of participants in the seven trials who reported race/ethnicity were white.[23,24,25,28,32,34,37]

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

On average, more than half (60%) of patients in the rotigotine trials had received previous RLS treatment, versus 26 percent and 44 percent, respectively, for pramipexole and ropinirole. Seven trials excluded patients with augmentation/end-of-dose rebound during previous RLS treatment. Study drugs were given orally on a daily (rather than as needed) basis, with the exception of rotigotine, which was delivered transdermally each day. Most studies used flexible up-titration based on symptom response and adverse effects, with doses ranging from 0.125 to 0.75 mg/day for pramipexole, 0.25 to 4 mg/day for ropinirole, and 1 to 3 mg/day for rotigotine. Four studies investigated multiple fixed doses of the drug in separate study arms.[25,34,37,39]

IRLS Responders (≥50% Score Reduction)

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

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

Responders on Clinician- and Patient-Rated Global Impressions Scale

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

IRLS-Mean Change From Baseline

Treatment with dopamine agonists resulted in a small reduction in symptom severity based on change in IRLS scale scores; the weighted mean difference (WMD) in pooled IRLS scores between treatment and placebo was -4.56 (95% CI, -5.42 to -3.70). The magnitude of reduction in IRLS scale scores was greater in studies of rotigotine[25,31,34,39] (-6.09 [95% CI, -7.71 to -4.46]) (k=4, n=585) than in studies of pramipexole[24,26,28,32,37] (-4.76 [95% CI, -6.24 to -3.28]) (k=5,

n=1,587) or ropinirole[23,27,35] (-3.49 [95% CI, -4.44 to -2.54]) (k=4, n=1,517) (p=0.02 for interaction). We found no clear evidence of a dose effect in the three fixed-dose studies of rotigotine or pramipexole that used different doses in separate arms.[25,34,37] The overall strength of evidence was high. Cabergoline[17] improved IRLS scores more than levodopa in a single trial lasting 30 weeks (n=361) among adults with severe IRLS symptoms (mean IRLS score=25.7) (WMD=-7.0 [95% CI, -9.1 to -4.9]) (moderate strength of evidence).

Quality of Life and Patient-Reported Sleep Outcomes

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

Alpha-2-Delta Ligands

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

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

evidence). In the maintenance trial, patients continuing gabapentin enacarbil therapy were significantly less likely to experience relapse (defined as an increase by ≥6 points from randomization to an IRLS score ≥15 points and a rating of much worse or very much worse on the CGI) than patients allocated to placebo, 9 percent and 23 percent, respectively (RR=0.41 [95% CI, 0.20 to 0.85]).[41]

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

Nonpharmacologic Therapies

Four small, short-term studies assessed nonpharmacologic therapies in adults with moderate to severe RLS.[18-21] A good quality RCT of pneumatic compression devices[18] worn for at least 1 hour each day for 4 weeks starting before the time of day when symptoms typically began found an improvement in IRLS symptom scale scores (p=0.006) and daytime somnolence (p=0.04) and complete resolution of symptoms more than sham devices (moderate strength of evidence). One low-quality RCT evaluated near-infrared light therapy compared with sham treatment. Twelve 30-minute near-infrared light treatment sessions were applied over 4 weeks. Near-infrared light treatment significantly improved IRLS symptom scores more than sham, -13.4 points versus -4.5 points, respectively, with a mean difference (MD) of -9.00 (95% CI=-13.21 to -4.79).[21] Treadmill walking and lower body resistance exercise performed three times weekly for 12 weeks improved IRLS scale scores (MD= -9.4 [95% CI =-13.9 to -4.9]) compared with usual care (moderate quality study and low- strength evidence).[19] However, results were reported only for 28 completers from 41 subjects enrolled. In a moderate-quality RCT of 48 adults with frequent and severe RLS symptoms, the botanical preparation valerian,[20] at 800 mg daily for 8 weeks, did not improve IRLS symptom scale scores more than placebo (p=0.69). The strength of evidence was low.

Comparative Effectiveness of RLS Treatment and Dose Response

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

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

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

a. What are the harms from RLS treatments when compared with placebo or no treatment?
b. What are the harms from RLS treatments when compared with other active treatments?
c. What are the long-term harms from treatment?

Key Points

- Study withdrawals (due to any reason) from RCTs were slightly less common with dopamine agonist treatments than with placebo (moderate-strength evidence).
- Study withdrawals due to adverse effects were more common with dopamine agonist treatment than with placebo (moderate-strength evidence). Differences between treatments were primarily due to an increase in withdrawals related to adverse effects (application site reactions) reported in three trials of transdermal rotigotine.
- More patients randomized to dopamine agonist had at least one adverse effect compared with placebo (high-strength evidence).
- Short-term adverse effects from treatment with dopamine agonists compared with placebo were nausea, vomiting, somnolence, and fatigue (high-strength evidence for all these outcomes).
- Application site reactions were much more common with transdermal rotigotine than with placebo (high-strength evidence).
- Study withdrawals (due to any reason) were less common in patients randomized to alpha-2-delta ligands than to placebo (high-strength evidence).
- Somnolence, unsteadiness or dizziness, and dry mouth were much more common with alpha-2-delta ligands than with placebo (high-strength evidence for all these outcomes).
- Incidences of diarrhea and blood phosphorus decrease were reported with intravenous iron therapy.
- No adverse events, except for a few cases of nausea, were reported in the trial evaluating bupropion.
- One small crossover trial reported higher incidences of augmentation and rebound (RLS symptoms in the early morning) with dual release levodopa/benserazide therapy versus pramipexole.
- Data from observation studies indicate that long-term augmentation ranged from 2.5 percent to 60 percent and varied markedly by type of dopamine agonist, followup time, study design, and method used to ascertain augmentation. We found no clear pattern to explain this variability.
- Withdrawal from mostly dopamine agonist and levodopa treatment was common, occurring in 13 percent to 57 percent of subjects due either to lack of efficacy or adverse effects. Most studies reported treatment withdrawals greater than 20 percent at 1 year.

Short-Term Harms

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

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

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

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

Three subjects each reported diarrhea (12.5%) and blood phosphorus decrease (12.5%) with intravenous iron therapy.[15] No subjects in the placebo arm reported these events. Two patients allocated to bupropion and one to placebo discontinued treatment due to nausea.[47] No other adverse events were reported.

Comparative Harms

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

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

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

Long-Term Harms and Withdrawal From Treatment

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

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

Key Points

- No RCTs examined the effect of patient or RLS characteristics on benefits and harms of treatments for primary RLS.
- No RCTs enrolled children or any women who were pregnant or recently postpartum, and nearly all specifically excluded these individuals.
- No eligible studies enrolled individuals with end-stage renal disease, and almost all specifically excluded these individuals.
- Two small randomized trials of iron therapy versus placebo in adults with iron deficiency provided low-strength evidence that iron may improve both the percentage of adults considered IRLS responders and the IRLS symptom scale scores.

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

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

Two small, good quality RCTs evaluated iron therapy (one intravenous and one oral) in patients with RLS secondary to iron deficiency.[66,67] One 12-week trial of 18 subjects found that compared with placebo, iron reduced IRLS scale scores by 9.16 points (95% CI,-15.2 to -3.1).[67] Another trial of intravenous iron sucrose (administered five times over 3 months to 60 subjects) found no difference versus placebo at 12 months in mean change in IRLS scale scores (p=0.47).[66] A post hoc analysis at 11 weeks found an increase in the percentage of subjects considered IRLS responders among those randomized to iron (RR=1.85; [95% CI, 1.07 to

3.18]).[66] By 12 months, 21 of 31 subjects (68%) in the placebo group and 9 of 29 (31%) in the iron group withdrew.[66] Of these, 19 and 5, respectively withdrew due to lack of efficacy. The strength of evidence for these outcomes was low.

Study Quality/Risk of Bias and Applicability

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

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

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

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

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

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

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

Outcome	Treatments	Number of Trials	n	Summary Statistics [95% CI]	Risk of Bias	Directness	Precision	Consistency	Evidence Rating
IRLS responders (≥50% score reduction)	All trials vs. placebo	3	503	RR 1.66 [1.33 to 2.09]	Low	Direct	Precise	Consistent	High
	Gabapentin enacarbil	1	321	RR 1.54 [1.18 to 2.01]	Low	Direct	Precise	Unknown	Moderate
	Pregabalin	2	182	RR 2.03 [1.33 to 3.11]	Low	Direct	Precise	Consistent	High
IRLS total score: mean change from baseline	All trials vs. placebo	3	475	WMD -4.26 [-5.75 to -2.77]	Low	Direct	Precise	Consistent	High
	Gabapentin enacarbil	2*	431	WMD -4.18 [-5.76 to -2.60]	Low	Direct	Precise	Consistent	High
	Pregabalin	1	44	WMD -4.90 [-9.41 to -0.39]	Low	Direct	Precise	Unknown	Moderate
Clinical global impressions: responders (much improved)	All trials vs. placebo	3	662	RR 1.60 [1.21 to 2.10]	Low	Direct	Precise	Consistent	High
	Gabapentin enacarbil	2**	538	RR 1.80 [1.51 to 2.14]	Low	Direct	Precise	Consistent	High
	Pregabalin	1	124	RR 1.14 [0.80 to 1.64]	Low	Direct	Imprecise	Unknown	Low
RLS quality of life	All trials vs. placebo	2	263	SMD 0.27 [-0.17 to 0.70]	Low	Direct	Imprecise	Inconsistent	Low
	Gabapentin enacarbil	1	220	SMD 0.42 [0.16 to 0.69]	Low	Direct	Precise	Unknown	Moderate
	Pregabalin	1	122	SMD -0.05 [-0.65 to 0.55] (300 mg dose)†	Low	Direct	Imprecise	Unknown	Low
Self-rated sleep MOS-sleep adequacy	*Gabapentin enacarbil*	2	431	SMD 0.53 [0.33 to 0.72]	Low	Direct	Precise	Consistent	High
Any study withdrawal	All trials vs. placebo	5	936	RR 0.71 [0.52 to 0.99]	Low	Direct	Precise	Consistent	High
	Gabapentin enacarbil	3	741	RR 0.70 [0.49 to 1.00]	Low	Direct	Precise	Consistent	High
	Pregabalin	2	195	RR 0.79 [0.37 to 1.68]	Low	Direct	Imprecise	Inconsistent	Low
Patients with ≥1 adverse event	All trials vs. placebo	5	933	RR 1.17 [0.1.00 to 1.36]	Low	Direct	Imprecise	Consistent	Moderate
	Gabapentin enacarbil	3	738	RR 1.09 [0.1.00 to 1.19]	Low	Direct	Precise	Consistent	High
	Pregabalin	2	195	RR 1.67 [0.74 to 3.80]	Low	Direct	Imprecise	Consistent	Moderate

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

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

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

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

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

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

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

Discussion

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

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

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

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

Only two RCTs directly compared pharmacologic options; specifically, cabergoline to levodopa, and pramipexole to dual-release levodopa/benserazide. We found no clear evidence of

a dose effect for the outcomes of IRLS responders and mean change in IRLS scale scores for either dopamine agonists (k=3) or the alpha-2-delta ligands (k=2). Because studies reported a large placebo response, we urge caution in using information from uncontrolled studies as the basis for increasing drug doses or altering administration timing if symptom response is inadequate. Similarly, we urge caution in attributing benefits that might be observed in clinical settings to dose adjustment.

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

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

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

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

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

Evaluating RLS treatments requires determining the change in scale scores that constitutes a minimum clinically important difference. These thresholds have not been established for the IRLS scale score and other scales commonly reported in RLS research. Further, high-quality research is needed to determine whether treatment benefits observed in short-term studies are

maintained, and whether the therapies are tolerated long term. The target populations for these drugs are patients with moderate to severe RLS, who may require daily treatment for decades. Even nonpharmacologic interventions and other treatments for those with milder symptoms are often long term. Yet, evidence is limited to short-term efficacy trials or observational studies among highly selected individuals.

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

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

Future Research Recommendations

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

Table D. Future research recommendations

Topical Issues	Specific Research Gaps	Recommendations
Limited evidence base	• Evidence base consists almost exclusively of pharmacologic treatments, and dopamine agonists in particular. • Many classes of drugs used in clinical practice such as opioids and sedative hypnotics have not been evaluated in clinical trials. • We found no evidence for effectiveness of therapies in specific subgroups such as children, older adults with multimorbidities, or individuals with secondary RLS.	• Randomized trials of nonpharmacologic treatments including herbal therapy, mind-body medicine, and manipulative treatments. • Randomized trials of classes of drugs other than dopamine agonists, such as opioids and sedative hypnotics. • Randomized trials of effectiveness of drugs in specific patient subgroups such as children, older adults, and individuals with secondary RLS.
Long-term durability of treatment benefits	• Long-term durability of treatment benefits remains unknown.	• High-quality, long-term, open-label extension studies from randomized trials that establish the time frame over which treatment benefits are sustained for different drugs and in specific group of patients.
Impact of patient characteristics on treatment outcomes	• We found no studies that address how patient characteristics, such as disease duration and previous therapy, affect treatment outcomes.	• Randomized trials that report effectiveness of treatments for subgroups of patients such as those with different disease duration, those new to treatment, and those for whom previous treatment failed.
Augmentation	• Augmentation is a significant harm with dopaminergic therapy and can lead to treatment discontinuation; yet, little is known about patient characteristics that may lead to augmentation.	• Long-term studies of augmentation with dopaminergic therapy. Potential study designs could include RCTs, prospective observational studies, and retrospective observational studies, including case-control studies.. • 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.

Table D. Future research recommendations (continued)

Methodological Issues	Findings	Research Needs
Severity of disease	• Clinical trials include patients with moderate to very severe disease typically by specifying a cut-off in IRLS scale score (IRLS score>15).	• Evaluate and report treatment effectiveness for RLS patients with different degrees of symptom severity. (e.g., categories of severity by IRLS scale scores: 1-10: mild; 11-20: moderate; 21-30: severe; 31-40: very severe).
Assessment of augmentation with dopaminergic therapy	• Considerable variation in reported prevalence of augmentation by type of drug, time frame of evaluation, and method of assessment.	• Assess augmentation with different dopaminergic drugs using standard criteria and methods of assessment.

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

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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.[1] 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 often 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. Severe restless legs syndrome, however, may require long-term treatment.[3]

RLS can result in reduced quality of life and negatively impact sleep leading to daytime fatigue. However, treatment effectiveness and harms are not well established and there is little guidance on diagnosis and treatment especially determining comparative effectiveness and whether treatments vary by key patient and disease characteristics. A comprehensive review of the effectiveness and harms of treatments for RLS could lead to improved care for individuals with RLS.

RLS is defined and diagnosed based solely on clinical criteria. The essential diagnostic criteria for RLS were established by the International Restless Legs Syndrome Study Group in 1995[1] and revised in 2003.[2] 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. These symptoms should not be solely accounted for by another condition such as leg cramps, positional discomfort, leg swelling or arthritis.

The etiology of RLS is unknown, but it may occur secondary to other conditions such as iron deficiency, end-stage renal disease, and pregnancy.[2] A family history of RLS is common and twin studies have shown heritability estimates of 54-83 percent. However, genome-wide association studies have shown inconsistent findings.[5] 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.[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 severity of RLS varies. Mild RLS may result in only minor annoyance; however, severe RLS can have a crippling impact on quality of life.[70] 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. Additional long-term complications from sleep disruption could include adverse cardiovascular events though little is known on the relationship between RLS sleep disruption and cardiovascular outcomes. Sleep deprivation and daytime fatigue are the most common reasons RLS patients seek treatment.[70]

Prevalence estimates for RLS range from 1.5 to 7.4 percent in adults, and are higher for women and older people.[4] The variation reflects different approaches to diagnosing RLS and defining its frequency and severity, and the fact that many RLS questionnaires do not account for individuals who have conditions with similar symptoms. (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 U.S. adults who responded to a telephone survey and answered questions about RLS fulfilled all four of the diagnostic criteria. Exclusion of secondary causes and mimic conditions (e.g. nocturnal leg cramps, periodic leg movements of sleep, positional discomfort, arthritis etc) 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 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. Because individuals who agree to answer survey questions about RLS are likely different from adults who do not agree to respond the prevalence and severity in a true population setting are not well known though likely lower and less severe. We draw attention to these distinctions because questions related to RLS prevalence, 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. Recommended nonpharmacological options include: exercise, avoiding potential RLS precipitants (caffeine, alcohol, antidepressants, and antihistamines); counter stimuli to sensory symptoms (hot or cold bath, limb massage, compression stockings, and 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, ropinirole, and rotigotine) and one alpha-2-delta ligand anticonvulsant drug (gabapentin enacarbil) 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).[7] Impulse control disorders have also been reported in up to 9-17 percent of RLS patients using these drugs for long term.[8]

The primary goal of RLS treatment is to manage symptoms and improve patient function, daytime fatigue 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 may not vary for primary and secondary forms of RLS.[6] For patients with RLS secondary to pregnancy, iron deficiency, or end-stage renal disease, recommendation advise treating 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.[9]

Table 1. Pharmacologic treatments for Restless Legs Syndrome

Treatment	Generic Name	U.S. Trade Name	Formulation/ Recommended Dosage*	FDA Approval for RLS
Dopaminergic agents	Carbidopa-levodopa	Sinemet®		
	Ropinirole	Requip®	Oral/ Initially 0.25 mg orally once daily, 1 to 3 hours before bedtime. Dosage can be increased to 0.5 mg once daily and to 1 mg once daily at the end of the first week of dosing to achieve efficacy (up to 4.0 mg total)	Yes
	Pramipexole	Mirapex®	Oral/ Initially 0.125 mg taken once daily 2-3 hours before bedtime. Dosage may be increased every 4-7 days up to 0.25 or 0.5 mg once daily if needed.	Yes
	Rotigotine	Neupro®	Transdermal patch/ Initially 1 mg patch applied once daily. Dosage can be increased as needed by 1 mg/24 hours at weekly intervals, up to 3 mg once daily	Yes
Anticonvulsants (alpha-2-delta ligands)	Gabapentin enacarbil	Horizant®	Oral/ 600 mg once daily with food around 5 PM	Yes
	Gabapentin	Neurontin®		
	Pregabalin	Lyrica®		
Sedative-hypnotics	Clonazepam	Rivotril®		
	Temazepam	Restoril®		
	Oxazepam	Serax®		
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	Many formulations			

FDA = Food and Drug Administration; RLS = restless legs syndrome
*For FDA approved drugs.

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).[71] 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 Syndrome Study Group (IRLS) Rating Scale is most widely reported.[72] The IRLS is a 10-item scale with scores ranging from 0 (no

symptoms) to 40. Scores >30 are considered very severe, severe (Score 21-30), moderate (scores 11-20) and ≤10, 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) percentage of patients with reduction of symptoms from very severe (>30) or severe (21–30) to moderate (11–20) to mild (≤10); (3) 50 percent or greater change in IRLS score from baseline; or (4) percentage 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 Restless Legs Syndrome Study Group (IRLS) Rating Scale[72]	• Intensity (5 items) • Frequency (1 item) • Consequences of RLS (4 questions on sleep quality, daytime tiredness, mood, and quality of life)	• 10-item scale. Each item rated on a 5-point scale (0=no symptoms, 4=severe/frequent symptoms) • Scores combined to give global assessment • 0: No RLS; 1-10: mild RLS; 11-20: moderate RLS; 21-30: severe RLS; 31-40: very severe RLS • Assessed by patient and investigator
Severity of disease and therapeutic effects	Clinical global impressions (CGI)[71]	• 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 not combined; often just one component of the scale (e.g. Improvement) is assessed by clinician
Quality of life	Restless Legs Syndrome Quality of Life Instrument (RLS-QLI) [71]	• 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 (RLS-QoL)[71]	• Daily function (8 items) • Social activities and travel arrangements (2 items) • Morning activities and concentration (5 items) • Sleep and sexual activity (3 items)	• 18 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

Table 2. Methods of assessment (continued)

Domain	Scale	Components of Scale	Attributes
Patient-reported day time sleepiness and sleep quality	Epworth Sleepiness Scale [73]	• Daytime sleepiness	• 8-item, 4-point questionnaire measuring daytime somnolence. • A score greater than 10 is characterized as "sleepy"; greater than 18 considered "very sleepy"
	Medical Outcomes Study Sleep Scale[74] (MOS-SPI-I or II)	• Sleep initiation • Maintenance • Quality • Quantity • Adequacy • Daytime somnolence	• 12 items that measure multiple aspects of sleep
	Pittsburgh Sleep Quality Index[75]	• 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 total score >5 indicates poor sleep quality
Augmentation	Augmentation Severity Rating Scale (ASRS)[76]	NA	• 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:

- **Impact of diagnostic criteria and distinguishing RLS from other disorders:** RLS is diagnosed based on clinical history using standard criteria. "Mimic" conditions (e.g. nocturnal leg cramps, periodic leg movements of sleep, positional discomfort, arthritis etc) 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 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).[77] RLS is distinct from sleep disorders such as periodic limb movements disorder.

  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.[68]
- **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-typically severe to very severe restless leg symptoms and/or associated sleep disturbance and daytime fatigue.[6,78] For the larger group of individuals with mild or moderate symptoms, determining the balance of treatment effectiveness with harms is more problematic. In addition, long-term risks and benefits of treatment are unclear. For older adults with multiple morbidities or children 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 legs syndrome.[6] However, little is known about the scientific validity of such an approach, the role of patient or disease characteristics in treatment selection or the comparative effectiveness and harms of currently recommended treatment options. Finally, most research has focused on pharmacologic interventions though nonpharmacologic options are widely used and recommended especially for individuals with mild symptoms, comorbid conditions or those failing pharmacologic options.

- **Measuring changes in disease status and impact of treatment** Lack of objective measures for assessing disease status presents a challenge in clinical practice.[71] 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 IRLS Rating Scale and Clinical Global Impressions scale.[71] However, the results of RLS severity scales cannot be meaningfully interpreted in the absence of clearly defined "minimum clinically important differences."
- **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, including the impact of leg symptoms and sleep disorders, on cardiovascular health is important. Furthermore there are little data on pharmacologic intervention adverse effects in patients older adults, those with multiple comorbidities (especially end stage kidney disease) and women either pregnant or potentially becoming pregnant as these individuals are often specifically excluded from studies.

Scope and Key Questions

Scope of the Review

We evaluated the efficacy, safety, and comparative effectiveness of pharmacologic and nonpharmacologic treatments for RLS. Pharmacologic interventions included drugs approved for use (for any condition) in the United States. We included individuals with RLS regardless of age or etiology. Although many patients with RLS also experience semi-rhythmic limb movements called 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. 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 and duration, prior treatment status, comorbidities, etiology (i.e., primary or secondary RLS), iron status, pregnancy, and end-stage renal disease.

Interventions

- Pharmacologic treatments (e.g. dopaminergic agents, anticonvulsant calcium channel alpha-2-delta) ligands, sedative-hypnotics, opioids, and iron supplementation)
- Nonpharmacological treatments (e.g. 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 IRLS symptom scale score from baseline ("IRLS scale responders" or remission of symptoms (IRLS score=0).

Secondary Otcomes

Mean change in symptom severity and impact assessed using the IRLS rating scale. Proportion of patients reporting "improved or much improved" on clinician assessed global impressions (CGI scale score) or patient assessed global impressions (PGI scale score); quality of life as measured by disease-specific scale (e.g., Restless Legs Syndrome 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)?

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

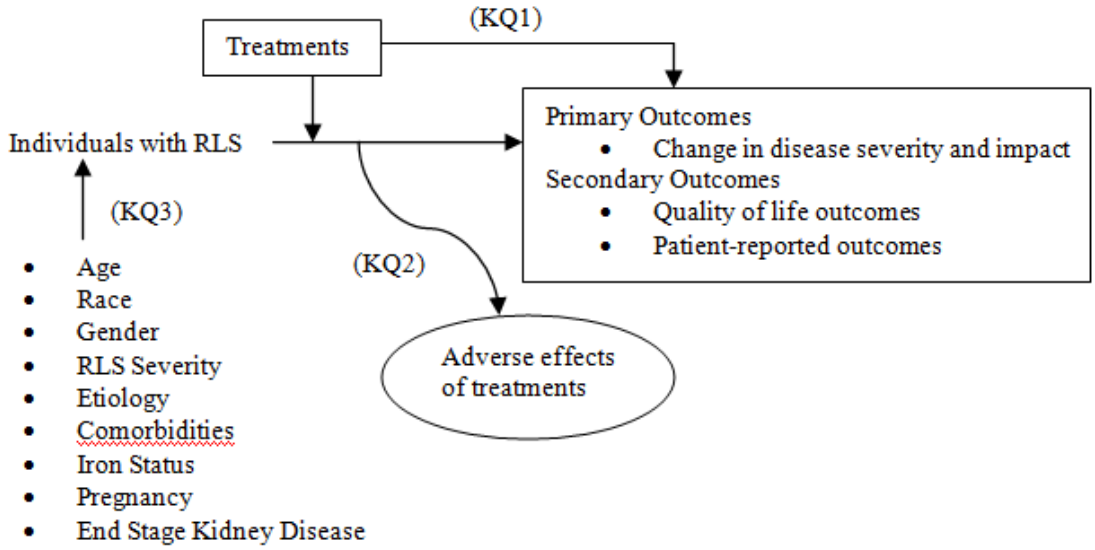
Key Question 2. What are the harms from RLS treatments?

a. What are the harms from RLS treatments when compared with placebo or no treatment?
b. What are the harms from RLS treatments when compared with other active treatments?
c. What are the long-term harms from treatment?

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

The analytical framework for our Key Questions is shown in Figure 1.

Figure 1. Analytical framework



KQ = Key Question; RLS = restless legs syndrome

Methods

We conducted the comparative effectiveness review (CER) of treatments for restless legs syndrome (RLS) following the methods suggested in the Agency for Healthcare Research and Quality (AHRQ) Methods Guide for Effectiveness and Comparative Effectiveness Reviews (www.effectivehealthcare.ahrq.gov/methodsguide.cfm). The main subsections in this section reflect the elements of the protocol publicly posted on the AHRQ Effective Health Care program Web site, and they correspond to the PRISMA checklist.[79] 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 through June 2012 for randomized controlled trials (RCTs) evaluating treatment efficacy and for observational studies (including open-label extensions of RCTs) reporting adverse effects and long-term adherence to RLS treatments. The search algorithm, developed with input from a biomedical librarian and independently reviewed by another librarian, consisted of a combination of search strings that described the condition and search filters designed to retrieve relevant RCTs and observational studies (Appendix A). To identify completed trials and to check for publication bias, we searched Cochrane Central, the International Controlled Trials Registry Platform (ICTRP), Clinicaltrials.gov, FDA Web sites, and the NIH RePORTer. We included other eligible unidentified trials referred by peer reviewers.

Inclusion and Exclusion Criteria

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

We included observational studies and open-label followup extensions of RCTs reporting long-term (>6 months) adverse effects and adherence. Pharmacologic interventions were limited to drugs approved for use (for any condition) in the United States. Specific eligibility criteria are listed in Table 3.

Table 3. Inclusion criteria

Domain	Criteria for Inclusion
Population	• Individuals diagnosed with RLS using RLS diagnostic criteria
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 using reported, validated RLS symptom or quality of life scale scores, clinician and patient global impressions scale scores, or measures of sleep quality.
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 June 2012
Language	• English

RCT = randomized controlled trial; RLS = restless legs syndrome

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

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

- Study characteristics including design (e.g. parallel or crossover, long-term extension studies), eligibility criteria, duration, setting, funding source, blinding, intention-to-treat analysis, reporting of dropouts/attrition
- Patient characteristics including age, race, sex, comorbidities, RLS diagnostic criteria, previous RLS medication history, duration of RLS (time since diagnosis), baseline RLS symptom severity and frequency, iron, pregnancy, and end-stage renal disease status
- Intervention/comparator characteristics including type, dosage, titration, and washout period (for crossover trials)
- Outcomes, including International Restless Legs Syndrome (IRLS) responders defined as "patients with ≥50 percent reduction in IRLS scale score" (our primary outcome), mean change in IRLS scale score from baseline, percentage of patients with complete remission, percentage of patients reporting "much improved" or "very much improved" on clinician-assessed global impressions (CGI) or patient-assessed global impressions (PGI) scales, RLS quality of life, patient-reported sleep quality, number of individuals

experiencing adverse effects, dropouts, dropouts due to adverse effects, treatment discontinuation due to adverse effects, specific adverse effects, and augmentation

Risk of Bias of Individual Studies

We assessed risk of bias of RCTs using the Cochrane risk of bias tool.[11] We addressed: (1) allocation concealment, (2) blinding methods (participant, investigator, and/or outcome assessor), (3) how incomplete data were addressed, (4) intention-to-treat principle, and (5) whether reasons for dropouts/attrition were reported. 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 that included similar populations, interventions, and outcomes and that presented sufficient data, we calculated pooled random-effects estimates of overall effect size, weighted mean differences (WMDs), or risk ratios (RRs). We used Review Manager 5.1 to pool and analyze the data.[12] We calculated risk ratios (RR) for dichotomous outcomes and WMD or standardized mean differences (SMDs) for continuous outcomes using a random-effects model. We assessed statistical heterogeneity between trials and for subgroups of drugs using the I^2 test and observation of the direction of the effect of the studies. A score of approximately 50 percent and if the effect sizes do not fall on the same side of "no effect" suggests substantial heterogeneity. For the fixed-dose trials, we analyzed only the doses recommended for current clinical practice if possible. Publication bias was assessed through inspection of funnel plots and the Egger intercept test.[80]

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[13] 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 CGI or 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

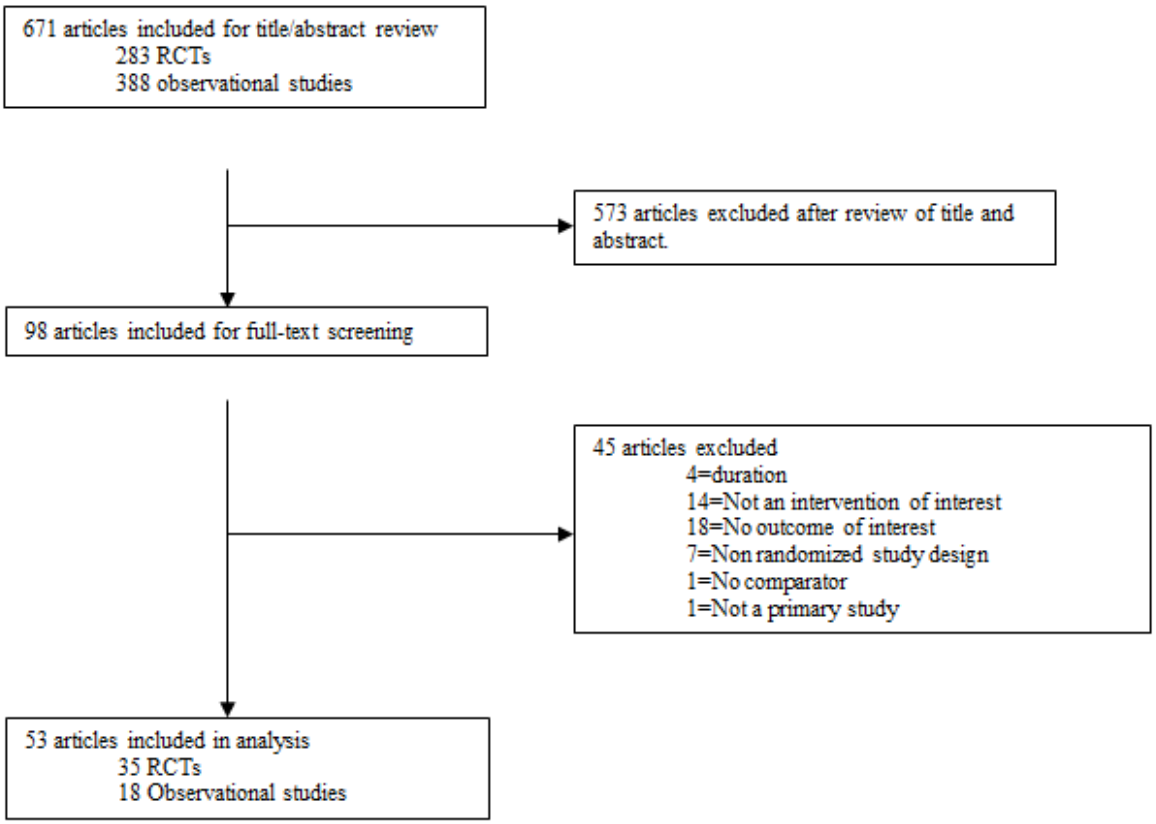
We assessed applicability separately from strength of evidence based on the following criteria: eligibility requirements used to select patient populations; characteristics of population enrolled such as demographics, baseline RLS severity, duration and etiology (primary or secondary) of RLS, history of previous therapy, and the length of followup.[14] 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 138 potentially relevant publications. Full-text screening resulted in 53 studies that fulfilled eligibility criteria and were included: of these 33 were randomized controlled trials (RCTs) (31 placebo or usual care controlled) and 18 were observational studies (including open-label extensions of included RCTs) that reported long-term treatment withdrawals, reasons for withdrawals, or percentage of patients developing augmentation. All RCTs that examined pharmacologic treatments were industry sponsored.

Figure 2. Flow diagram of search strategy



RCT = randomized controlled trial

Description of Included Studies

Of the 53 studies included[17-20,22-37,42-44,48-59,61-67,81,82], 33 placebo-controlled RCTs[15,18-44,46,47,66,67,82] and two [16,17] direct comparison RCTs provided efficacy and harms data, and 18 observational studies[48-59,61-65,81] contributed data on long-term harms (Appendix F). Of the 33 RCTs included, 31 evaluated pharmacological treatments[15-17,22-30,32-44,46,47,58,66,67,82] and three evaluated nonpharmacologic treatments.[18-20] Pharmaceutical agents evaluated were dopamine agonists (19),[17,22-30,32-39,58] alpha-2-delta ligands (7),[40,42-44,46,82] and iron therapy (2).[66,67] Dopamine agonists evaluated were ropinirole (7),[22,23,27,29,35,36,38] pramipexole (5),[24,26,28,32,37] rotigotine (4),[25,31,34,39] and cabergoline (3).[17,30,33] Anticonvulsant alpha-2-delta ligands were prodrug gabapentin enacarbil (3),[40,41,43,82] pre-gabalin (2),[42,44] or gabapentin.[43] Miscellaneous pharmacologic treatments included intravenous iron[15] and antidepressant bupropion.[47] Nonpharmacologic studies evaluated exercise (1),[19] near-infrared light (1),[21] a botanical extract of the herb valerian (1),[20] and a pneumatic compression device (1).[18] Except for the two small trials of iron therapy[66,67] and the three trials evaluating nonpharmacologic treatments[18-20], 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 taking restless legs syndrome (RLS) drugs and or had adverse events or failure to respond. Studies did not report comorbidities. Most studies required an International Restless Legs Syndrome (IRLS) scale score of $\geq$15 (at least "high moderate" severity) and frequent symptoms (>2 to 3 times/week) for a prolonged period. Three studies[27,34,35] enrolled patients with IRLS scale scores of >20 (severe or very severe). One small study (n=22)[42] 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 is little used, 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 16 studies of dopamine agonists and six studies of anticonvulsant alpha-2-delta ligands.

Study Quality and Publication Bias

We report our assessment of individual study trial quality in Appendix D. 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.[19] 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.[31,34] 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 F)

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

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

Key Points

- RCT results were limited to short-term efficacy studies versus placebo or usual care (≤6 months).
- Compared to placebo, dopamine agonists (ropinirole, pramipexole, and rotigotine) increased the percent of patients with a clinically important response (≥50% reduction in IRLS symptom scale scores or who were "improved" or "much improved" on patient or clinician-reported global impressions scale), reduced RLS symptoms, and improved disease-specific quality of life and patient-reported sleep outcomes (high-strength evidence).
- Alpha-2-delta ligands, gabapentin enacarbil, and pregabalin, increased the percentage of patients with a clinically important response (≥50% reduction in IRLS), improved clinician-reported global impressions (high-strength evidence), disease-specific quality of life and other patient-reported sleep outcomes compared to placebo (low-strength evidence). Gabapentin enacarbil improved sleep adequacy based on the medical outcome scale (MOS)-sleep adequacy domain (high-strength evidence).
- We found no clear evidence of a dose effect for the outcomes of IRLS responders or mean change in IRLS scale scores for either dopamine agonists or alpha-2-delta ligands.
- There is limited indirect comparison evidence that the effect on clinically important response may vary somewhat by specific type of dopamine agonist or alpha-2-delta ligand.
- Intravenous ferric carboxymaltose slightly improved IRLS symptom scale scores and disease-specific quality of life compared to placebo (moderate-strength evidence) and improved patient-reported sleep outcomes (low-strength evidence) in patients without iron deficiency.[15]
- No eligible studies assessed opioids, sedative hypnotics, or tramadol, though these are used clinically for RLS treatment.
- One small crossover trial found no significant improvement in IRLS scores with dopamine agonist pramipexole treatment compared to dual release levodopa/benserazide therapy (low-strength evidence).[16] One study[17] found that the dopamine agonist cabergoline improved scores on the IRLS symptom scale and RLS quality of life scale more than Levodopa (moderate-strength evidence).
- Four small RCTs[18-21] addressed nonpharmacologic interventions. Pneumatic compression devices[18] reduced IRLS symptom scale scores more than sham (moderate-strength evidence). Near-infrared light treatment improved IRLS symptom scores more than sham

(low-strength evidence).[21] Strength training and treadmill walking[19] improved IRLS symptoms but adherence was poor (low-strength evidence). The botanical extract valerian[20] was not effective (low-strength evidence).

- Applicability to broader populations may be limited because studies enrolled middle-aged adults who were nonpregnant and primarily white and who had few comorbidities and RLS symptoms that were long term, frequent, and high-moderate to very severe.
- Observational studies and long-term open-label followup from RCTs of pharmacologic interventions found that treatment withdrawal due to lack of efficacy at 1 year or more ranged from 6 to 32 percent.

Dopamine Agonists

Efficacy of dopamine agonists was evaluated in 18 randomized, double-blind, placebo-controlled studies[22-38] and two comparative effectiveness studies.[16,17] Two of the placebo-controlled studies[30,33] and the only comparative effectiveness trial assessed the dopaminergic analog cabergoline[17] which is not FDA approved for treatment of RLS and is rarely used in the United States. We do not include outcomes or characteristics of the two cabergoline placebo controlled studies [30,33]. We do describe the findings of the comparative effectiveness trial of cabergoline versus levodopa because the primary intent of this report is a comparative effectiveness review.[17]

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

Two additional randomized trials assessed cabergoline. 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=25.1). RLS duration varied with a mean of 17 years for ropinirole to 2 years for rotigotine trials. Trials enrolled newly diagnosed and not previously treated patients and those who had received prior RLS treatments. On average, over one half (60%) of patients in the rotigotine trials had received previous RLS treatment, versus 26 percent and 44 percent respectively for pramipexole and ropinirole. Seven trials excluded patients with augmentation/end-of-dose rebound during previous RLS treatment. Study drugs were given orally on a daily (rather than "as needed") basis, with the exception of rotigotine, which was delivered transdermally each day. Most studies used flexible up-titration, 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. Four 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=21.2 weeks), (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%). There was evidence of incomplete outcome reporting (Table 4). All 16 studies reported on mean change from baseline in the IRLS total score. Thirteen studies provided data sufficient

for pooling. The second most frequently reported outcome was the Clinical Global Impressions scale score (CGI) (k=14). 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% reduction in IRLS scale scores, Table 7) was reported in only six studies, none of which assessed ropinirole.

IRLS Responders (≥50% Score Reduction) (Table 7)

Seven trials (three pramipexole trials, n=1007,[28,32,37] and four rotigotine trials, n=1139[25,31,34,39]) 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 (risk ratio [RR]=1.60; [95% confidence interval {CI}, 1.38 to 1.86]). The absolute effect in terms of responders per 100 patients was 24 more (95% CI, 15 more to 35 more) in the dopamine agonist treatment group than with placebo (high strength evidence). Results suggested some effect heterogeneity between drugs (I^2=53.1%, p=0.14), with a larger effect seen in studies involving rotigotine (RR=1.76; [95% CI, 1.47 to 2.10], 25 more responders per 100 patients) than in studies of pramipexole (RR=1.46; [95% 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 three studies of rotigotine that assessed the effect of different doses on IRLS responders.(Appendix F) Doses ranged from 0.5 mg per day to 4.0 mg per day. In the study by Hening,[25] 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% 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% CI, 0.92 to 1.78]). The study by Oertel[39] evaluated five doses, ranging from 0.5 mg to 4.0 mg per day. The results versus placebo were statistically significant for the 2.0 and 3.0 mg per day doses but 95% confidence intervals were also wide and overlapped across doses used. The largest effect was seen in the 3.0 mg per day dose (RR=1.66; [95% CI, 1.16 to 2.37]). The study by Trenkwalder[34] 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-Assessed Global Impressions Scale (Figures 4 and 5, Table 8)

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 1.45; [95% CI, 1.36 to 1.55] (k=15, n=4446) and 1.66; [95% CI, 1.45 to 1.90] (k=6, 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 impressions (CGI) outcomes (I^2=51.5%, p=0.13), but not patient-assessed global impressions (PGI) outcomes (I^2=6.5%, p=0.30). Trials of pramipexole (k=5) demonstrated slightly larger effects on clinician-assessed global impressions scores (RR=1.61; [95% CI, 1.40 to 1.86]) than studies of either ropinirole (k=6) or rotigotine (k=4).

IRLS-Mean Change From Baseline (Figure 6)

Treatment with dopamine agonists resulted in a small reduction in symptom severity and impact compared to placebo based on change in IRLS scale scores; the weighted mean difference (WMD) in pooled IRLS score between treatment and placebo was -4.48; (95% CI, -5.36 to -3.60) (k=13, n=3578). We found near evidence of effect heterogeneity between drugs (I^2=62%, p=0.07). The magnitude of reduction in IRLS scale scores was slightly greater in studies of rotigotine[25,31,34,39] (-6.07; [95% CI, -8.33 to -3.81]) (k=4, n=1286) than in studies of pramipexole[24,26,28,32,37] (-4.76; [95% CI, -6.24 to -3.28]) (k=5, n=1587) or ropinirole[23,27,35] (-3.49; [95% CI, -4.44 to -2.54]) (k=5, n=1517). 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 [25,34,37] (Appendix F) 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 F)

Four studies reported on the number of individuals in whom RLS symptoms completely resolved (remitters).[22,25,31,34] 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=2.24; [95% CI, 1.49 to 3.35).[25,31,34] In a crossover study of ropinirole (n=44), eight of 22 (26.4%) individuals had remission on ropinirole versus no individuals receiving placebo.[22]

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=9, n=2140). The effect size is considered small to medium in magnitude (standard mean difference (SMD)=-0.37; [95% CI, -0.48 to -0.27]). Results were similar across studies of pramipexole (k=2), ropinirole (k=2) and rotigotine (k=4), and the I^2 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% 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).

Alpha-2-Delta Ligands

Efficacy of anticonvulsant drugs was evaluated in seven randomized, double-blind, placebo-controlled studies (n=1066)[40-45] (Tables 9 and 10). All studies involved alpha-2-delta ligands (prodrug gabapentin enacarbil, four trials; pregabalin, two trials, or gabapentin, one trial). Trials were short (one crossover trial of two 4-week intervals,[46] three 6-week trials,[43-45] and three 12-week trials.[40-42] The mean age of study participants was 51 years. Women constituted 61 percent (range of means 59 to 66) of all participants randomized In the four studies that reported race,[40,44-46] study participants were predominantly white All participants had primary RLS. Mean symptom severity at baseline was severe (mean IRLS scale score=24). Mean RLS duration was

12 years. All 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 Lee[40] used fixed doses of 600 and 1200 mg/day of gabapentin enacarbil and two trials used a fixed dose of 1200 mg/day of gabapentin enacarbil.[45,46] One maintenance trial had an initial 24-week single-blind period where all patients received gabapentin enacarbil, which was titrated up to 1200 mg.[41] Individuals (n=194) who at week 24 showed a response to treatment, defined as an IRLS score <15 that had decreased by ≥6 points compared to baseline and were rated "much improved" or "very much improved" on the CGI, were then randomized to continuing gabapentin enacarbil 1200 mg or placebo in a 12-week double-blind phase. A multi-arm trial of pregabalin versus placebo by Allen[42] assessed five different fixed doses that ranged from 50 mg per day to 450 mg per day.

IRLS Responders (≥50% Score Reduction) (Figure 9)

Three trials[40,42,44] (low risk of bias) evaluated IRLS responders. Alpha-2-delta ligands compared to placebo significantly increased the percentage of IRLS responders (RR=1.66; [95% CI, 1.33 to 2.09]).[40,42,44] The absolute effect in terms of responders per 100 patients was 25 more (95% CI, 12 more to 41 more). The strength of evidence was high. There was no clear evidence of dose effect based on IRLS responders or IRLS total scores in the studies by Lee[40] or Allen.[42] In the trial by Allen, a total of 137 subjects were enrolled across study arms and doses. While effect sizes increased with higher doses, confidence intervals were wide and overlapped across doses.

Responders on Clinician and Patient-Assessed Global Impressions Scale (Figures 10)

The proportion of patients who reported improved or very much improved on the CGI was significantly greater for the alpha-2-delta ligand group though there was evidence of heterogeneity between treatment subgroups (RR=1.60 [95% CI, 1.21 to 2.10]). Improvement was significant for gabapentin enacarbil therapy but not for pregabalin treatment (p=0.03 for interaction). In the crossover trial (not pooled) by Winkelman 74 percent of patients treated with gabapentin enacarbil were considered much improved or very much improved on the CGI compared to 36 percent of patients treated with placebo (p<0.001).[46]

IRLS-Mean Change From Baseline (Figure 11, Appendix F)

Gabapentin enacarbil[40,43,45] (k=2), pregabalin [42,44](k=2), and gabapentin (ref 33) reduced symptom severity compared to placebo. The pooled weighted mean change in IRLS score from baseline between alpha-2-delta ligands and placebo groups was -4.26; [95% CI, -5.75 to -2.77] (k=3). (WMD=-4.26; [95% CI, -5.75 to -2.77]). The crossover trial (not pooled) by Winkelman also found mean change in IRLS score from baseline significantly favored gabapentin enacarbil.[46] The mean treatment difference versus placebo was -6.6 points [95% CI, -8.6 to -4.6]. Strength of evidence was high. 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% 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%, p=0.14). The strength of evidence was moderate. In a maintenance trial, patients continuing gabapentin

enacarbil therapy were significantly less likely to experience relapse (defined as an increase by ≥6 points from randomization to a IRLS score ≥15 points and a rating of "much worse" or "very much worse" on the CGI) than patients allocated to placebo, 9 percent and 23 percent, respectively (RR=0.41; [95% CI, 0.20 to 0.85]).[41]

RLS Remitters

One multi-arm gabapentin enacarbil trial (n=325) reported the number of patients who achieved an IRLS score of zero points.[40] The percentages of remitters in the 600 and 1200 mg dose groups were 26 and 23 percent, respectively, compared to 12 percent in the placebo group. After pooling the two dose groups, the RR was 2.13 [95% CI, 1.17 to 3.89]. One pregabalin trial reported the number of patients who achieved an IRLS score of zero points (Garcia-Borreguero 2010 ref). There were nine remitters (30%) in the pregabalin group compared with four (14%) in the placebo group, a difference that was not statistically significant (RR=2.10; [95% CI, 0.73 to 6.06]).

RLS Relapse

Fewer patients maintained on gabapentin enacarbil compared to placebo experienced RLS relapse. Nine percent of patients randomized to gabapentin enacarbil experienced relapse, defined as an increase by ≥6 points from randomization to a IRLS score ≥15 points and a rating of "much worse" or "very much worse" on the CGI, compared to 23 percent of the placebo patients (RR=0.41; [95% CI, 0.20 to 0.85]).[41] Mean change from randomization in IRLS scores were also significantly smaller in the gabapentin enacarbil group (1.9 points) compared to placebo (3.9 points). The mean difference was -2.00 points [95% CI -3.91 to -0.09].

RLS Quality of Life

Two trials showed mixed results on quality of life measures (SMD=0.27 [95% CI, -0.17 to 0.70]) (low strength of evidence). [42,45] One fixed-dose study of pregabalin found no statistically significant improvement in the Johns Hopkins Restless Legs Syndrome Quality of Life questionnaire (RLS-QoL) with any dose versus placebo over a 6-week period (k=1, n=122).[42] The strength of evidence was low. Gabapentin enacarbil improved RLS-QoL scores at week 12 compared with placebo (mean [SD] change from baseline: gabapentin enacarbil, 21.4 [17.00]; placebo, 14.1 [17.32]; RLS treatment difference 7.8; $P < 0.0001$) (SMD=0.42 [95% CI, 0.16 to 0.69]).[45] The strength of evidence was moderate.

Patient-Reported Sleep Quality

All four studies provided information on self-rated sleep. All demonstrated a statistically significant improvement due to alpha-2-delta ligands versus placebo. However, variation in scales used and reporting methods precluded pooling all studies, and in some cases, precluded identifying the magnitude of effect. Four studies used the Medical Outcomes Scale, either the full nine-item Medical Outcome Study sleep problem indexes I or II

(MOS-SPI-I orII scale) or MOS-sleep adequacy,[40,43-45,83] In two trials,[40,45] treatment with gabapentin enacarbil significantly improved sleep adequacy based on the pooled MOS-sleep adequacy domain (SMD=0.53; [95% CI, 0.33 to 0.72], k=2). The magnitude of effect was considered moderate and strength of evidence was high. Self-rated daytime sleepiness using the Epworth Sleepiness Scale was not significantly different in one study reporting this outcome.[45]

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 11). Studies reported on gabapentin, "multiple opioids," methadone, levodopa, and the dopamine agonists 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. Withdrawal due to lack of efficacy occurred in 6 to 32 percent.

Miscellaneous Pharmacological and Nonpharmacological Therapies

Two miscellaneous pharmacological studies and four small, short-term studies assessed nonpharmacological therapies in adults with moderate to severe RLS (Table 12 and 13, Appendix E, and Appendix F). One small good quality short-term RCT (n=46)[15] found intravenous iron (ferric carboxymaltose) significantly improved IRLS symptom scale scores compared to placebo over 28 days of therapy. Mean improvements for iron and placebo were reductions of 8.9 and 4.0 points, respectively, with a mean difference of -4.90 [95% -9.27 to -0.53]. The strength of evidence was moderate. There were also significantly greater improvements in CGI, RLS-QoL, and sleep measures (MOS total score) versus placebo.

One small good quality RCT[47] evaluated the antidepressant bupropion. Mean change in IRLS symptom scores after 6 weeks compared to baseline were 10.4 points lower with bupropion compared 7.6 points lower with placebo, a non statistically significant difference (p=0.11). Strength of evidence was considered low.

A good quality RCT[18] 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 vs. 10.6 +/- 3.8; p=0.04) and complete resolution of symptoms (8 [38.1%] vs. 0 [0%]; 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_2O of air pressure with each inflation cycle, while sham devices generated a 3 to 4 cm H_2O 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. It is possible that blinding was inadequate as patients could have detected differences in compression due to air pressure from the intervention versus the sham devices.

One low quality RCT[21] of 34 patients evaluated near-infrared light treatment compared to sham treatment. Twelve 30-minute near-infrared light treatment sessions were applied over four

weeks. Near-infrared light treatment significantly improved IRLS symptom scores more than sham, -13.4 points versus -4.5 points, respectively, with a MD of -9.00 [95% CI=-13.21 to -4.79].[21] However, the trial has questionable internal validity as they used an odd/even method of randomization resulting in a low strength of evidence. 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% CI, -13.9 to -4.9]) compared with 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

We describe two studies 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 small crossover trial (n=39)[16] compared dopamine agonist pramipexole treatment to dual release levodopa/benserazide therapy over two periods of four weeks in patients not previously diagnosed or treated. Improvement of IRLS scores from baseline trended toward significance with pramipexole treatment, with a mean reduction of 7.2 points compared to 4.0 points for dual therapy (p=0.054). For patients with severe RLS (38%, denoted by an IRLS baseline score >20), there was a significant mean reduction in IRLS scores with pramipexole versus levodopa/benserazide, -8.5 versus -4.3 points, respectively (p=0.047). The quality of evidence was low.

One 30-week study[17] (n=361) found that the dopamine agonist cabergoline improved IRLS symptom scale scores (WMD=-6.80; [95% CI, -9.02 to -4.58]) and RLS quality of life more than Levodopa (WMD=-7.10; [95% CI, -9.94 to -4.26]) in white adults with severe RLS (IRLS scale score=25.7) (Appendixes 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, three studies of rotigotine assessed the effect of doses ranging from 0.5 mg per day to 3.0 mg per day (Appendix F). In the study by Hening,[25] 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% 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% CI, 0.92 to 1.78]). The study by Oertel[39] evaluated five doses, ranging from 0.5 mg to 4.0 mg per day. The results versus placebo were statistically significant for the 2.0 and 3.0

mg per day doses but 95% confidence intervals were also wide and overlapped across doses used. The largest effect was seen in the 3.0 mg per day dose (RR=1.66; [95% CI, 1.16 to 2.37]). The study by Trenkwalder[34] 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 F).

For alpha-2-delta ligands, we found no clear evidence of dose effect based on IRLS responders or IRLS total scores in the study by Allen[42] 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 F).

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

a. What are the harms from RLS treatments when compared with placebo or no treatment?
b. What are the harms from RLS treatments when compared with other active treatments?
c. What are the long-term harms from treatment?

Key Points

- Study withdrawals due to adverse effects were more common with dopamine agonist treatment than with placebo (moderate-strength evidence). Differences between treatments were primarily due to an increase in withdrawals related to adverse effects (application site reactions) reported in three trials of transdermal rotigotine
- Study withdrawals (due to any reason) from RCTs were slightly less common with dopamine agonist treatments than with placebo (moderate-strength evidence)
- More patients randomized to dopamine agonist had at least one adverse effect compared to placebo (high-strength evidence)
- Short-term adverse effects from treatment with dopamine agonists compared to placebo were nausea, vomiting, somnolence, and fatigue (high-strength evidence for all these outcomes)
- Application site reactions were much more common with transdermal rotigotine than with placebo (high-strength evidence)
- Study withdrawals (due to any reason) were less common in patients randomized to alpha-2-delta ligands than to placebo (high-strength evidence)
- Somnolence, unsteadiness or dizziness, and dry mouth were much more common with alpha-2-delta ligands than with placebo (high-strength evidence for all these outcomes)
- Incidences of diarrhea and blood phosphorus decrease were reported with intravenous iron therapy.
- No adverse events, except a few cases of nausea, were reported in the trial evaluating bupropion

- One small crossover trial reported higher incidences of augmentation and rebound (RLS symptoms in the early morning) with dual release levodopa/benserazide therapy versus pramipexole
- Data from observation studies 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 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 G) (Figures 16–17). Patients were less likely to withdraw from dopamine agonist treatment than from placebo treatment (20% vs. 24%; RR=0.79; [95% CI, 0.66 to 0.94], k=16) (moderate strength of evidence). Study withdrawals due to adverse effects were more common with dopamine agonist treatment (10% vs. 6%; RR=1.37; [95% CI, 1.03 to 1.82], k=16) (high strength of evidence). More patients experienced at least one adverse effect with dopamine agonist than with placebo (RR=1.19; [95% CI, 1.12 to 1.28], k=16) (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 G).

We observed more short-term adverse effects with dopamine agonists than with placebo, as follows: nausea (23% vs. 7%, RR=3.31 [95% CI, 2.53 to 4.33], k=15), vomiting (7% vs. 2%, RR=4.48 [95% CI, 2.68 to 7.48], k=8), and somnolence (12% vs. 6%, RR=2.04; [95% CI, 1.50 to 2.76], k=8). (overall high strength evidence for these outcomes). These adverse effects occurred in across of the evaluated dopamine agonists though magnitude of effect varied slightly by type of dopamine agonist. Application site reactions were much more common with transdermal rotigotine than with placebo, 29 versus 3 percent, respectively (RR=8.32; [95% CI, 3.45 to 20.05], k=4) (high strength of evidence). The frequencies of reactions were generally greater with increasing doses although not significantly.

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

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

Three subjects each reported diarrhea (12.5%) and blood phosphorus decrease (12.5%) with intravenous iron therapy.[15] No subjects in the placebo arm reported these events. Two patients

allocated to bupropion and one to placebo discontinued treatment due to nausea.[47] No other adverse events were reported.

Comparative Harms

One small moderate quality crossover trial (n=39)[16] of two four-week periods reported higher incidences of augmentation and rebound (RLS symptoms in the early morning) with dual-release levodopa/benserazide therapy versus pramipexole treatment in de novo patients (Appendix G). A higher incidence of nausea, headache, and vomiting was associated with pramipexole.

One good quality 30-week randomized trial reported that compared to levodopa, cabergoline resulted in less augmentation and less augmentation leading to withdrawal (Appendix G). 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.

We observed some subgroup differences across types of dopamine agonist in certain adverse events (Appendixes 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%, 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%, 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 F). 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 risk ratios 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 11). 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%). 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.

Data from two unpublished ropinirole 52-week extension studies reported that adverse events described as "restless legs syndrome" (presumably augmentation) occurred in 9 percent (28/309) of patients in a European study (study number 101468/192) (www.gsk-clinicalstudyregister.com/result_comp_list.jsp?compound=Ropinirole) and 16 percent (13/81) of patients in an American study (study number 101468/243) (Information about both studies can be found at www.gsk-clinicalstudyregister.com/result_comp_list.jsp?compound=Ropinirole. The number of subjects withdrawing in the European study was 19 percent, 8 percent due to adverse events and 4 percent due to lack of efficacy. The respective percents in the American study (101468/243) were 26, 9, and 1 percent.

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

Key Points

- No RCTs examined the effect of patient or RLS characteristics on benefits and harms of treatments for primary RLS.
- No RCTs enrolled children or 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 of whom had been treated previously, and whose symptoms were frequent and high-moderate to severe.

Studies typically excluded patients with psychiatric or other serious comorbid conditions including renal or liver disease and pregnant women or those contemplating becoming pregnant. No studies assessed treatments in pregnant women, and no eligible studies assessed treatments in patients with end-stage renal disease. The minimum age for entry to studies was always at least 18 years, thus we found no information on treatment of RLS in children or adolescents.

Two small good quality RCTs evaluated iron therapy[66,67] (one intravenous and one oral) in patients with RLS secondary to iron deficiency (Table 14, Appendix E). One 12-week trial of 18 subjects found that compared to placebo, iron reduced IRLS scale scores by 9.16 points (95% CI,-15.2 to -3.1). 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). A post hoc analysis at 11 weeks found an increase in the percentage of subjects considered IRLS responders among those randomized to iron (RR=1.85; [95% CI, 1.07 to 3.18]). By 12 months, 21 of 31 subjects (68%) in the placebo group and nine of 29 (31%) 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 alpha-2-delta ligands 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 Impressions: Responders (Much Improved)	Patient Global Impressions: Responders (Much Improved)	MOS Patient-Reported Sleep Quality Scale	RLS Quality of Life	Augmentation
Benes, 2011[38]	✓	NR	NR	✓	NR	NR	NR	NR
Högl, 2011[26]	✓	NR	NR	✓	✓	NR	NR	✓
Montagna, 2011[28]	✓	✓	NR	✓	✓	NR	✓	NR
Hening, 2010[25]	✓	✓	✓	✓	NR	✓	✓	✓
Oertel, 2010[31]	✓	✓	✓	✓	NR	✓	✓	NR
Ferini-Stambi, 2008[24]	✓	NR	NR	✓	✓	✓	✓	NR
Kushida, 2008[27]	✓	NR	NR	✓	✓	✓	NR	NR
Oertel, 2008[39]	✓	✓	NR	✓	NR	NR	✓	NR
Trenkwalder, 2008[34]	✓	✓	✓	✓	NR	✓	✓	NR
Oertel, 2007[32]	✓	✓	NR	✓	✓	NR	NR	NR
Bogan, 2006[23]	✓	NR	NR	✓	NR	✓	✓	✓
Montplaisir, 2006[57]	NR	NR	NR	✓	NR	NR	NR	NR
Winkelman, 2006[37]	✓	✓	NR	✓	✓	NR	✓	NR
Adler,*2004[22]	NR	NR	✓	NR	NR	NR	NR	NR
Trenkwalder, 2004[35]	✓	NR	NR	✓	NR	✓	✓	NR
Walters, 2004[36]	✓	NR	NR	✓	NR	✓	✓	NR
Totals	**14**	**7**	**4**	**15**	**6**	**8**	**10**	**3**

IRLS = International Restless Legs Syndrome Study Group Rating Scale; MOS = Medical Outcomes Scale; NR = not reported; RLS = restless legs syndrome
*Crossover trial

Table 5. Study duration and baseline characteristics of patients (means and range) in placebo-controlled 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)[24,26,28,32,37]	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 (7)[22,23,27,35,36,38,57]	11.9 (8 to 12)	1696 (22 to 381)	54.1 (50.9 to 60)	62 (55 to 73)	19.1 (16.8 to 22.8; *5 trials***)	25.0 (22 to 29)	44.3 (40.9 to 44.6; *2 trials***)
Rotigotine (4)[25,31,34,39]	21.2 (6 to 28)	1371 (67 to 505)	56.0 (52.4 to 59.4)	65 (58 to 74)	2.1 (2.1 to 2.2; *2 trials***)	26.2 (23.3 to 28.1)	60.1 (35.8 to 80.8)
Overall (n=16)	15 (6 to 28)	4861 (22 to 505)	55.1 (50.9 to 60)	65 (55 to 74)	8.9 (2.1 to 22.8; *13 trials***)	25.1 (22 to 28.6)	41.0 (21.8 to 80.8; *11 trials***)

IRLS = International Restless Legs Syndrome Study Group Rating Scale; RLS = restless legs syndrome

*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 or reported median durations).

Table 6. Overall strength of evidence for individual outcomes in placebo-controlled studies of dopamine agonists

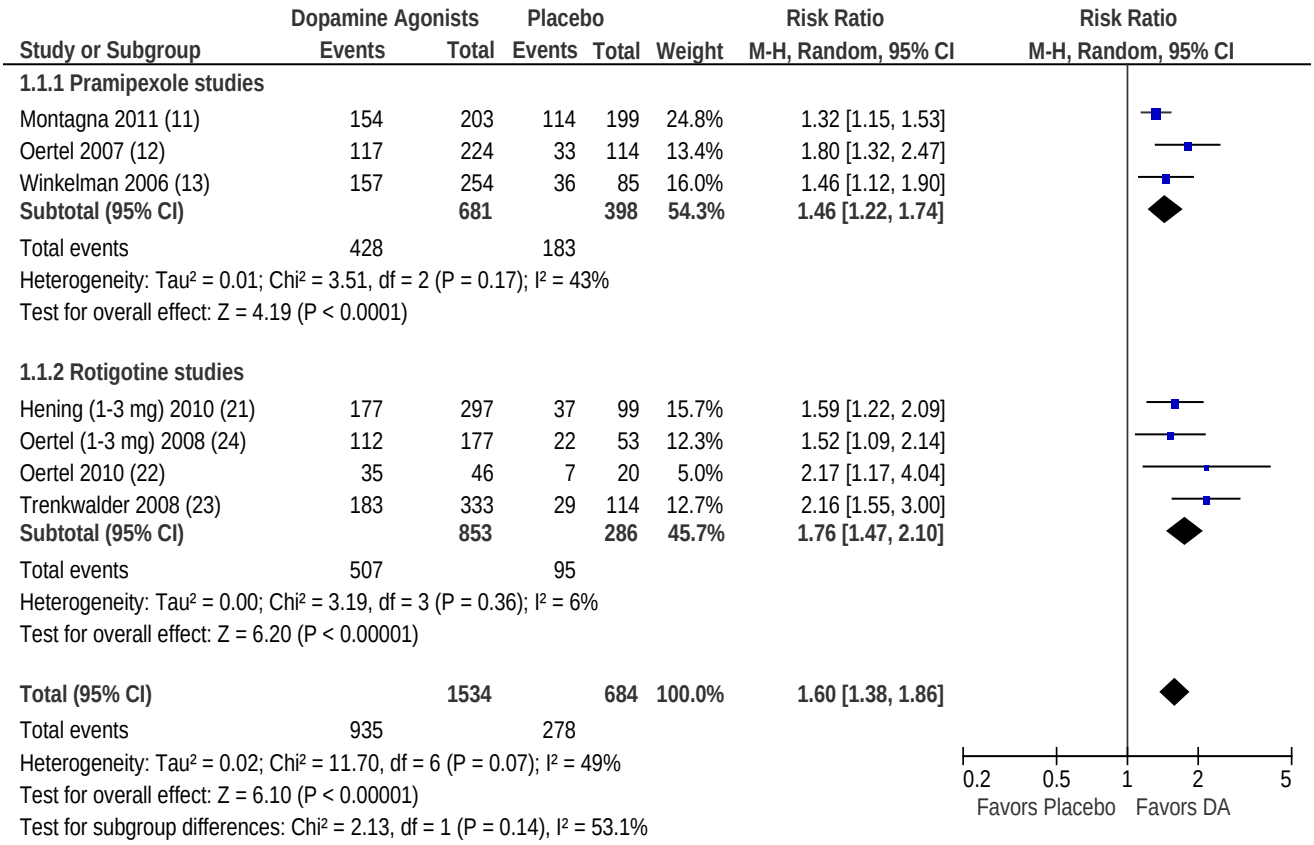
Outcome	Treatments	Number of Trials	n	Summary Statistics [95% CI]	Risk of Bias	Directness	Precision	Consistency	Evidence Rating
IRLS responders (≥50% score reduction)	All trials vs. placebo	7	2218	RR 1.60 [1.38 to 1.86]	Low	Direct	Precise	Consistent	High
	pramipexole	3	1079	RR 1.46 [1.22 to 1.74]	Low	Direct	Precise	Consistent	High
	rotigotine	4	1139	RR 1.76 [1.47 to 2.10]	Low	Direct	Precise	Consistent	High
IRLS total score: mean change from baseline	All trials vs. placebo	14	3578	WMD -4.56 [-5.42 to -3.70]	Low	Direct	Precise	Consistent	High
	pramipexole	5	1578	WMD -4.76 [-6.24 to -3.28]	Low	Direct	Precise	Consistent	High
	ropinirole	5	1517	WMD -3.49 [-4.44 to -2.54]	Low	Direct	Precise	Consistent	High
	rotigotine	4	585	WMD -6.09 [-7.71 to -4.46]	Low	Direct	Precise	Consistent	High
Clinical global impressions responders: (much-very much improved)	All trials vs. placebo	15	4446	RR 1.45 [1.36 to 1.55]	Low	Direct	Precise	Consistent	High
	pramipexole	5	1747	RR 1.61 [1.40 to 1.86]	Low	Direct	Precise	Consistent	High
	ropinirole	6	1608	RR 1.37 [1.25 to 1.50]	Low	Direct	Precise	Consistent	High
	rotigotine	4	1091	RR 1.37 [1.22 to 1.54]	Low	Direct	Precise	Consistent	High
Patient global impressions 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	9	2140	SMD -0.37 [-0.48 to -0.27]	Low	Direct	Precise	Consistent	High
	pramipexole	3	912	SMD -0.43 [-0.61 to -0.25]	Low	Direct	Precise	Consistent	High
	ropinirole	2	643	SMD -0.30 [-0.45 to -0.14]	Low	Direct	Precise	Consistent	High
	rotigotine	4	585	SMD -0.37 [-0.60 to -0.13]	Low	Direct	Precise	Consistent	High
Self-rated sleep MOS-SPI-II	All trials vs. placebo	8	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

Table 6. Overall strength of evidence for individual outcomes in placebo-controlled studies of dopamine agonists (continued)

Outcome	Treatments	Number of Trials	n	Summary Statistics [95% CI]	Risk of Bias	Directness	Precision	Consistency	Evidence Rating
Any study withdrawal	All trials vs. placebo	16	4860	RR 0.79 [0.66 to 0.94]	Low	Direct	Precise	Inconsistent	Moderate
	pramipexole	5	1792	RR 0.71 [0.50 to 1.01]	Low	Direct	Imprecise	Inconsistent	Low
	ropinirole	7	1698	RR 0.84 [0.67 to 1.06]	Low	Direct	Imprecise	Consistent	Moderate
	rotigotine	4	1370	RR 0.83[0.54 to 1.26]	Low	Direct	Imprecise	Inconsistent	Low
Study withdrawals due to an adverse event	All trials vs. placebo	16	4860	RR 1.37 [1.03 to 1.82]	Low	Direct	Precise	Consistent	High
	pramipexole	5	1791	RR 0.97 [0.69 to 1.35]	Low	Direct	Imprecise	Consistent	Moderate
	ropinirole	7	1698	RR 1.48 [0.99 to 2.20]	Low	Direct	Imprecise	Consistent	Moderate
	rotigotine	4	1370	RR 2.50 [1.33 to 4.70]	Low	Direct	Precise	Consistent	High
Patients with ≥1 adverse event	All trials vs. placebo	16	4854	RR 1.19 [1.12 to 1.28]	Low	Direct	Precise	Consistent	High
	pramipexole	5	1790	RR 1.16 [1.04 to 1.29]	Low	Direct	Precise	Inconsistent	Moderate
	ropinirole	7	1695	RR 1.20 [1.10 to 1.32]	Low	Direct	Precise	Consistent	High
	rotigotine	4	1369	RR 1.25 [1.00 to 1.59]	Low	Direct	Precise	Consistent	High

CI = confidence interval; IRLS = International Restless Legs Syndrome Study Group Rating Scale; MD = mean difference; MOS-SPI-II = Medical Outcomes Scale - Sleep Problems Index II; RLS = restless legs syndrome; RR = risk ratio; SMD = standardized mean difference; WMD = weighted mean difference (a negative SMD or 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 percent reduction in mean IRLS score from baseline



CI = confidence interval; DA = dopamine agonist; M-H = Mantel Haenszel (statistical method)

Table 7. Responders to treatment, International Restless Legs Syndrome Study Group Rating Scale responders (≥50% score reduction): Absolute effect per 100 patients

Study	Number of Studies	Treatment % (n/N)	Placebo % (n/N)	RR [95% CI]	Absolute Effect [95% CI]
All dopamine agonist studies	7	61.0 (935/1534)	40.6 (278/684)	1.60 [1.38 to 1.86]	24 more per 100 [15 more to 35 more]
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	4	59.4 (507/853)	33.2 (95/286)	1.76 [1.47 to 2.10]	25 more per 100 [16 more to 37 more]
All alpha-2-delta ligands studies	3	61.5 (220/358)	37.2 (54/145)	1.66 [1.33 to 2.09]	25 more per 100 [12 more to 41 more]
Gabapentin enacarbil	1	60.9 (137/225)	39.6 (38/96)	1.54 [1.18 to 2.01]	21 more per 100 [7 more to 40 more]
*Pregabalin**	2	62.4 (83/133)	32.7 (16/49)	2.03 [1.33 to 3.11]	34 more per 100 [11 more to 69 more]

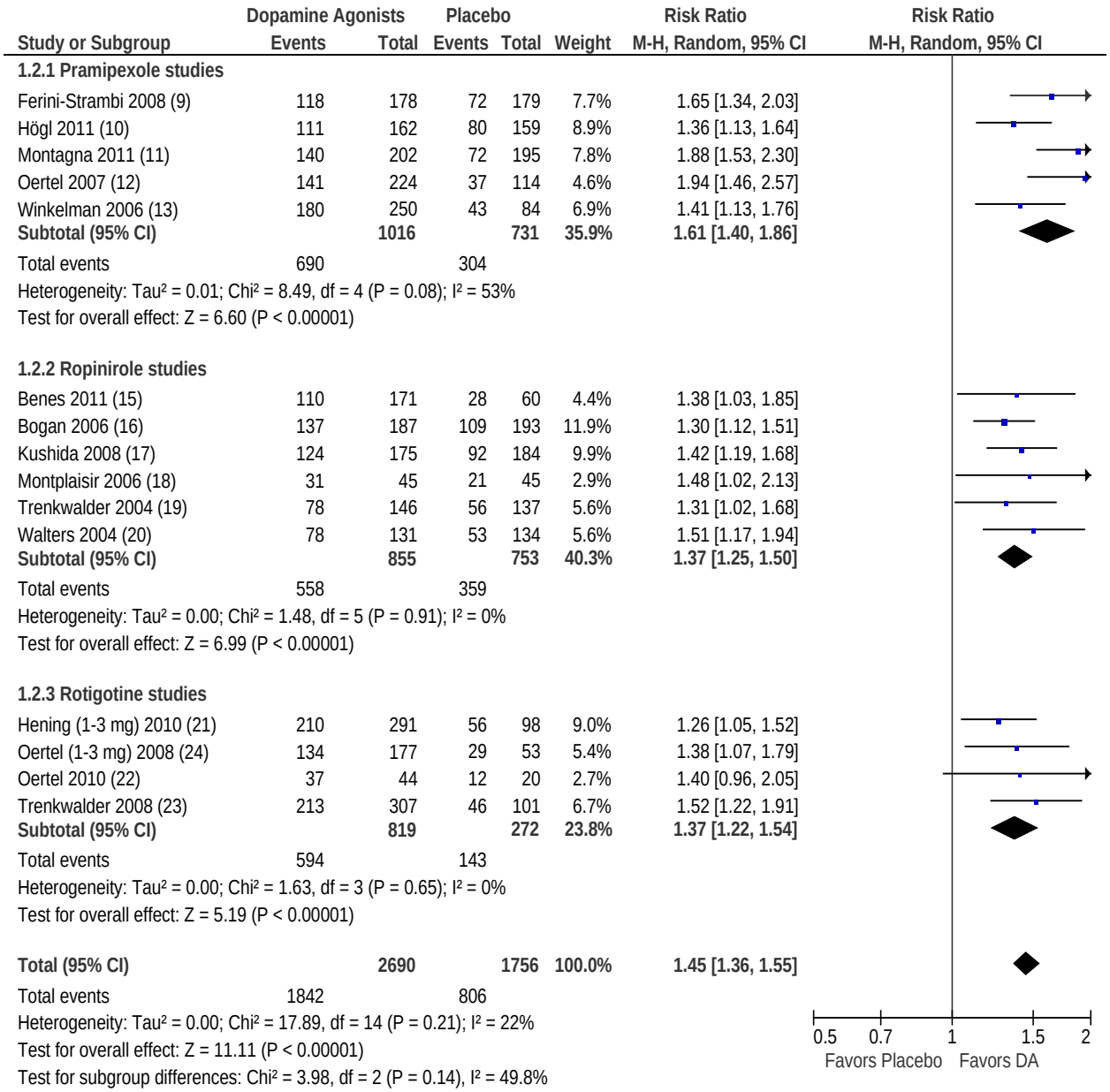
CI=confidence interval; FDA = Food and Drug Administration; IRLS = International Restless Legs Syndrome Study Group Rating Scale; n/N = number of subjects responding/number of subjects analyzed; RLS = restless legs syndrome; RR = risk ratio;
*Not FDA approved for treatment of RLS

Table 8. Responders to treatment, Clinician-rated global impressions (CGI) responders: participants who reported improved or much improved: absolute effect per 100 patients

Study	Number of Studies	Treatment % (n/N)	Placebo % (n/N)	RR [95% CI]	Absolute Effect [95% CI]
All dopamine agonist studies	15	68.5 (1842/2690)	45.9 (806/1756)	1.45 [1.36 to 1.55]	21 more per 100 [17 more to 25 more]
Pramipexole	5	67.9 (690/1016)	41.6 (304/731)	1.61 [1.40 to 1.86]	25 more per 100 [17 more to 36 more]
Ropinirole	6	65.3 (558/855)	47.7 (359/753)	1.37 [1.25 to 1.50]	18 more per 100 [12 more to 24 more]
Rotigotine	4	72.5 (594/819)	52.6 (143/272)	1.37 [1.22 to 1.54]	19 more per 100 [12 more to 28 more]
All alpha-2-delta ligands studies	3	74.4 (325/437)	43.6 (98/225)	1.60 [1.21 to 2.10]	26 more per 100 [9 more to 48 more]
Gabapentin enacarbil	2	75.4 (252/334)	41.7 (85/204)	1.80 [1.51 to 2.14]	33 more per 100 [21 more to 48 more]
*Pregabalin**	1	70.9 (73/103)	61.9 (13/21)	1.14 [0.80 to 1.64]	9 more per 100 [12 fewer to 40 more]

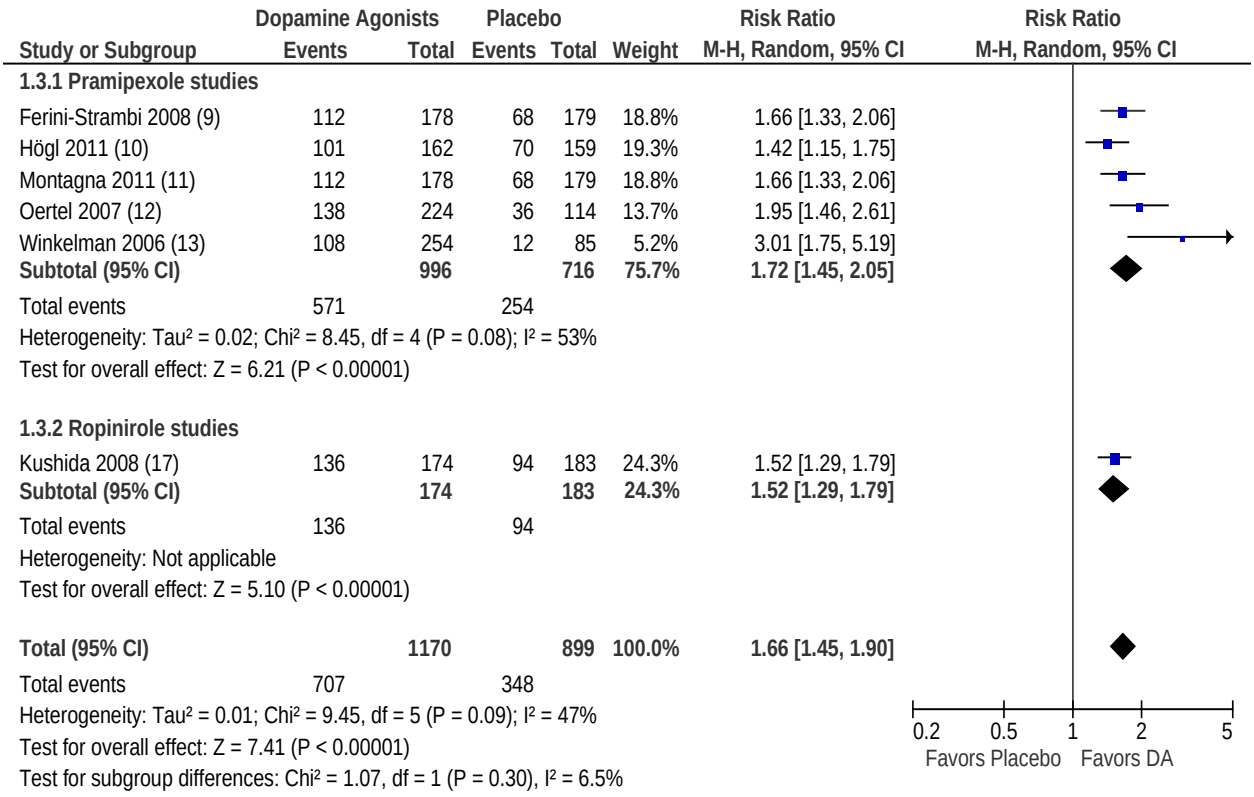
CI = confidence interval; FDA = Food and Drug Administration; n/N = number of subjects reported improved/number of subjects analyzed; RLS = restless legs syndrome
*Not FDA approved for treatment of RLS

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)



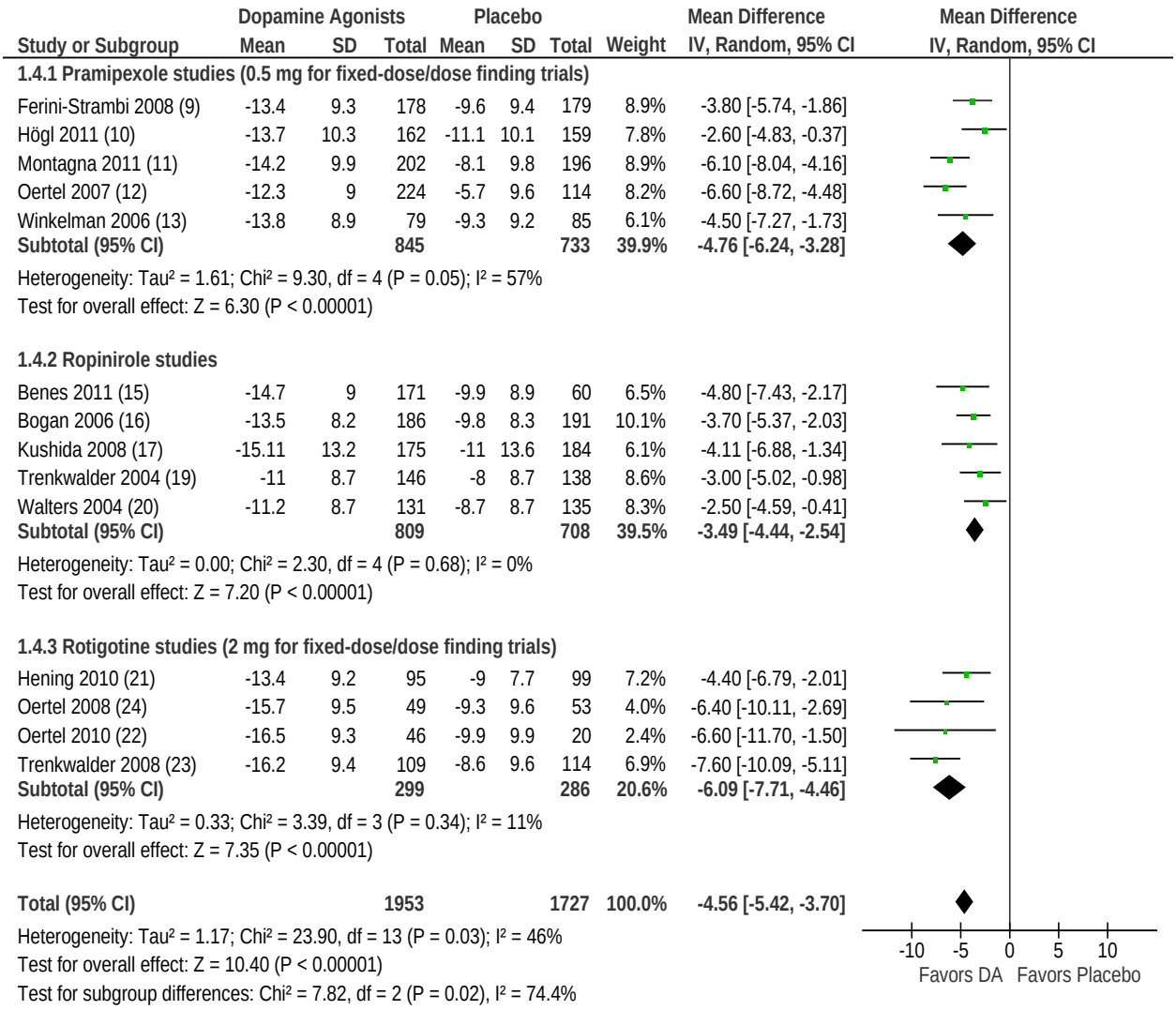
CI = confidence interval; DA = dopamine agonist; M-H = Mantel Haenszel (statistical method)

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)



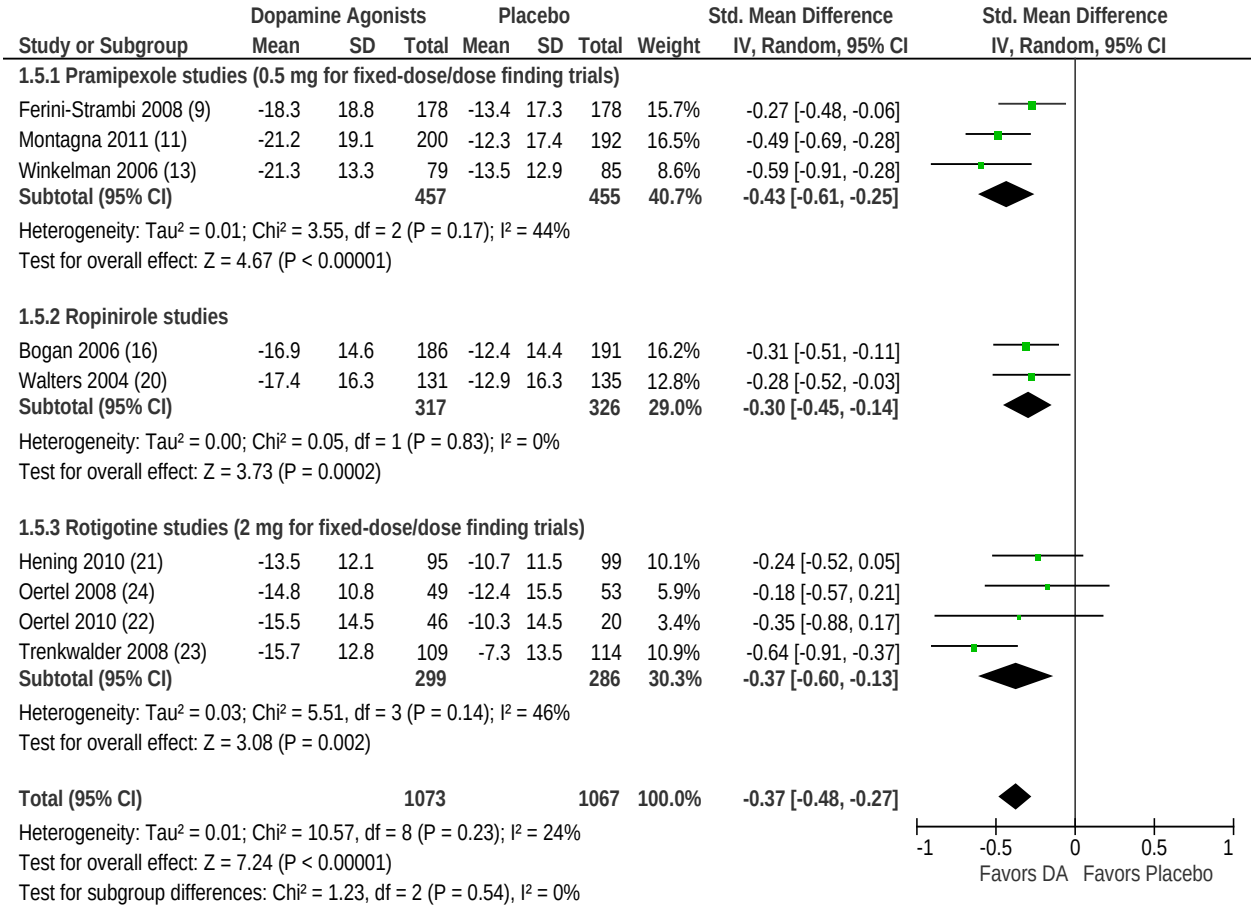
CI = confidence interval; DA = dopamine agonist; M-H = Mantel Haenszel (statistical method)

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



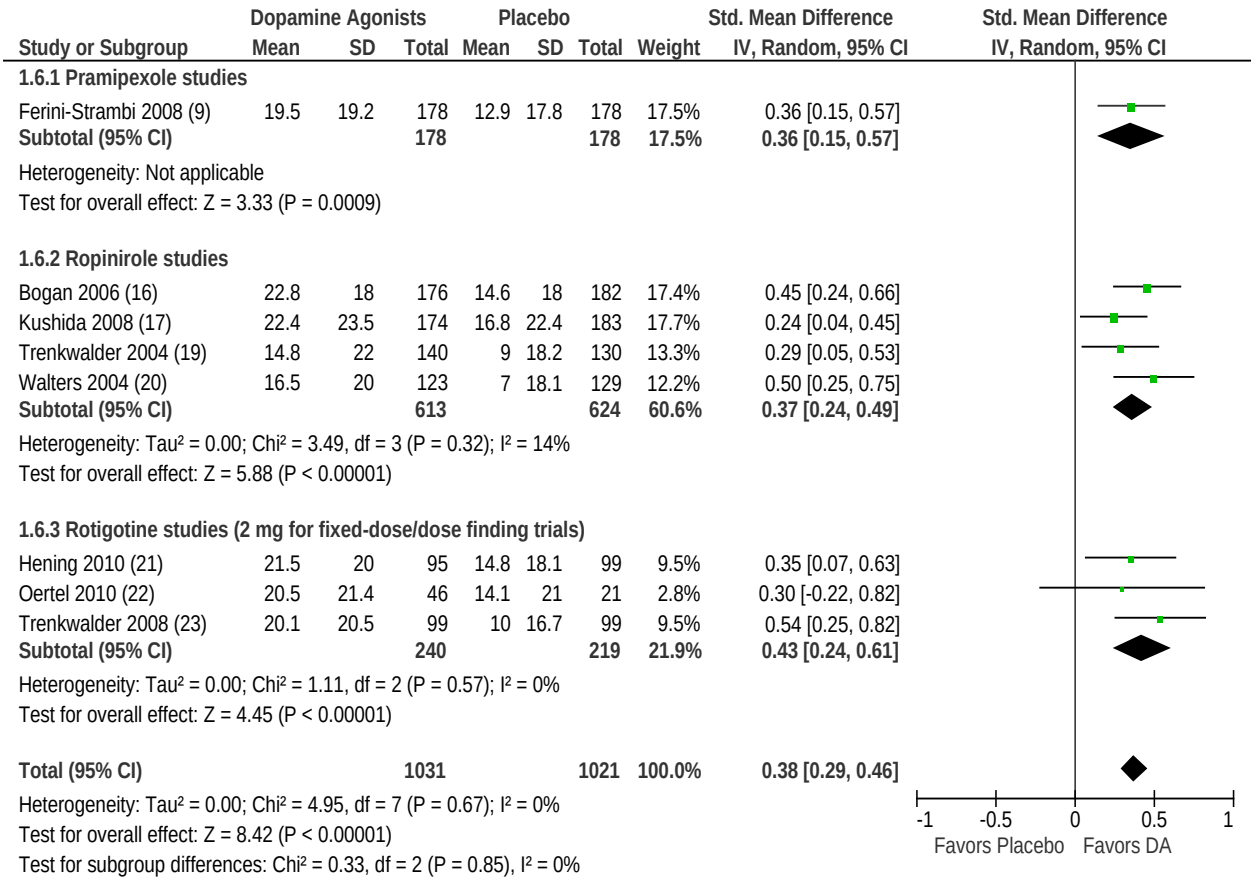
CI = confidence interval; DA = dopamine agonist; IRLS = International Restless Legs Syndrome Study Group; IV = Inverse variance (statistical method); SD = standard deviation

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



CI = confidence interval; DA = dopamine agonist; IV = Inverse variance (statistical method); SD = standard deviation; Std = standardized

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



CI = confidence interval; DA = dopamine agonist; IV= Inverse variance (statistical method); SD = standard deviation; Std = standardized

Table 9. Summary of study baseline characteristics for alpha-2-delta ligand drugs trials

Characteristic	Mean (Range)*	Number of Trials Reporting
Total number of patients evaluated	1096 (24 to 325)	7
Age of subjects, years	50.7 (49 to 55.0)	7
Women, %	60 (58 to 66)	7
Race/ethnicity, white %	94 (92 to 97)	5 [a,c,e,f,g]
RLS disease duration, years	13.2 (7.7 to 15.2)	5 [a,b,d,e,f]
Baseline IRLS total score (range 0 to 40)	23.7 (20 to 25.4)	7
Patients with severe disease, % (number of patients)	8 (17)	1 [c]
Previous RLS therapy, %	36 (32 to 42)	4 [c,e,f,g]
Trials evaluating gabapentin enacarbil, % (number of patients)	80 (877)	4 [c,e,f,g]
Trials evaluating gabapentin, % (number of patients)	2 (24)	1 [d]
Trials evaluating pregabalin, % (number of patients)	18 (195)	2 [a,b]
Crossover trials, % (number of patients)	15 (160)	2 [d,g]

a = Allen 2010; b = Garcia-Borreguero 2010; c = Kushida 2009; d = Garcia-Borreguero 2002; e = Lee 2011; f = Bogan 2010; g = Winkelman 2011; IRLS = International Restless Legs Syndrome Study Group Rating Scale; RLS = restless legs syndrome
*Unless otherwise shown

Table 10. Overall strength of evidence for individual outcomes in placebo-controlled studies of alpha-2-delta ligands

Outcome	Treatments	Number of Trials	n	Summary Statistics [95% CI]	Risk of Bias	Directness	Precision	Consistency	Evidence Rating
IRLS responders (≥50% score reduction) reduction)	All trials vs. placebo	3	503	RR 1.66 [1.33 to 2.09]	Low	Direct	Precise	Consistent	High
	Gabapentin enacarbil	1	321	RR 1.54 [1.18 to 2.01]	Low	Direct	Precise	Unknown	Moderate
	Pregabalin	2	182	RR 2.03 [1.33 to 3.11]	Low	Direct	Precise	Consistent	High
IRLS total score: mean change from	All trials vs. placebo	3	475	WMD -4.26 [-5.75 to -2.77]	Low	Direct	Precise	Consistent	High
Baseline	*Gabapentin enacarbil*	2*	431	WMD -4.18 [-5.76 to -2.60]	Low	Direct	Precise	Consistent	High
	Pregabalin	1	44	WMD -4.90 [-9.41 to -0.39]	Low	Direct	Precise	Unknown	Moderate
Clinical global impressions: responders (much improved)	All trials vs. placebo	3	662	RR 1.60 [1.21 to 2.10]	Low	Direct	Precise	Consistent	High
	Gabapentin enacarbil	2**	538	RR 1.80 [1.51 to 2.14]	Low	Direct	Precise	Consistent	High
	Pregabalin	1	124	RR 1.14 [0.80 to 1.64]	Low	Direct	Imprecise	Unknown	Low
RLS quality of life	All trials vs. placebo	2	263	SMD 0.27 [-0.17 to 0.70]	Low	Direct	Imprecise	Inconsistent	Low
	Gabapentin enacarbil	1	220	SMD 0.42 [0.16 to 0.69]	Low	Direct	Precise	Unknown	Moderate
	Pregabalin	1	43	SMD -0.05 [-0.65 to 0.55] (300 mg dose)†	Low	Direct	Imprecise	Unknown	Low
Self-rated sleep MOS-sleep adequacy	*Gabapentin enacarbil*	2	431	SMD 0.53 [0.33 to 0.72]	Low	Direct	Precise	Consistent	High

Table 10. Overall strength of evidence for individual outcomes in placebo-controlled studies of alpha-2-delta ligands (continued)

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

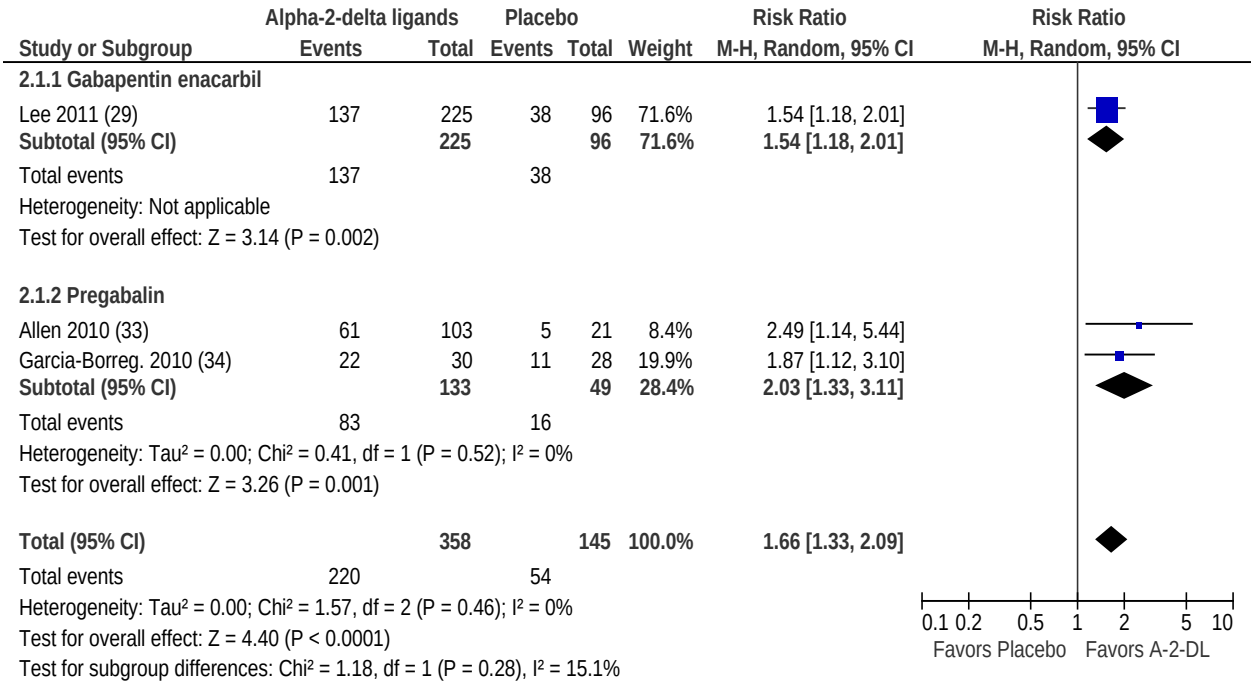
CI = confidence interval; IRLS = International Restless Legs Study Group; MD = main difference; MOS = medical outcome scale; RLS = restless legs syndrome; RR = risk ratio; SMD = standardized mean difference; WMD = weighted mean difference

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

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

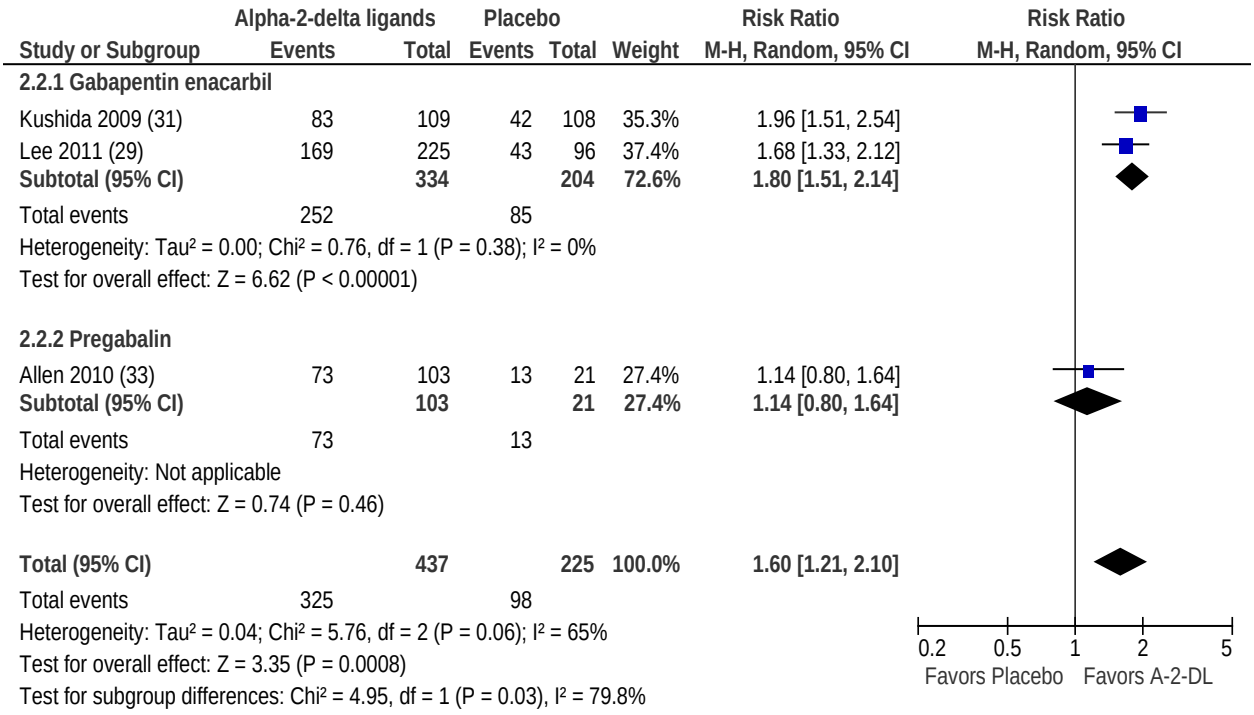
†Fixed-dose trial (5 doses, 50-450 mg), range of SMDs from -0.05 to -0.43. No dose was significantly superior to placebo.

Figure 9. Efficacy outcomes for treatment with alpha-2-delta ligands: IRLS responders (≥50% scale score reduction)



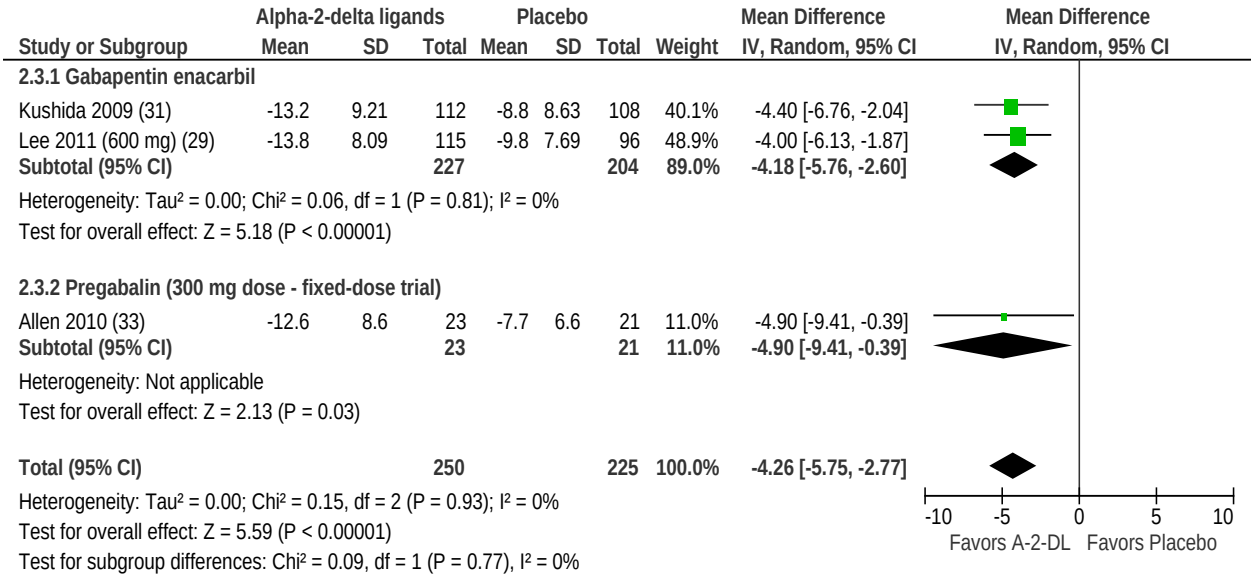
A-2-DL = Alpha-2-delta ligands; CI = confidence interval; IRLS = International Restless Legs Syndrome Study Group Rating Scale; M-H = Mantel Haenszel (statistical method)

Figure 10. Efficacy outcomes for treatment with alpha-2-delta ligands: proportion of patients who reported improved or much improved on the clinician-rated global impressions scale (CGI)



A-2-DL = Alpha-2-delta ligands; CI = confidence interval; M-H = Mantel Haenszel (statistical method)

Figure 11. Efficacy outcomes for treatment with alpha-2-delta ligands: mean change in IRLS scale score from baseline



A-2-DL = Alpha-2-delta ligands; CI = confidence interval; IRLS = International Restless Legs Syndrome Study Group Rating Scale; IV = Inverse variance (statistical method)

Table 11. 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 (alpha-2-delta ligand)	**Gabapentin**	Ellenbogen, 2011[50]	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	**Multiple opioids [tilidine; dihydrocodeine; oxycodone; propoxyphene; methadone]**	Walters, 2001[64]	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[62]	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[60]	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	**Levodopa**	Högl, 2011[26]	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[63]	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

Table 11. Long-term harms with pharmacologic treatment: augmentation (continued)

Class of Drugs	Drug	Study (Year)	Design	Duration (Years)	Augmentation	Withdrawal From Treatment	Reason for Withdrawal (% of all Withdrawals)	Adverse Events
Dopamine agonists	**Pramipexole**	Inoue, 2010[56]	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[61]	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
	Pramipexole	Silver, 2011[62]	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[51]	Open, label case series	0.5	8.3% (5/60)	NR	NR	Nausea, excessive daytime sleepiness, sedation
	Pramipexole	Montplaisir, 2006[57]	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[65]	Retrospective	1.8	32% (19/59)	NR	NR	NR
	Ropinirole	Garcia-Borreguero, 2007[53]	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[58]	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

Table 11. Long-term harms with pharmacologic treatment: augmentation (continued)

Class of Drugs	Drug	Study (Year)	Design	Duration (Years)	Augmentation	Withdrawal From Treatment	Reason for Withdrawal (% of All Withdrawals)	Adverse Events
Dopamine agonists (continued)	**Rotigotine**	Benes, 2009[49]	Retrospective	1	9.7 % (60/620)	NR	NR	NR
	Multiple dopamine agonists [pramipexole; ropinirole; pergolide]	Ondo, 2004[59]	Retrospective	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.
	Multiple dopaminergic drugs (levodopa, pramipexole, ropinirole, rotigotine). *Results not reported for individual drug*	Godau, 2010[54]	Prospective	1	24% (14/60)	NR	NR	Sleepiness, nausea, dizziness, headache, vivid dreams, leg edema, erectile dysfunction
	Multiple dopaminergic drugs	Frauscher, 2009[52]	Prospective	1.5	11% (13/118)	NR	NR	NR
	Multiple dopaminergic drugs (ropinirole, pramipexole, levodopa)	Allen, 2011[48]	Cross-sectional	2.7 (mean)	20% (53/266)	NR	NR	NR

NA = not applicable; NR = not recorded; RCT = randomized controlled trial

Table 12. Strength of evidence for the miscellaneous pharmacologic trials

Intervention	Outcome	Number of Trials	n	Summary Statistics, [95% CI]	Risk of Bias	Directness	Precision	Consistency	Evidence Rating
Bupropion	IRLS total score: Mean change from baseline	1	60	WMD -2.80 [-7.25 to 1.65]	Low	Direct	Imprecise	Unknown	Low

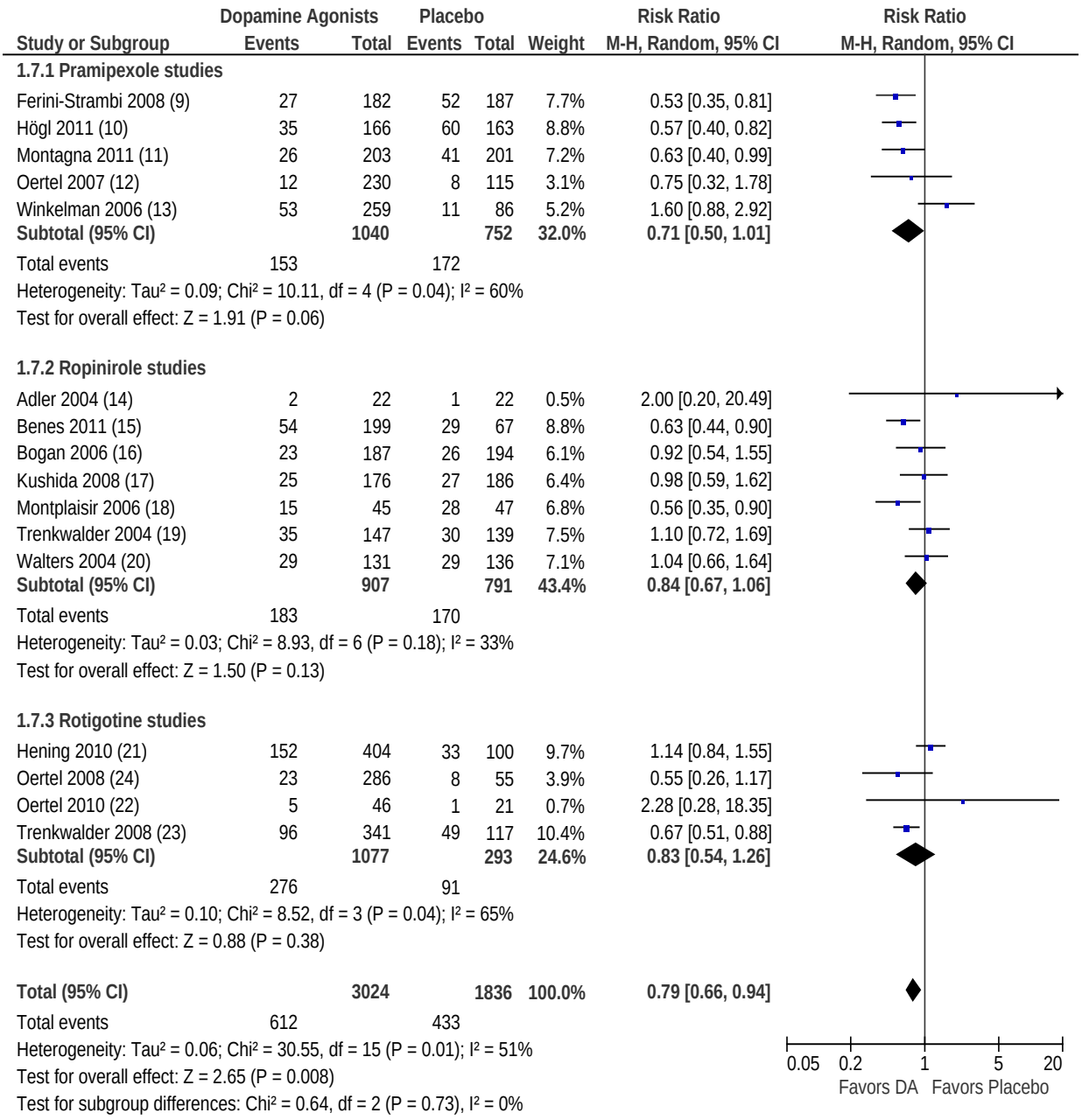
CI = confidence interval; IRLS = International Restless Legs Syndrome Study Group Rating Scale; WMD = weighted mean difference

Table 13. Strength of evidence for the nonpharmacologic trials

Intervention	Outcome	Number of Trials	n	Summary Statistics, [95% CI]	Risk of Bias	Directness	Precision	Consistency	Evidence Rating
Near infrared light[21]	IRLS total score: Mean change from baseline	1	34	WMD -9.00 [-13.21 to -4.79]	Moderate	Direct	Precise	Unknown	Low
Valerian (botanical)[20]	IRLS total score: Mean change from baseline	1	37	WMD 1.30 [-5.08 to 7.68]	Moderate	Direct	Imprecise	Unknown	Low
Exercise[19]	IRLS total score: Mean score at endpoint	1	28	WMD -9.40 [-13.86 to -4.94]	Moderate	Direct	Precise	Unknown	Low
Compression device[18]	IRLS total score: Mean score at endpoint	1	35	MD -5.70 [-8.21 to -3.19]	Low	Direct	Precise	Unknown	Moderate

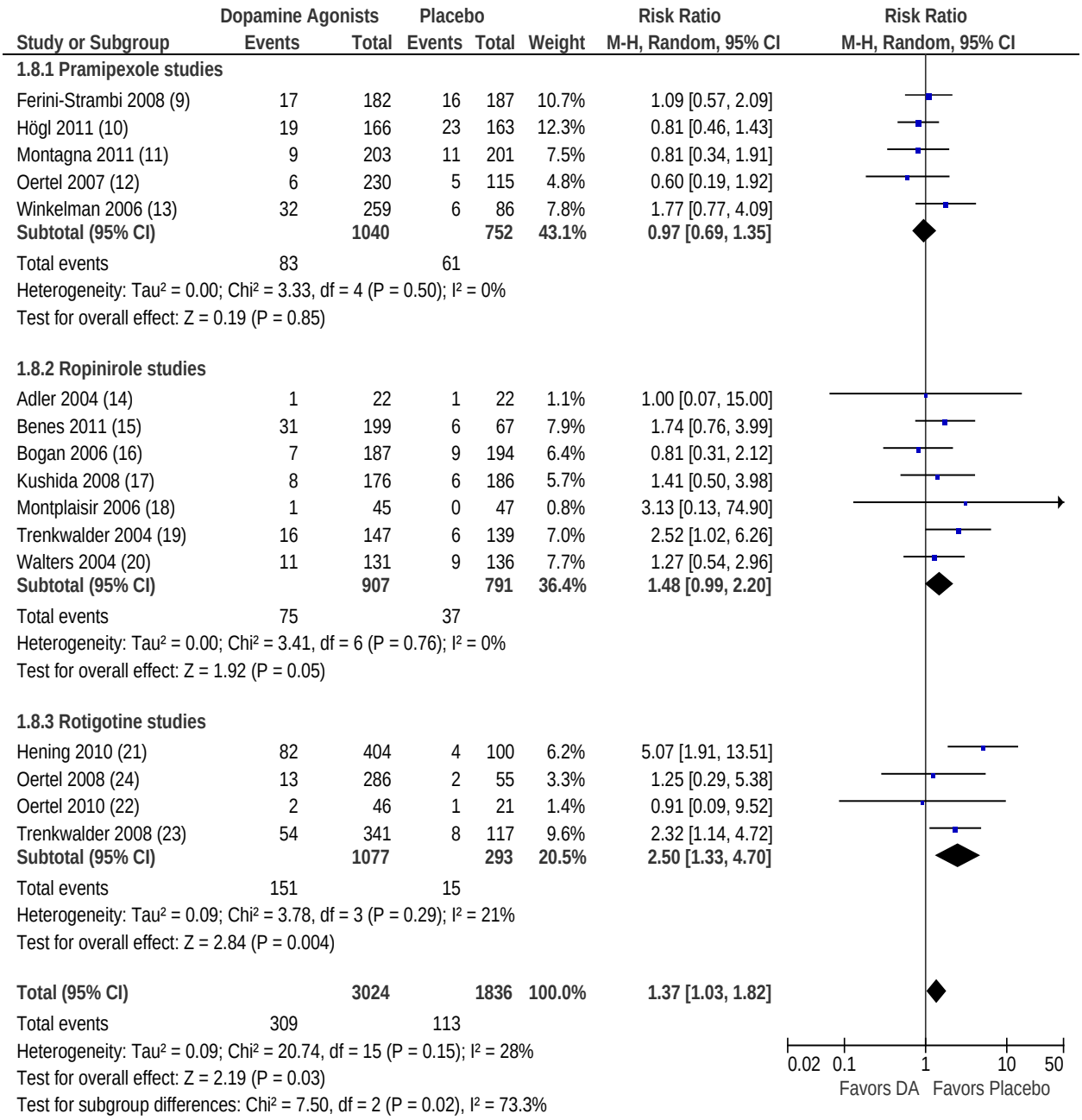
IRLS = International Restless Legs Syndrome Study Group Rating Scale; WMD=weighted mean difference; MD=mean difference.

Figure 12. Short-term harms of treatment with dopamine agonists: any study withdrawal



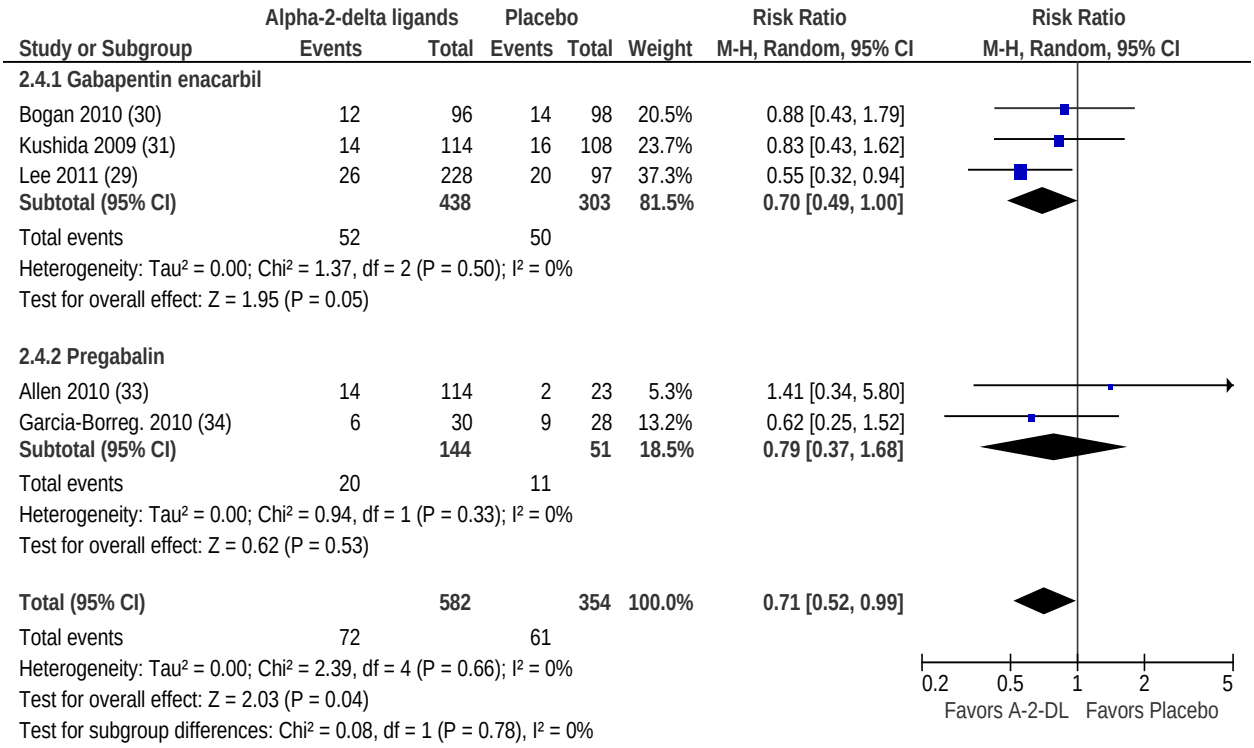
CI = confidence interval; DA = dopamine agonist; M-H = Mantel Haenszel (statistical method)

Figure 13. Short-term harms of treatment with dopamine agonists: study withdrawals due to adverse events



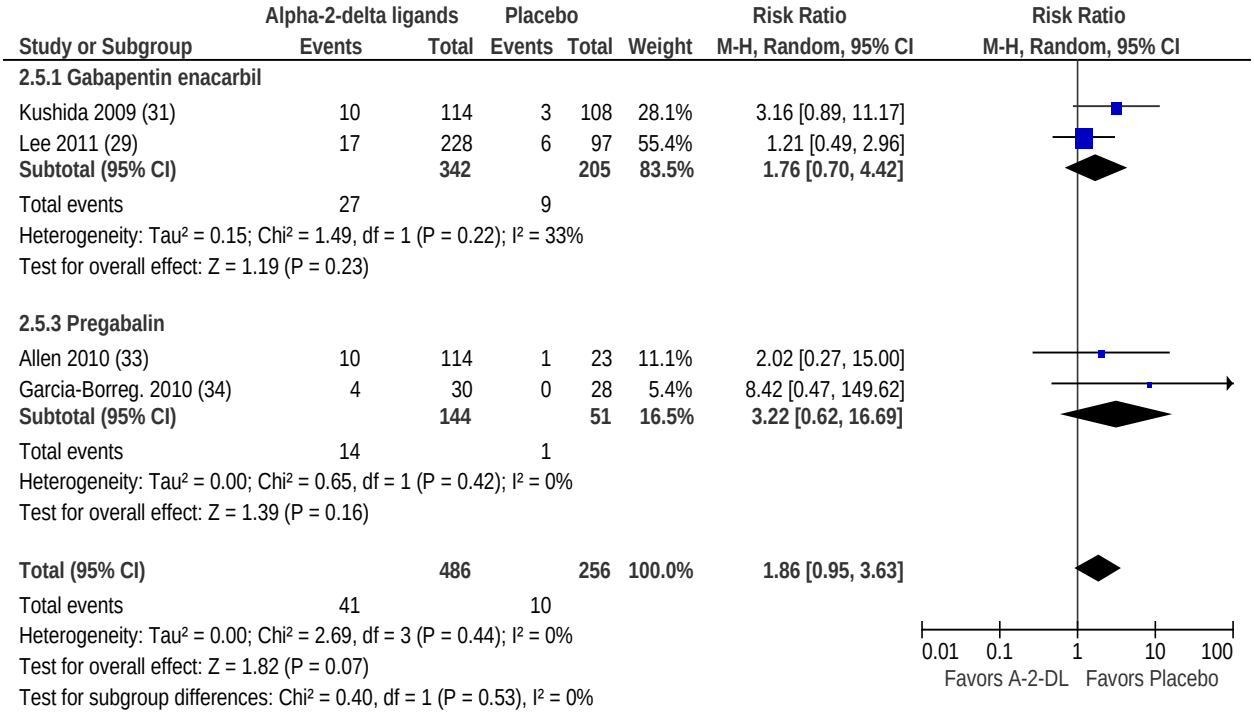
CI = confidence interval; DA = dopamine agonist; M-H = Mantel Haenszel (statistical method)

Figure 14. Short-term harms of treatment with alpha-2-delta ligands: any study withdrawals



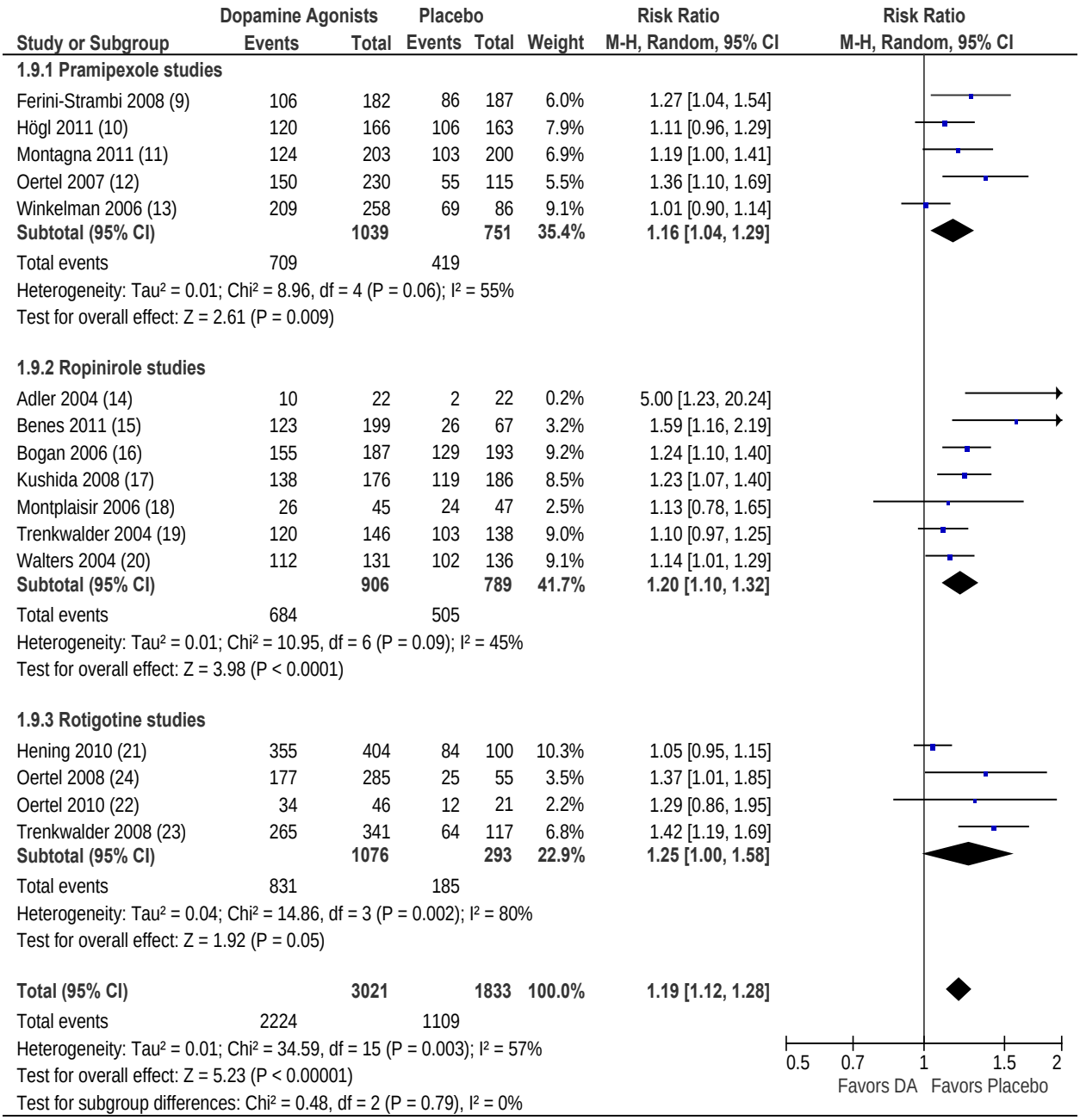
A-2-DL = Alpha-2-delta ligands; CI = confidence interval; M-H = Mantel Haenszel (statistical method)

Figure 15. Short-term harms of treatment with alpha-2-delta ligands: study withdrawals due to adverse events



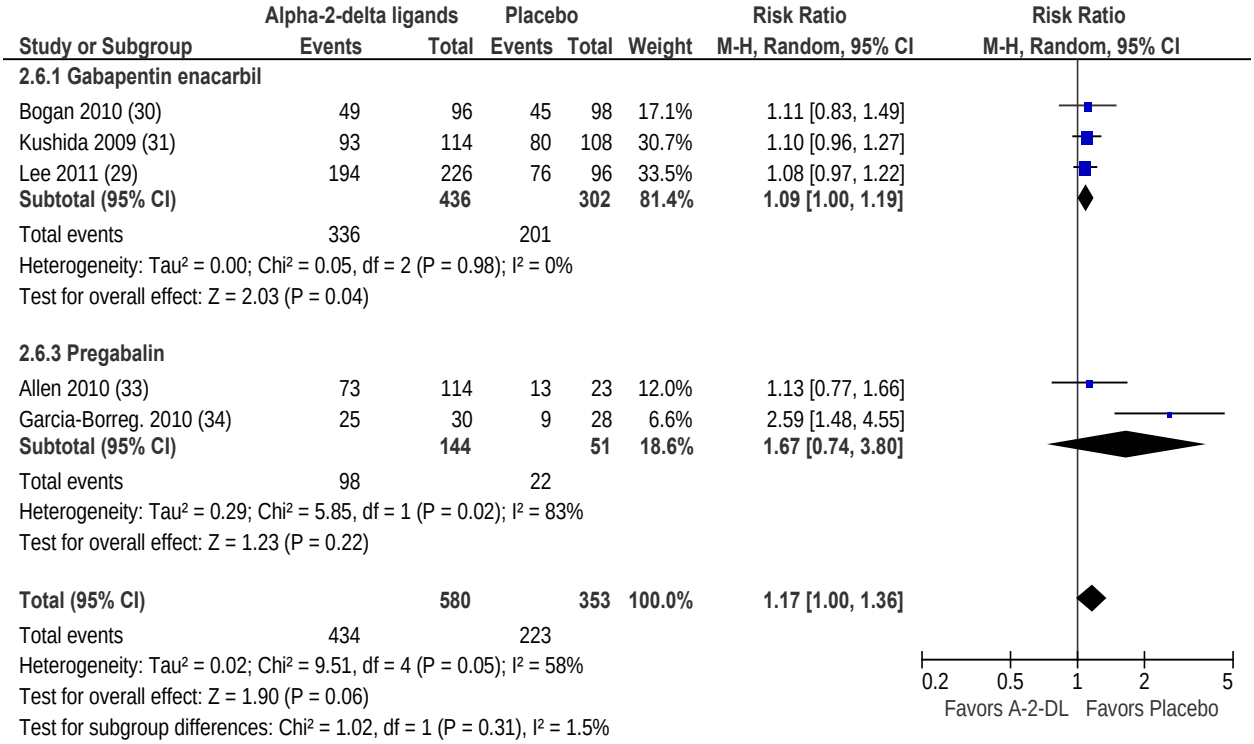
A-2-DL = Alpha-2-delta ligands; CI = confidence interval; M-H = Mantel Haenszel (statistical method)

Figure 16. Patients with ≥1 adverse effect, dopamine agonist trials



CI = confidence interval; DA = dopamine agonist; M-H = Mantel Haenszel (statistical method)

Figure 17. Patients with ≥1 adverse effect, alpha-2-delta ligands trials



A-2-DL = Alpha-2-delta ligands; CI = confidence interval; M-H = Mantel Haenszel (statistical method)

Table 14. 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

CI = confidence interval; RLS = restless legs syndrome; RR=risk ratio; WMD=weighted mean difference

*Post hoc analysis

Discussion

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

Evidence is lacking about the long-term effectiveness in, and applicability to, adults with less severe or less frequent RLS symptoms, children, or individuals with secondary RLS including those with iron deficiency, end-stage renal disease, or pregnant women or those intending to become pregnant. Studies of pharmacologic therapies consisted mainly of dopaminergic agents; a few studies assessed alpha-2-delta ligands. All studies administered therapies daily rather than "as needed." Although the effectiveness, harms, and adherence to "as needed" therapy are unknown, current recommendations note this as an option.[6] Few nonpharmacologic therapies were assessed, and no individual nonpharmacologic treatment was studied in more than a single trial. Randomized controlled trials (RCTs) were short in duration and enrolled highly selected populations with symptoms that were very severe to high-moderate, frequent, and long-standing. Additional meta-analyses are supportive of our findings.[84-86]

Exclusion criteria were many, and subjects were typically recruited from RLS clinics rather than primary care or mental health settings; both settings are frequent sites for 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.

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

Only two RCTs directly compared pharmacologic options; specifically cabergoline to levodopa and pramipexole to dual-release levodopa/benserazide. We found no clear evidence of a dose effect for the outcomes of IRLS responders and mean change in IRLS scale scores for either dopamine agonists (k=3) or the alpha-2-delta ligands (k=2). Because studies reported a large placebo response, we urge caution in using information from uncontrolled studies as the basis for 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. One study comparing pramipexole versus pregabalin has recently been completed and is expected to be published shortly.

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.[87] Another small short-term RCT assessed intravenous iron versus placebo in patients on hemodialysis with normal iron stores. This study found no benefit. We identified one other study in adults with RLS believed secondary to end-stage renal disease. This study compared gabapentin to placebo, did not report validated RLS symptom scale scores, and showed no benefit with the drug.

For individuals unable to initiate or tolerate dopaminergic agents, or for whom these drugs have failed, recommended pharmacologic treatments include off-label opioids (morphine, oxycodone and methadone), sedative hypnotics, and tramadol. None of these are FDA approved for treatment of RLS and all have the potential for long-term abuse especially given the subjective nature of RLS symptoms and the large placebo response seen in other pharmacologic studies. We found no eligible studies evaluating these agents. A single crossover study of 11 patients assessed oxycodone versus placebo and reported improvement in leg sensation, motor restlessness, and alertness.

Randomized controlled studies should be initiated to evaluate the benefits of these therapies not approved for treatment of RLS in individuals who are refractive to standard pharmacologic treatment.

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

No 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[6] and presumably used in clinical practice.

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 pharmacologic treatment are not sustained over time, and that these treatments result in adverse effects and are often discontinued. Augmentation, a drug-induced exacerbation of the disease, can occur with dopaminergic drugs.

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

Given such limited evidence, patients and providers face uncertainty regarding the benefits and risks of RLS treatments for individuals whose symptoms are less severe, less frequent, of shorter duration, or diagnosed based on criteria that differ from RLS consensus definitions. Results from short-term efficacy trials in highly selected population of RLS patients should be carefully interpreted for their applicability to the more heterogeneous population of RLS patients in primary care settings. Applicability concerns are even more salient in light of direct-to-consumer marketing that has raised awareness of potential RLS symptoms. 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 whose symptoms mimic RLS (e.g., periodic leg movement disorders, nocturnal leg cramps, vascular or neurogenic claudication). They may also be younger, older, or have more comorbidities than subjects included in available RCTs.

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

Future Research Recommendations

Table 15 summarizes our main recommendations for future research based on the gaps identified in this review.

Table 15. Future research recommendations

Topical Issues	Specific Research Gaps	Recommendations
Limited evidence base	• Evidence base consists almost exclusively of pharmacologic treatments and dopamine agonists in particular. • Many classes of drugs used in clinical practice such as opioids and sedative hypnotics have not been evaluated in clinical trials. • We found no evidence for effectiveness of therapies in specific subgroups such as children, older adults with multimorbidities, or individuals with secondary RLS.	• Randomized trials of nonpharmacologic treatments including herbal therapy, mind-body medicine and manipulative treatments. • Randomized trials of classes of drugs other than dopamine agonists such as opioids and sedative hypnotics. • Randomized trials of effectiveness of drugs in specific patient subgroups such as children, older adults, and individuals with secondary RLS.
Long-term durability of treatment benefits	• Long-term durability of treatment benefits remains unknown.	• High-quality, long-term open-label extension studies from randomized trials that establish the time frame over which treatment benefits are sustained for different drugs and in specific group of patients.
Impact of patient characteristics on treatment outcomes	• We found no studies that address how patient characteristics including disease duration and previous therapy affect treatment outcomes.	• Randomized trials that report effectiveness of treatments for subgroups of patients such as those with different disease duration, new to treatment and for whom previous treatment failed.
Augmentation	• Augmentation is a significant harm with dopaminergic therapy and can lead to treatment discontinuation; yet, little is known about patient characteristics that may lead to augmentation.	• Long-term studies of augmentation with dopaminergic therapy. Potential study designs could include RCTs, prospective observational studies, and retrospective observational studies, including case-control studies. • 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).

Table 15. Future research recommendations (continued)

Methodological Issues	Findings	Research Needs
Time frame for evaluation of treatments	• Most clinical trials were of short duration (typically 12 weeks); yet RLS patients whose symptoms are severe confront a chronic, progressive disease that may require lifelong treatment.	• Longer term (>6 months) studies to establish if treatment benefits are sustained over time and to ascertain long-term harms such as augmentation.
Severity of disease	• Clinical trials include patients with moderate to very severe disease typically by specifying a cut-off in IRLS scale score (IRLS score>15).	• Evaluate and report treatment effectiveness for RLS patients with different degrees of symptom severity (e.g., categories of severity by IRLS scale scores: 1-10: mild; 11-20: moderate; 21-30: severe; 31-40: very severe).
Assessment of augmentation with dopaminergic therapy	• Considerable variation in reported prevalence of augmentation by type of drug, time frame of evaluation, and method of assessment.	• Assess augmentation with different dopaminergic drugs using standard criteria and methods of assessment.

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

References

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Acronyms and Abbreviations

AHRQ	Agency for Healthcare Research and Quality
CER	comparative effectiveness review
CGI	clinician-assessed global impressions
CI	confidence interval
FDA	Food and Drug Administration
ICTRP	International Controlled Trials Registry Platform
IRLS	International Restless Legs Syndrome Study Group Rating Scale
MD	Mean difference
MOS	Medical Outcomes Study Sleep Problem Index
MOS-SPI-II	Medical Outcome Study sleep problem indexes (SPI-I, SPI-II)
NIH	National Institutes of Health
PGI	patient-assessed global impressions
PLM	periodic limb movements
RCT	randomized controlled trials
RLS	Restless legs syndrome
RR	risk ratios
SMD	standardized mean difference
TEP	technical expert panel
WMD	weighted mean difference

Appendix A. Search Strategy

1 "restless leg$ syndrome".mp.
2 "Ekbom syndrome".mp.
3 Randomized Controlled Trials as Topic
4 randomized controlled trial/
5 random allocation/
6 double blind method/
7 single blind method/
8 clinical trial, phase i.pt.
9 clinical trial, phase ii.pt.
10 clinical trial, phase iii.pt.
11 clinical trial, phase iv.pt.
12 controlled clinical trial.pt.
13 randomized controlled trial.pt.
14 multicenter study.pt.
15 clinical trial.pt.
16 exp Clinical Trials as topic/
17 (clinical adj trial$).tw.
18 ((singl$ or doubl$ or treb$ or tripl$) adj (blind$3 or mask$3)).tw.
19 PLACEBOS/
20 placebo$.tw.
21 randomly allocated.tw.
22 (allocated adj2 random$).tw.
23 or/3-22
24 or/1-2
25 24 and 23
26 (case reports or comment or editorial or historical article or letter or news or newspaper article or"review").pt.
27 25 not 26
28 Epidemiologic studies/
29 exp case control studies/
30 exp cohort studies/
31 case control.tw.
32 (cohort adj (study or studies)).tw.
33 (Follow up adj (study or studies)).tw.
34 (observational adj (study or studies)).tw.
35 Longitudinal.tw.
36 Retrospective.tw.
37 cross sectional.tw.
38 cross-sectional studies/
39 or/1-2
40 or/28-38
41 39 and 40
42 (case reports or comment or editorial or historical article or letter or news or newspaper article or "review").pt.
43 41 not 42

Appendix B. Excluded Studies

1. Bliwise DL, Freeman A, Ingram CD, et al. Randomized, double-blind, placebo-controlled, short-term trial of ropinirole in restless legs syndrome. Sleep Medicine. 2005 Mar;6(2):141-7. PMID: 15716217. duration<4wks
2. Saletu M, Anderer P, Saletu-Zyhlarz GM, et al. Comparative placebo-controlled polysomnographic and psychometric studies on the acute effects of gabapentin versus ropinirole in restless legs syndrome. Journal of Neural Transmission. 2010 Apr;117(4):463-73. PMID: 20049491. duration<4wks
3. Saletu M, Anderer P, Saletu-Zyhlarz G, et al. Restless legs syndrome (RLS) and periodic limb movement disorder (PLMD): acute placebo-controlled sleep laboratory studies with clonazepam. European Neuropsychopharmacology. 2001 Apr;11(2):153-61. PMID: 11313161. duration<4wks
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5. Collado-Seidel V, Kazenwadel J, Wetter TC, et al. A controlled study of additional sr-L-dopa in L-dopa-responsive restless legs syndrome with late-night symptoms. Neurology. 1999 Jan 15;52(2):285-90. PMID: 9932945. *no primary outcome*
6. 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. *no primary outcome*
7. Earley CJ, Horska A, Mohamed MA, et al. A randomized, double-blind, placebo-controlled trial of intravenous iron sucrose in restless legs syndrome. Sleep Medicine. 2009 Feb;10(2):206-11. PMID: 18280205. *no primary outcome*
8. Happe S, Klosch G, Saletu B, et al. Treatment of idiopathic restless legs syndrome (RLS) with gabapentin. Neurology. 2001 Nov 13;57(9):1717-9. PMID: 11706121. *no primary outcome*
9. Inoue Y, Hirata K, Kuroda K, et al. Efficacy and safety of pramipexole in Japanese patients with primary restless legs syndrome: A polysomnographic randomized, double-blind, placebo-controlled study. Sleep Medicine. 2010 Jan;11(1):11-6. PMID: 19962941. *no primary outcome*
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15. Benes H, Kurella B, Kummer J, et al. Rapid onset of action of levodopa in restless legs syndrome: a double-blind, randomized, multicenter, crossover trial. Sleep. 1999 Dec 15;22(8):1073-81. PMID: 10617168. *no primary outcome*
16. Allen R, Becker PM, Bogan R, et al. Ropinirole decreases periodic leg movements and improves sleep parameters in patients with restless legs syndrome. Sleep. 2004 Aug 1;27(5):907-14. PMID: 15453549. *no primary outcome*
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Appendix C. Baseline Characteristics Tables

Appendix C. Table 1. Summary of study baseline characteristics for placebo-controlled, dopamine agonist trials (n=16)

Characteristic	Mean (range) *Unless otherwise note*	Number of trials reporting
Total number of patients evaluated	4861 (22 to 505)	16
Age of subjects, years	55.1 (50.9 to 60.0)	16
Women, %	65 (55 to 74)	16
Race/ethnicity, white %	96 (86 to 100)	7 [h,j-o]
RLS disease duration, years	8.9 (2.1 to 22.8)	13 [a,b,d-m,o]
Baseline IRLS total score (range 0 to 40)*	25.1 (22.0 to 28.6)	16
Patients with very severe disease, % (number of patients)	17.2 (3.3 to 37.1)	3 [m,n,p]
Studies with a mean IRLS score >30, indicating severe disease*	none	-
Previous RLS therapy, %	41.0 (21.8 to 80.8)	11 [a,d,h-p]
Patients who failed (experienced augmentation or rebound) with previous treatment, % (number of patients)	NR	NR**
Trials evaluating pramipexole, % (number of patients)	37 (1794)	5 [h-l]
Trials evaluating ropinirole, % (number of patients)	35 (1696)	7 [a-g]
Trials evaluating rotigotine (transdermal patch),% (number of patients)	28 (1371)	4 [m-p]
Crossover trials, % (number of patients)	0.5 (22)	1 [a]
Trial duration (double-blind phase), weeks	15 (6 to 28)	16
# of trials with a duration ≥6 months (%, number of patients)	3 [i,m,n] (37, n=1655)	
# of trials conducted in the Europe (%, number of patients)	9 [f,g,i-l, n-p] (59, n=2867)	
# of trials conducted in the US (%, number of patients)	5 [a-c,g,l] (33, n=1615)	
# of trials conducted in the Australia, Europe and North America, (%, number of patients)	2 [d,e] (8, n=379)	

* 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).
** 2 pramipexole trials (Högl, Winkelman) and 5 ropinirole trials (Bogan, Kushida, Montplaisir, Trenkwalder 2004, Walters) reported augmentation/end-of-dose rebound during previous RLS treatment as an exclusion criterion.

a=Adler; b=Bogan; c=Kushida; d=Waters; e=Montplasir; f=Trenkwalder 2004a; g=Benes *Ropinirole*
h=Winkelman; i=Högl; j=Montagna; k=Ferini-Strambi; l=Oertel 2007; *Pramipexole*
m=Hening; n=Trenkwalder 2008; o= Oertel 2010; p=Oertel 2008;*Rotigotine*

Appendix C. Table 2. Summary of study baseline characteristics for pramipexole trials

Characteristic	Mean (range) *Unless otherwise note*	Number of trials reporting
Total number of patients evaluated	1794 (331 to 404)	5
Age of subjects, years	55.2 (51.4 to 56.9)	5
Women, %	65 (60 to 70)	5
Race/ethnicity, white %	95.2 (86.4 to 99.5)	4 [a,c-e]
RLS disease duration, years	4.9 (3.4 to 5.7)	5
Baseline IRLS total score (range 0 to 40)*	24.5 (23.5 to 25.9)	5
Studies with a mean IRLS score >30, indicating severe disease*	none	-
Previous RLS therapy, %	26.0 (21.8 to 30.8)	5
Trial duration (double-blind phase), weeks	13.4 (6 to 26)	5
Trials with a duration ≥6 months, % (number of patients)	18 (331)	1 [b]
Trials conducted in the Europe, % (number of patients)	81 (1449)	4 [b-e]
Trials conducted in the US, % (number of patients)	19 (345)	1 [a]
Trials conducted in the Australia, Europe and North America, % (number of patients)	none	-

IRLS = International Restless Legs Scale
a=Winkelman; b=Högl; c=Montagna; d=Ferini-Strambi; e=Oertel 2007.
*Scoring criteria are: Mild (score 1-10); Moderate (score 11-20); Severe (score 21-30); Very severe (score 31-40)

Appendix C. Table 3. Summary of study baseline characteristics for ropinirole trials

Characteristic	Mean (range) *Unless otherwise note*	Number of trials reporting
Total number of patients evaluated	1696 (22 to 381)	7
Age of subjects, years	54.1 (50.9 to 60)	7
Women, %	62 (55 to 73)	7
Race/ethnicity, white %	NR	0
RLS disease duration, years	17.4 (10.5 to 22.8)	6 [a,b,d,e,f,g]
Baseline IRLS total score (range 0 to 40)*	25.0 (22 to 28.6)	7
Studies with a mean IRLS score >30, indicating severe disease*	none	-
Previous RLS therapy, %	44.3 (40.9 to 44.6)	2 [a,d]
Trial duration (double-blind phase), weeks	11.9 (8 to 12)	7
Trials with a duration ≥6 months	none	-
Trials conducted in the Europe, % (number of patients)	33 (522)	2 [f,g]
Trials conducted in the US, % (number of patients)	45 (765)	3 [a-c]
Trials conducted in the Australia, Europe and North America, % (number of patients)	22 (379)	2 [d,e]

IRLS = International Restless Legs Scale
a=Adler; b=Bogan; c=Kushida; d=Waters; e=Montplaisir; f=Trenkwalder 2004a; g=Benes 2011.
* Scoring criteria are: Mild (score 1-10); Moderate (score 11-20); Severe (score 21-30); Very severe (score 31-40)

Appendix C. Table 4. Summary of study baseline characteristics for rotigotine trials

Characteristic	Mean (range) *Unless otherwise note*	Number of trials reporting
Total number of patients evaluated	1371 (67 to 505)	4
Age of subjects, years	56.0 (52.4 to 59.4)	4
Women, %	65 (58 to 74)	4
Race/ethnicity, white %	97 (94 to 100)	3
RLS disease duration, years	2.1 (2.1 to 2.2)	2 [a,c]
Baseline IRLS total score (range 0 to 40)*	26.2 (23.3 to 28.1)	4
Studies with a mean IRLS score >30, indicating severe disease*	none	-
Previous RLS therapy, %	60.1 (35.8 to 80.8)	4
Trial duration (double-blind phase), weeks	21.2 (7 to 29)	4
Trials with a duration ≥6 months, % (number of patients)	70 (963)	2 [a,b]
Trials conducted in the Europe, % (number of patients)	63 (866)	3 [b-d]
Trials conducted in the US, % (number of patients)	49 (505)	1 [a]
Trials conducted in the Australia, Europe and North America, % (number of patients)	none	-

IRLS = International Restless Legs Scale
a=Hening; b=Trenkwalder 2008; c=Oertel 2010; d=Oertel 2008.
* Scoring criteria are: Mild (score 1-10); Moderate (score 11-20); Severe (score 21-30); Very severe (score 31-40)

Appendix D. Study Quality/Risk of Bias Tables

Appendix D. Table 1. Individual Study Quality for the Dopamine agonist trials

Study	Allocation concealment	Blinding	Intention-to treat analyses	Withdrawals adequately described	Quality
Bassetti, 2011[1]	Unclear	Double	No, patients required to complete both treatment periods (28 excluded, 42%)	Yes	Fair
Benes, 2011[2]	Adequate	Double	No, treatment and post-baseline data required (35 excluded, 13%)	Yes	Fair
Högl, 2011[3]	Unclear	Double*	No, treatment and post-baseline data** required (10 excluded, 3%)	No, only due to adverse effects	Fair
Montagna, 2011[4]	Unclear†	Double*	No, treatment and post-baseline data required (2 excluded, <1%)	Yes	Good
Hening, 2010[5]	Adequate	Double	No, post-baseline data** required (11 excluded, 2%)	Yes	Good
Oertel, 2010[35]	Adequate	Double	No, 1 excluded	Yes	Good
Ferini-Stambi, 2008[7]	Adequate	Double*	No, treatment and post-baseline data required (12 excluded, 3%)	Yes	Good
Kushida, 2008[8]	Unclear	Double	No, post-baseline data** required (3 excluded, <1%)	No, only due to adverse effects	Fair
Trenkwalder, 2008[10]	Adequate	Double	No, post-baseline data** required (11 excluded, 2%)	Yes	Good
Oertel, 2008[9]	Adequate	Double	No, treatment required (8 excluded, 2%)	Yes	Good
Oertel, 2007[11]	Unclear†	Double	No, treatment and post-baseline data required (7 excluded, 2%)	Yes	Good
Bogan, 2006[13]	Adequate	Double*	No, treatment required (1 excluded, <1%)	Yes	Good
Montplaisir, 2006[14]	Adequate	Double*	Yes	Yes	Good
Winkelman, 2006[15]	Adequate	Double	No, post-baseline data required (5 excluded, 1%)	Yes	Good
Adler, 2004[12]	Adequate	Double	Yes	Yes	Good
Trenkwalder, 2004[16]	Adequate	Double*	No, treatment required (2 excluded, <1%)	Yes	Good
Walters, 2004[17]	Adequate*	Double	Yes	Yes	Good

Double blinding denotes participants and investigators
*plus study team personnel and/or end points adjudicated by blinded committee
** primary efficacy outcome
† noted as adequate based on information in a Cochrane systematic review (Scholz H,Trenkwalder C,Kohnen R,Kriston L, Riemann D,Hornyak M. Dopamine agonists for the treatment of restless legs syndrome. *Cochrane Database of Systematic Reviews* 2011, Issue 3. Art. No.: CD006009. DOI: 10.1002/14651858.CD006009.pub2). This information was not evident in the trial publication but is presumed to have been obtained directly from the study sponsor.

Appendix D. Table 2. Individual Study Quality for the alpha-2-delta ligands trials

Study	Allocation concealment	Blinding	Intention-to treat analyses	Withdrawals adequately described	Quality
Bogan, 2010[21]	Unclear	Double	No, one subject withdrew consent (<1%)	Yes	Fair
Lee, 2011[18]	Adequate	Double*	No, IRLS score at baseline and at least once during treatment required (4 excluded, 1%)	Yes	Good
Winkelman, 2011[19]	Adequate	Double*	No, post-baseline data required	Yes	Good
Allen, 2010[20]	Adequate	Double	Yes	Yes	Good
Garcia-Borreguero**, 2010[22]	Adequate	Double	Yes	Yes	Good
Kushida, 2009[23]	Unclear	Double	No, treatment and post-baseline data required (2 excluded, <1%)	Yes	Fair
Garcia-Borreguero, 2002[24]	Adequate	Double	No, treatment required (2 excluded from each phase* 8.3%)	Yes	Good

*Double blinding denotes participants and investigators; **crossover trial.

Appendix D. Table 3. Individual Study Quality for the iron and miscellaneous trials

Study /Intervention	Allocation concealment	Blinding	Intention-to treat analyses	Withdrawals adequately described	Quality
Allen, 2011[26] Iron	Adequate	Double	No, 3 patients (7%) did not take or complete treatments	Yes	Good
Bayard, 2011[25] Bupropion	Adequate	Double	Yes	Partially	Good
Mitchell, 2011[36] Near infra-red light	Unclear, possibly inadequate (drawing "1" or "2" out of a bag	Single	Yes	Yes (none withdrew)	Fair
Grote, 2009[30] Iron	Adequate	Double	Yes	Yes	Good
Wang, 2009[31] Iron	Adequate	Double	Yes	Yes (none withdrew)	Good
Cuellar, 2009[32] Valerian	Adequate	Double*	No, study completers only (11 excluded, 23%)	Yes	Fair
Lettieri, 2009[33] Compression device	Adequate	Double*	Yes	Yes	Good
Aukerman, 2006[34] Exercise	Unclear	NR	No, 13 patients (32%) were unable to participate	Partially	Fair

Double blinding denotes participants and investigators
* Plus additional study personnel
CI = confidence intervals

Appendix E. Evidence Tables

Appendix E. Table 1. Evidence Table for primary RLS: dopamine agonist trials

Study Characteristics and Design	Inclusion/Exclusion criteria	Participant Characteristics	Intervention (daily dose) /Comparator (daily dose)	Risk of bias and Applicability
Study ID Bassetti, 2011[1] **Geographical Location**: Switzerland **Funding source**: Industry **Study Design**: crossover **Duration**: two treatment periods of 4 weeks	**Inclusion criteria**: • Adults 25 to 85 years of age, meeting diagnostic criteria of the IRLS. • RLS symptoms almost every day • *de novo* patients **Exclusion criteria**: none stated	**N**=67 (demographic information only for 39 patients in the per protocol population) **Age** (mean yr): 57 **Gender (Male %)**: 41 **Race/Ethnicity** (%): White 100% **Comorbidities**: NR **Criteria used to define RLS** *See inclusion criteria* **Baseline Severity**: moderate to severe. Baseline mean IRLS score: 21. 15 patients had severe RLS (score >20) with a mean baseline mean IRLS score of 26 **Previous RLS medication history**: 0% (see inclusion criteria)	**Intervention:** Pramipexole 0.125 mg and could be increased up to 0.75 mg (3 capsules) if tolerated and needed or decreased due to side effects. Mean daily dose was 0.49 mg. **Comparator:** Levodopa/ beserazide 125-375 mg (initiated at 100/25 mg) and could be increased up to 3 capsules) if tolerated and needed or decreased due to side effects. Mean daily dose was 192/48 mg. **A. Change in Disease Status and Impact** IRLS Scale Score **B. Quality of life** SF-36 **Subjective Sleep Quality** Epworth Sleepiness Scale **Definition of clinically significant Improvement:** NR **Adverse Effects Reported:** yes	**Assessment of Internal Validity** Sequence generation: unclear Allocation concealment: adequate Blinding: patients and personnel Incomplete outcome data: yes, 28 patients excluded from the analyses (42%) Selective outcome reporting: yes (no CGI reported) **Reviewer Comments** Very large dropout rate **Notes** Sponsor participated in the design and conduct of the study and in the management of the data
Study ID Benes, 2011[2] **Geographical Location**: Germany	**Inclusion criteria**: • aged 18-80 years of age with moderate to severe idiopathic RLS meeting diagnostic criteria of the IRLS (IRLS score ≥15 and ≥11 on	**N**=266 **Age** (mean yr): 58.5 **Gender (Male %)**: 29	**Intervention**: Ropinirole 0.25-4.0 mg/d (n=199). Patients who could not tolerate the 0.5mg dose were discontinued from the study.	**Assessment of Internal Validity** Sequence generation: adequate Allocation concealment: adequate

Study Characteristics and Design	Inclusion/Exclusion criteria	Participant Characteristics	Intervention (daily dose) /Comparator (daily dose)	Risk of bias and Applicability
Funding source: Industry **Study Design**: parallel design, dose-titration **Duration**: 12 weeks	the RLS Diagnostic Index • experienced ≥15 nights with symptoms of RLS in the previous 4 weeks or, if receiving treatment at screening, reported that they had symptoms of this frequency before treatment. In nights with RLS symptoms, patients had slept < 6 hours per night • mild depressive symptoms indicated by C12 points on the Montgomery–Asberg Depression Rating Scale **Exclusion criteria**: • secondary RLS (e.g., caused by renal insufficiency or iron insufficiency with baseline serum ferritin level <10 ng/ml) • other movement or primary sleep disorders • patients requiring treatment for RLS during the day/time clinically relevant DSM-IV psychiatric disorder like schizophrenia, bipolar disorder, or substance abuse • pregnant, not using effective contraception or suffering from medical conditions that would affect assessment (e.g., independent pain syndromes)	**Race/Ethnicity** (%): NR **Comorbidities**: mild depressive symptoms **Criteria used to define RLS** *See inclusion criteria* **Baseline Severity**: moderate to severe. Baseline mean IRLS score: 28.6 **Previous RLS medication history**: NR (not an exclusion)	Mean daily dose was 1.9 mg. **Comparator:** Placebo (n=67) **Outcomes reported:** A. **Change in Disease Status and Impact** IRLS Scale Score CGI-I Scale Score **B. Quality of life** NR **Subjective Sleep Quality** MOS sleep scale **Definition of clinically significant Improvement:** Responders defined as 1) ≥6 point reductions on the IRLS score from baseline, and 2) those who rated very much improved or much improved on CGI-I or PGI scale scores **Adverse Effects Reported:** yes	Blinding: patients and personnel Incomplete outcome data: yes, 35 patients excluded from the analyses (13%) – modified ITT (one study dose and one post-baseline assessment) Selective outcome reporting: no **Applicability:** patients with high RLS severity and comorbid depressive symptoms
Study ID Högl, 2011[3] **Geographical Location**: Europe **Funding source**: Industry **Study Design**: parallel design, dose-	**Inclusion criteria**: • Adults 18 to 85 years of age, meeting diagnostic criteria of the IRLS (>15 points) and have experienced RLS symptoms 2-3 days/week throughout the previous 3 months. **Exclusion criteria**: • serum ferritin ≤ 30 ng/mL • known hypersensitivity to	**N**=331 (2 patients not included in demographic data) **Age** (mean yr): 56.9 **Gender (Male %)**: 40.4 **Race/Ethnicity** (%): NR **Comorbidities**: NR	**Intervention:** Pramipexole 0.125 mg and could be increased up to 0.75 mg based on clinically efficient response (PGI) (n=166) **Comparator:** Placebo (n=163) **A. Change in Disease Status and Impact** IRLS Scale Score	**Assessment of Internal Validity** Sequence generation: not defined Allocation concealment: not defined Blinding: patients and personnel Incomplete outcome data: yes, 2 patients did not receive any treatment Selective outcome reporting: no

Study Characteristics and Design	Inclusion/Exclusion criteria	Participant Characteristics	Intervention (daily dose) /Comparator (daily dose)	Risk of bias and Applicability
titration **Duration**: 26 weeks	pramipexole • augmentation during previous RLS treatment, unsuccessful previous treatment with non-ergotamine dopamine agonists (e.g. pramipexole, ropinirole) • any non-RLS sleep disorder • any major psychiatric disorder within last 2 years, change in any antidepressant regimen with last 4 weeks (or any anticipated change) • any use of dopamine agonists, levodopa, or any medication or dietary supplement capable or altering RLS symptoms • women with child bearing potential (pregnant, breastfeeding women, inadequate contraception)	**Criteria used to define RLS** *See inclusion criteria* **Baseline Severity**: moderate to severe. Baseline mean IRLS score: 23.7 **Previous RLS medication history**: NR (see exclusion criteria) **Iron Status**: patients with serum ferritin ≤30 ng/m excluded	CGI Scale Score **B. Quality of life** RLS-QoL **Subjective Sleep Quality** RLS-6 **Definition of clinically significant Improvement:** 4.5 point difference between pramipexole and placebo at week 26 **Adverse Effects Reported:** yes	
Study ID Montagna, 2011[4] **Geographical Location:** International (52 hospitals, specialist offices, and primary care centers in Finland, France, Germany, Ireland, Italy, Korea, Spain , Sweden and the United Kingdom) **Funding source:** Industry **Study Design:** Parallel group **Duration:** 12 weeks	**Inclusion criteria:** • age 18 to 80 years • RLS diagnosed with IRLSSG criteria • RLS Severity; IRLS>15 (AND) • IRLS item 10 scale score≥ 2 (i.e., at least moderate RLS-associated mood disturbance) • RLS symptoms present ≥2 days per week during the prior two months **Exclusion criteria:** • patients with baseline Beck Depression Inventory-II score >28, with current presence of major depression, psychosis, or any other severe mental disorder requiring medical therapy or history of suicidal ideation • any clinical condition that could interfere with study participation or evaluation of results or that could increase patient's health risk • concomitant or prior treatment	**N**=362 **Age** (mean, yr): 55.5 **Gender (Male %):** 30 **Race/Ethnicity (%):** White 86%, Asian 13% **Comorbidities**: NR **Criteria used to define RLS** IRLSSG diagnostic criteria **Baseline Severity:** Severe RLS Baseline mean IRLS score: 25.9 **Previous RLS medication history**: Previous treatment I: 27.5%	**Intervention:** Pramipexole (n=203), daily, 1-3 hrs before bedtime. Dose started at 0.25 mg/day and titrated upwards during weeks 1 to 7 until patients were receiving maximum dose (4.0 mg/day) or optimal dose **Comparator:** Placebo (n=201) **Outcomes reported:** A. **Change in Disease Status and Impact** IRLS Scale Score **B. Quality of life** RLS QoL **Subjective Sleep Quality** NR **Definition of clinically significant Improvement:**	**Assessment of Internal Validity** Sequence generation: adequate Allocation concealment: adequate Blinding of participants and personnel, outcome assessors: yes Incomplete outcome data: yes, had to have received at least one dose of study drug and at least 1 post-baseline IRLS assessment Selective outcome reporting: no

Study Characteristics and Design	Inclusion/Exclusion criteria	Participant Characteristics	Intervention (daily dose) /Comparator (daily dose)	Risk of bias and Applicability
	(within 2 wks) with any drug that could influence RLS symptoms or depressive symptoms (e.g., anxiolytics or hypnotics) was forbidden • pregnant or breast feeding women	C:29.1% **Iron Status**: NR	Responders for IRLS scale score defined as those with ≥50% improvement from baseline **Adverse Effects Reported:** yes	
Study ID Hening, 2010[5] **Geographical Location:** US **Funding source:** Industry **Study Design:** Parallel group, fixed-dose **Duration:** 6 months	**Inclusion criteria:** • age 18 to 75 years • idiopathic RLS diagnosed with IRLS criteria • de novo patients (no pervious dopaminergic medication) or positive response to dopaminergic treatment (excluding rotigotine) • ≥15 points on IRLS scale, a score of ≥4 on CGI item 1 for disease severity **Exclusion criteria**: • secondary RLS • current history of sleep disorders • treatment with dopamine agonists within 28 days or levodopa within 7 days prior to baseline visit • concomitant treatment with hypnotics, antidepressants, anxiolytics, anticonvulsives, opioids, benzodiazepines, monoamine oxidase inhibitors, catechol-O-methyltransferase inhibitors, sedative antihistamines, psycho-stimulants, or amphetamines. Treatment with any of these drugs required a washout period of at least 7 days prior to baseline • concomitant diseases such as polyneuropathy, akathisia, claudication, varicosis, muscle fasciculation, painful legs and	**N**=505 **Age (mean yr)**: 52.4 **Gender (Male %):** 40 **Race/Ethnicity (%):** White 94% **Comorbidities**: NR **Criteria used to define RLS** IRLS criteria **Baseline Severity:** Moderate-Severe. Baseline mean IRLS score: 23 **Previous RLS medication history**: 36% **Iron Status**: NR	**Intervention:** Rotigotine transdermal patch, 0.5 mg/24 hour (n=99) 1.0 mg/24 hour (n=101) 2.0 mg/24 hour (n=99) 3.0 mg/24 hour (n=106) **Comparator:** Placebo (n=100) **Outcomes reported:** A. **Change in Disease Status and Impact** IRLS Scale Score CGI Scale Score **B. Quality of life** RLS QoL **Subjective Sleep Quality** MOS Sleep **Definition of clinically significant Improvement:** Responders for IRLS scale score defined as those with ≥50% improvement from baseline **Adverse Effects Reported:** yes	**Assessment of Internal Validity** Sequence generation: adequate Allocation concealment: adequate Blinding of participants and personnel: yes Incomplete outcome data: yes, post-baseline data required or at least one dose for safety analyses Selective outcome reporting: no

Study Characteristics and Design	Inclusion/Exclusion criteria	Participant Characteristics	Intervention (daily dose) /Comparator (daily dose)	Risk of bias and Applicability
	moving toes, or radiculopathy; other central nervous system diseases such as Parkinson's disease, dementia, progressive supranuclear paresis, multisystem atrophy, Huntington's Chorea, amyotrophic lateral sclerosis, or Alzheimer's disease • previous psychotic episodes • skin hypersensitivity to adhesives or other transdermals • myocardial infarction over the previous 12 months • clinically relevant cardiac, renal or hepatic dysfunction; arterial peripheral vascular disease • a QTc interval ≥500 ms at screening or an average QTc ≥500 ms (3 measurements) at baseline; symptomatic orthostatic hypotension at screening or baseline • any other condition which may jeopardize or compromise the subject's ability to participate in the trial • pregnant or lactating women, women without effective contraceptive methods • subjects with work-related irregular sleep patterns			
Study ID Oertel, 2010[6] **Geographical Location:** Europe (Austria, Finland, Germany, Italy and Spain) **Funding source:** Industry	**Inclusion criteria:** • Male and female subjects aged 18-75 yrs • RLS diagnosed with IRLSSG criteria • De novo subjects; i.e., no previous dopaminergic RLS treatment or previous positive response to dopaminergic RLS treatment • PLM index (PLMI) score of ≥ 15 PLM/h time in bed as documented	**N**=362 **Age** (mean yr): 59.4 **Gender (Male %):** 26 **Race/Ethnicity (%):** NR **Comorbidities**: NR	**Intervention:** Rotigotine transdermal patch, dose ranging from 1 mg/24 hour to optimal dose or a maximum dose of 3mg/ 24hr (n=46) **Comparator:** Placebo (n=20) **Outcomes reported:** A. **Change in Disease Status and Impact**	**Assessment of Internal Validity** Sequence generation: adequate Allocation concealment: adequate Blinding of participants and personnel, outcome assessors Yes Incomplete outcome data: yes, had to have received at least one dose of study medication, a

Study Characteristics and Design	Inclusion/Exclusion criteria	Participant Characteristics	Intervention (daily dose) /Comparator (daily dose)	Risk of bias and Applicability
	using polysomnography, AND IRLSSG rating scale score≥15 AND CGI item 1, severity of symptom score ≥4		IRLS Scale Score % of responders on CGI-I scale Score	valid baseline assessment and at least 1 post-baseline assessment
Study Design: Parallel group	• ability to remove/apply patches correctly and consistently	**Criteria used to define RLS** IRLS criteria	**B. Quality of life** NR	Selective outcome reporting: no
Duration: 4 weeks	**Exclusion criteria:** • previous Rotigotine treatment • secondary RLS • history of sleep disturbances other than owing to RLS • treatment with dopamine agonists within 28 days or levodopa within 7 days prior to baseline visit • concomitant diseases such as attention deficit hyperactivity disorder, polyneuropathy, akathisia, claudication, varicosis, muscle fasciculation, painful legs or moving toes, or radiculopathy; other central nervous system disorders such as Parkinson's disease, dementia, progressive supanuclear palsy, multiple system atrophy, Huntington's chorea, Alzheimer's. • previous psychotic episodes • skin hypersensitivity to adhesives or other transdermals • clinically relevant cardiac, renal, or hepatic dysfunction; venous or arterial peripheral vascular disease; or symptomatic orthostatic hypertension • concomitant treatment with neuroleptics, hypnotics, antidepressants, anxiolytics, anticonvulsants, budipine, opiods, benzodiazepenes, monoamine oxidase inhibitors, catechol-O-methlytransferase inhibitors, sedative antihistamines,	**Baseline Severity:** Moderate-Severe. Baseline mean IRLS score: 26 **Previous RLS medication history**: NR **Iron Status**: NR	**Subjective Sleep Quality** MOS sleep scale **Definition of clinically significant Improvement:** Responders defined as: • ≥50% score improvement in IRLS scale at the end of maintenance phase vs. baseline Remitters • IRLSSG rating scale≤10 or IRLS score =0 at the end of maintenance **Adverse Effects Reported:** yes	**Notes** "sponsor was involved in the design of the study, analysis and interpretation of the data, writing of the report, and in the decision to submit the paper for publication"

Study Characteristics and Design	Inclusion/Exclusion criteria	Participant Characteristics	Intervention (daily dose) /Comparator (daily dose)	Risk of bias and Applicability
	psychostimulants, amphetamines, or dopamine antagonist antiemetics except domperidone. • pregnant or nursing women; women without effective contraceptive methods • subjects with work-related irregular sleep patterns			
Study ID Ferini-Strambi, 2008[7] Geographical Location: Europe Funding source: Industry Study Design: parallel design, flexible dose Duration: 12 weeks	**Inclusion criteria**: • adults,18 to 80 years of age, meeting diagnostic criteria of the IRLS (>15 points) and have experienced RLS symptoms 2-3 days/week throughout the previous 3 months. **Exclusion criteria**: • clinically significant liver or renal disease, insulin-dependent diabetes, clinically significant laboratory abnormalities • present or past history of another sleep disorder • major depression, psychiatric disorders, suicidal behavior/ ideation • malignant melanoma • women who were pregnant, lactating, or of child bearing potential and did not use or had inadequate contraception • current use of medications that might affect RLS symptoms (e.g. levodopa, dopamine agonists, or antidepressants)	**N**=369 **Age** (mean yr): 56.6 **Gender** (Male %): 32 **Race/Ethnicity** (%): white 99.5 **Comorbidities**: NR **Criteria used to define RLS** *See inclusion criteria* **Baseline Severity**: moderate to severe symptoms. Baseline mean IRLS score: 24.4 **Previous RLS medication history**: 26.6% **Iron Status**: NR	**Intervention**: Pramipexole 0.125 mg and could be increased up to 0.75 mg based on clinically efficient response (PGI) and tolerability (n=182) **Comparator:** Placebo (n=187) **A. Change in Disease Status and Impact** IRLS Scale Score CGI Scale Score PGI Scale Score **B. Quality of life** RLS-QoL **Subjective Sleep Quality** Medical Outcomes Study (MOS) Sleep Scale **Definition of clinically significant Improvement:** none **Adverse Effects Reported:** yes	**Assessment of Internal Validity** Sequence generation: adequate Allocation concealment: adequate (blister packs) Blinding: patients, investigators, and study personnel, Incomplete outcome data: Selective outcome reporting: no
Study ID Kushida, 2008[8] **Geographical Location:** USA Multi center trial	**Inclusion criteria:** • age 18 to 79 years • RLS diagnosed with IRLS criteria, IRLS >20 points • baseline score ≥15 on the Insomnia severity index • symptom onset no later than 5 pm	**N**=362 **Age** (mean yr): 50.9 **Gender** (Male %): 40 **Race/Ethnicity (%):**	**Intervention**: Ropinirole 0.5-6.0 mg/d administered in divided doses (n=175) **Comparator:** Placebo (n=184) **Outcomes reported:**	**Assessment of Internal Validity** Sequence generation: NR Allocation concealment: NR Blinding of participants and personnel, outcome assessors NR

Study Characteristics and Design	Inclusion/Exclusion criteria	Participant Characteristics	Intervention (daily dose) /Comparator (daily dose)	Risk of bias and Applicability
Funding source: Industry **Study Design:** Parallel group **Duration:** 12 weeks	• ≥15 nights of RLS symptoms during the previous month **Exclusion criteria:** • secondary RLS • patients who had experienced augmentation or rebound with previous treatment • patients with other primary sleep disorders, movement disorders or medical conditions that would affect the assessment of RLS • experiencing daytime RLS symptoms that required treatment • taking medications known to affect RLS or sleep • experiencing withdrawal/ introduction/dose change of medications known to inhibit or induce P450CYP1A2	NR **Comorbidities**: NR **Criteria used to define RLS** IRLS criteria **Baseline Severity:** Moderate-Severe. Baseline mean IRLS score: 26 **Previous RLS medication history**: NR **Iron Status**: NR	A. **Change in Disease Status and Impact** IRLS Scale Score % of responders on CGI-I scale Score **B. Quality of life** NR **Subjective Sleep Quality** **xx** **Definition of clinically significant Improvement:** Responders defined as those who rated very much improved or much improved on CGI-I or PGI scale scores **Adverse Effects Reported:** yes	Incomplete outcome data: yes, had to have received at least one dose of study drug and at least 1 post-baseline IRLS assessment Selective outcome reporting**:** no **Reviewer Comments** No description of randomization procedures and no description of participant baseline characteristics except for age, gender and disease severity
Study ID Oertel, 2008[9] **Geographical Location**: Europe **Funding source**: Industry **Study Design**: parallel design, fixed-dose **Duration**: 6 weeks	**Inclusion criteria:** • 18 and 75 (inclusive) years of age; met the diagnosis of idiopathic RLS based on the revised four essential diagnostic criteria according to the IRLS Study Group • no previous treatment for RLS (de novo patients or intermittently untreated patients) or, if pretreated, had responded previously, according to medical history information, levodopa therapy and/or treatment with a dopamine agonist • had a body mass index (BMI) between 18 and 35 kg/m2 • IRLS sum score of ≥15 (at least moderate RLS) at baseline.	**N**=341 (demographic information on 333) **Age** (mean yr): 58.4 **Gender** (Male %): 33 **Race/Ethnicity (%):** NR **Comorbidities**: NR **Criteria used to define RLS** IRLS criteria **Baseline Severity:** Moderate-Severe. Baseline mean IRLS score: 27.9 **Previous RLS medication**	**Intervention:** Rotigotine transdermal patch, 0.5 mg/24 hour (n=52) 1.0 mg/24 hour (n=64) 2.0 mg/24 hour (n=49) 3.0 mg/24 hour (n=65) 4.0 mg/24 hour (n=56) **Comparator:** Placebo (n=55) **Outcomes reported:** A. **Change in Disease Status and Impact** IRLS Scale Score CGI Scale Score **B. Quality of life** RLS QoL **Subjective Sleep Quality** MOS Sleep	**Assessment of Internal Validity** Sequence generation: adequate Allocation concealment: adequate (blister packs) Blinding: patients, investigators Incomplete outcome data: yes, efficacy and safety analysis was performed for all patients who were treated with at least one dose of trial medication

Study Characteristics and Design	Inclusion/Exclusion criteria	Participant Characteristics	Intervention (daily dose) /Comparator (daily dose)	Risk of bias and Applicability
	Exclusion criteria: • secondary RLS associated with, for example, end-stage renal disease or iron-deficiency anemia • history of sleep disturbances if not caused by RLS • other concomitant neurological (e.g., symptoms or signs of polyneuropathy) or central nervous diseases or psychotic episodes • concomitant therapy with neuroleptics, hypnotics, antidepressants, anxiolytic drugs, anticonvulsive therapy, psycho-stimulatory drugs, levodopa or opioids was prohibited and must have been washed out for a sufficient period of time (at least 7 days or at least five half-lives if longer) at baseline. Pretreatment with dopamine agonists had to be discontinued four weeks prior to enrollment. In addition, patients who had a medical history indicating intolerability to prior dopaminergic therapy (if pretreated) were excluded • QTc-interval in resting ECG >450 ms in males and >470 ms in females, history of symptomatic orthostatic hypotension within 28 days prior to screening, or a systolic blood pressure <105 mmHg at trial entry.	**history**: 80.8%. Previous augmentation 25.5% **Iron Status**: NR	**Definition of clinically significant Improvement:** Responders for IRLS scale score defined as those with ≥50% improvement from baseline **Adverse Effects Reported:** yes	
Study ID Trenkwalder, 2008[10] **Geographical Location:** Europe (49 centers in Austria, Finland, Germany, Italy,	**Inclusion criteria:** • age 18 to 75 years • idiopathic RLS diagnosed with IRLS criteria • either no pervious dopaminergic medication for RLS or positive response to dopaminergic treatment	**N**=458 **Age** (mean, yr): 57.7 **Gender (Male %):** 27 **Race/Ethnicity (%):** White 99	**Intervention:** Rotigotine 1mg/24hr (n=115) Rotigotine 2mg/24 hr (n=112) Rotigotine 3mg/24 hr (n=114) **Comparator:** Placebo (n=117) **Outcomes reported:**	**Assessment of Internal Validity** Sequence generation: adequate Allocation concealment: adequate Blinding of participants and personnel, outcome assessors yes

Study Characteristics and Design	Inclusion/Exclusion criteria	Participant Characteristics	Intervention (daily dose) /Comparator (daily dose)	Risk of bias and Applicability
Netherlands, Spain, Sweden, UK) **Funding source:** Industry **Study Design:** Parallel group, fixed-dose **Duration:** 6 months	• ≥15 points on IRLS scale, a score of ≥4 on CGI item 1 for disease severity • ability to remove apply patches correctly and consistently **Exclusion criteria:** • secondary RLS • current history of sleep disturbances (sleep apnea syndrome, narcolepsy, • concomitant treatment with several types of drug (neuroleptics, hypnotics, antidepressants, anxiolytics, anticonvulsives, opioids, benzodiazepines, monoamine oxidase inhibitors, catechol-O methyltransferase inhibitors, sedative anti histamines, psychostimulants, or amphetamines) • concomitant diseases such as polyneuropathy, akathisia, claudication, varicosis, muscle fasciculation, painful legs and moving toes, orradiculopathy; other CNS diseases (eg, Parkinson's disease, dementia, progressive supranuclear palsy, multisystem atrophy, Huntington's disease, amyotrophic lateral sclerosis, or Alzheimer's disease); • previous psychotic episodes • skin hypersensitivity to adhesives or other transdermal preparations; • myocardial infarction over the past 12 months • clinically relevant cardiac, renal or hepatic dysfunction • arterial peripheral vascualar disease	**Comorbidities**: NR **Criteria used to define RLS** IRLSSG diagnostic criteria **Baseline Severity:** Moderate-Severe. Baseline mean IRLS score: 28.1 **Previous RLS medication history**: NR **Iron Status**: NR	A. **Change in Disease Status and Impact** IRLS Scale Score CGI-I scale Score **B. Quality of life** RLS QoL Generic health related quality of life SF-36) **Subjective Sleep Quality** MOS sleep scale **Definition of clinically significant Improvement:** Remission (IRLS sum score=0 or <10) Responders defined as having minimum 50% improvement from baseline in IRLS score or a CGI item 2 rating of "much improved" **Adverse Effects Reported:** yes Severity of Augmentation assessed with ASRS scale score	Incomplete outcome data: yes, had to have received at least one dose of study drug and at least 1 post-baseline IRLS assessment Selective outcome reporting: no **Reviewer Comments** Not ITT; patients analyzed different from patients randomized. Study sponsor involved in conception and design of the study and in data analysis and interpretation but had no role in data collection

Study Characteristics and Design	Inclusion/Exclusion criteria	Participant Characteristics	Intervention (daily dose) /Comparator (daily dose)	Risk of bias and Applicability
	• Qtc interval of 500 ms or longer at screening • symptomatic orthostatic hypotension at screening or baseline • intake of investigational drug 28 days before baseline visit • pregnant or lactating women • women without effective contraceptive methods • patients with work-related irregular sleep patterns			
Study ID Oertel, 2007[11] **Geographical Location**: Europe **Funding source**: Industry **Study Design**: parallel design, dose-response **Duration**: 6 weeks	**Inclusion criteria**: • male and female patients, 18 to 80 years of age, with a diagnosis of primary RLS based on IRLS criteria (score >15 points) • RLS symptoms present for at least 2 to 3 days per week in the 3 months before study entry. **Exclusion criteria**: • pregnant, breastfeeding women or using inadequate contraception • diabetic or had significant renal, hepatic, gastrointestinal, pulmonary, or endocrine disorders, other neurologic disease • sleep disorders unrelated to RLS, psychotic disorders • mental disorders, patients with a history of substance abuse.	**N**=345 **Age** (mean yr): 55.5 **Gender** (Male %): 34 **Race/Ethnicity** (%): white 99 **Comorbidities**: NR **Criteria used to define RLS** *See inclusion criteria* **Baseline Severity**: moderate to severe symptoms. Baseline mean IRLS score: 24.8 **Previous RLS medication history**: 31%. All pharmacologic treatment for RLS was discontinued within 14 days before the study's start **Iron Status**: NR	**Intervention:** Pramipexole 0.125 mg and could be increased up to 0.75 mg according to the Patient Global Impression scale (PGI) rating and overall tolerability of the drug (n=230) **Comparator:** Placebo (n=115) **A. Change in Disease Status and Impact** IRLS Scale Score CGI Scale Score **B. Quality of life** NR **Subjective Sleep Quality** none **Definition of clinically significant Improvement:** IRLS responders if they had an at least 50% reduction in their baseline IRLS score at week 6 **Adverse Effects Reported:** yes	**Assessment of Internal Validity** Sequence generation: not defined Allocation concealment: not defined Blinding: patients and personnel Incomplete outcome data: yes, had to have received one dose of study drug Selective outcome reporting: no
Study ID	**Inclusion criteria**:	**N**=22	**Intervention:** Ropinirole 0.5 to	**Assessment of Internal**

Study Characteristics and Design	Inclusion/Exclusion criteria	Participant Characteristics	Intervention (daily dose) /Comparator (daily dose)	Risk of bias and Applicability
Adler, 2004[12] **Geographical Location**: US **Funding source**: Industry **Study Design**: crossover **Duration**: 4 weeks of placebo then ropinirole or ropinirole then placebo with a 1-week wash-out between treatments	• IRLS criteria for RLS and needed a IRLS score ≥10. Patients were not allowed to be on RLS medication for at least 2 weeks prior to the baseline visit. **Exclusion criteria**: • previous use of ropinirole, secondary RLS • significant medical disease that would not allow use of ropinirole • an inability to complete diary forms • pregnancy or lactation.	**Age** (mean yr): 60 **Gender** (Male %): 27 **Race/Ethnicity** (%): NR **Comorbidities**: NR **Criteria used to define RLS** baseline total score ≥10 points on IRLS **Baseline Severity**: moderate to severe symptoms. Baseline mean IRLS score: 25.9 **Previous RLS medication history**: NR, none with ropinirole	6.0 mg (mean dose was 4.6 mg), administered in divided doses (n=22). **Comparator:** Placebo (n=22) **A. Change in Disease Status and Impact** IRLS Scale Score Global change score (-3 markedly worse to +3 markedly improved) **B. Quality of life** none **Subjective Sleep Quality** Epworth Sleepiness Scale **Definition of clinically significant Improvement:** none **Adverse Effects Reported:** yes	**Validity** Sequence generation: not defined Allocation concealment: adequate, packaging identical in appearance Blinding: patients, investigators Incomplete outcome data: no Selective outcome reporting: no
Study ID Bogan, 2006[13] **Geographical Location**: US **Funding source**: Industry **Study Design**: parallel design, flexible dose **Duration**: 12 weeks	**Inclusion criteria**: • adults, aged 18 to 79 years, with a diagnosis of primary RLS, using the IRLS diagnostic criteria (baseline total score ≥15 points • ≥15 nights of RLS symptoms during the previous month, and documented RLS symptoms for at least 4 of the 7 nights during the screening/ washout phase (between the screening visit and baseline visit)). **Exclusion criteria**: • signs of secondary RLS, including renal failure, pregnancy, and iron deficiency anemia. Iron deficiency	**N**=381 **Age** (mean yr): 52.3 **Gender** (Male %): 39 **Race/Ethnicity** (%): NR **Comorbidities**: NR **Criteria used to define RLS** *See inclusion criteria* **Baseline Severity**: moderate to severe symptoms. Baseline mean IRLS score: 22	**Intervention:** Ropinirole 0.25-4.0 mg (n=187) **Comparator:** Placebo (n=194) **A. Change in Disease Status and Impact** IRLS Scale Score CGI Scale Score **B. Quality of life** Johns Hopkins RLS Quality of Life questionnaire **Subjective Sleep Quality** Medical Outcomes Study (MOS) Sleep Scale	**Assessment of Internal Validity** Sequence generation: not defined Allocation concealment: adequate, packaging identical in appearance Blinding: patients, investigators, site monitors Incomplete outcome data: 1 patient from the placebo group did not receive any study medication Selective outcome reporting: no

Study Characteristics and Design	Inclusion/Exclusion criteria	Participant Characteristics	Intervention (daily dose) /Comparator (daily dose)	Risk of bias and Applicability
	was determined by each investigator based on clinical judgment of serum iron, ferritin, iron binding capacity, and percent saturation data obtained in each patient at screening. • patients who had experienced augmentation or rebound with previous treatment or had daytime symptoms as a part of their usual RLS symptom pattern were also excluded.	**Previous RLS medication history**: NR but patients who had experienced augmentation or rebound with previous treatment were excluded **Iron Status**: subjects with iron deficiency anemia excluded	**Definition of clinically significant Improvement:** NR **Adverse Effects Reported:** yes	
Study ID Montplasir, 2006[14] **Geographical Location:** 18 centers in Australia, Austria, Canada, Germany and South Africa **Funding source:** Industry **Study Design:** Parallel group **Duration:** 12 wks (Trial consisted of 24-week single blind phase during which all patients received ropinirole followed by 12 wk double blind, placebo controlled phase for treatment responders defined as those with reduction in total IRLS score of at least 6 points from baseline)	**Inclusion criteria:** • age 18 to 80 years • male or female patients • RLS diagnosed with IRLS criteria (IRLS ≥15 points) • ≥15 nights of RLS symptoms during the previous month; for patients who had been receiving treatment for RLS investigators used their best clinical judgment to assess whether or not the patient would have experienced a minimum of 15 nights of symptoms if the patient had not been treated **Exclusion criteria:** • patients with other primary sleep disorders that might affect the symptoms of RLS • patients with movement disorders • patients with a medical condition that would affect assessment of RLS or the tolerability of ropinirole • experiencing daytime RLS symptoms that required treatment • experiencing augmentation or end of dose rebound from previous therapy • secondary RLS (end stage renal disease, iron deficiency anemia or	**N**=362 **Age** (mean (SD), yr): 53.5 **Gender (Male %):** 45 **Race/Ethnicity (%):** NR **Comorbidities**: NR **Criteria used to define RLS** IRLSSG diagnostic criteria **Baseline Severity:** Moderate-Severe. Baseline mean IRLS score: initially 26 (single-blind phase) **Previous RLS medication history**: NR **Iron Status**: NR	**Intervention** Ropinirole (n=45) daily, 1-3 hrs before bedtime. Doses started at 0.25mg/day and titrated upwards to a maximum dose of 4 mg/day. **Comparator:** Placebo (n=47) **Outcomes reported:** A. **Change in Disease Status and Impact** IRLS Scale Score CGI-I scale Score **B. Quality of life** RLS QoL Generic health related quality of life SF-36) **Subjective Sleep Quality** MOS sleep scale **Definition of clinically significant Improvement:** NR **Adverse Effects Reported:** yes	**Assessment of Internal Validity** Sequence generation: adequate Allocation concealment: adequate Blinding of participants and personnel, outcome assessors yes Incomplete outcome data: yes, had to have received at least one dose of study drug and at least 1 post-baseline IRLS assessment Selective outcome reporting: no

Study Characteristics and Design	Inclusion/Exclusion criteria	Participant Characteristics	Intervention (daily dose) /Comparator (daily dose)	Risk of bias and Applicability
	pregnancy • history of alcohol or drug abuse • previous intolerance to dopamine agonists			
Study ID Winkelman, 2006[15] **Geographical Location:** United States Multicenter Trial(43 Sites) **Funding source:** Industry **Study Design:** Parallel group (4 arms; comparison of 3 fixed doses of pramipexole with placebo) **Duration:** 12 weeks	**Inclusion criteria:** • adults (age 18 to 80 years) • RLS diagnosed with IRLSSG criteria • moderate to severe disease; IRLS score>15 and symptoms at least 2 to 3 days per week for at least the previous 3 months **Exclusion criteria:** • recent RLS treatment (concurrently or during the prior 2 wks) • history of failed RLS treatment • recent use of dietary supplement or medication with potential to affect RLS symptoms • any medical condition that could affect assessment or contraindicate pramipexole • any sleep disorder other than RLS	**N**=345 **Age** (mean, yr): 51.4 **Gender (Male %):** 38% **Race/Ethnicity (%):** %White=97.3 **Comorbidities**: NR **Criteria used to define RLS** IRLSSG criteria **Baseline Severity:** Moderate-Severe disease. Baseline mean IRLS score: 23.5 **Previous RLS medication history**: NR **Iron Status**: NR	**Intervention:** Pramipexole (n=254) at fixed doses of 0.25 (n=89), 0.5 (n=80) and 0.75 (n=90) mg/day, taken each evening 2 to 3hrs before anticipated bedtime **Comparator:** Placebo (n=86) **Outcomes reported:** A. **Change in Disease Status and Impact** IRLS Scale Score CGI-I Scale Score **B. Quality of life** RLS-QoL **Subjective Sleep Quality** Epworth Sleepiness Scale (ESS**)** **Length of follow-up** **Definition of clinically significant Improvement:** Responder= patient with CGI-I score of very much improved or improved (or) at least 50% reduction in IRLS score from baseline **Adverse Effects Reported:** yes	**Assessment of Internal Validity** Sequence generation: adequate, computer generated randomization schedule Allocation concealment: unclear Blinding of participants and personnel, outcome assessors Yes Incomplete outcome data: yes, had to have received one dose of study drug Selective outcome reporting: no
Study ID Trenkwalder, 2004[16]	**Inclusion criteria:** • age 18 to 79 years • RLS diagnosed with IRLS criteria	**N**=362 **Age** (mean (SD), yr): 55.1	**Intervention** Ropinirole (n=147) daily, 1-3 hrs before bedtime. Dose starting at 0.25mg/day	**Assessment of Internal Validity** Sequence generation: adequate

Study Characteristics and Design	Inclusion/Exclusion criteria	Participant Characteristics	Intervention (daily dose) /Comparator (daily dose)	Risk of bias and Applicability
Geographical Location: Europe (43 hospitals and sleep clinics in: Austria, Belgium, France, Germany, Italy, Netherlands, Norway, Spain, Sweden, and the UK) **Funding source:** Industry **Study Design:** Parallel group **Duration:** 12 weeks	• RLS Severity; IRLS>20 • baseline score≥ 15 on the Insomnia severity index (AND) • ≥15 nights of RLS symptoms during the previous month, or if receiving treatment reported they had had symptoms of this frequency before treatment **Exclusion criteria:** • patients with other primary sleep disorders or other clinically relevant conditions affecting assessments • experiencing daytime RLS symptoms that required treatment • experiencing augmentation or end of dose rebound • secondary RLS (end stage renal disease, iron deficiency anemia or pregnancy • history of alcohol or drug abuse • previous intolerance to dopamine agonists	**Gender (Male %):** 37% **Race/Ethnicity (%):** NR **Comorbidities**: NR **Criteria used to define RLS** IRLSSG diagnostic criteria **Baseline Severity:** Moderate-Severe. Baseline mean IRLS score: 24.8 **Previous RLS medication history**: NR **Iron Status**: NR (secondary RLS de to iron deficiency an exclusion)	and titrated upwards during weeks 1 to 7 until patients were receiving maximum dose (4.0 mg/day) or optimal dose **Comparator:** Placebo (n=139) **Outcomes reported:** A. **Change in Disease Status and Impact** IRLS Scale Score CGI-I scale Score **B. Quality of life** RLS QoL Generic health related quality of life SF-36) **Subjective Sleep Quality** MOS sleep scale **Definition of clinically significant Improvement:** NR **Adverse Effects Reported:** yes	Allocation concealment: adequate Blinding of participants and personnel, outcome assessors yes Incomplete outcome data: yes, had to have received at least one dose of study drug and at least 1 post-baseline IRLS assessment Selective outcome reporting: no **Applicability** Primary RLS patients with severe disease experiencing night time symptoms and insomnia
Study ID Walters, 2004[17] **Geographical Location:** International, Multicenter (Australia, Europe, North America) **Funding source:** Industry **Study Design:** Parallel group	**Inclusion criteria:** • age 18 to 79 years • RLS diagnosed with IRLSSG criteria • RLS Severity; IRLS>20 • ≥15 nights of RLS symptoms during the previous month; if patient was undergoing treatment for RLS, then clinician judged whether or not patient would have experienced at least 15 nights of symptoms if they had not been treated **Exclusion criteria:** • experiencing daytime RLS	**N**=267 **Age** (mean (SD), yr): 55.5 **Gender (Male %):** 40 **Race/Ethnicity (%):** NR **Comorbidities**: NR **Criteria used to define RLS** IRLSSG diagnostic criteria	**Intervention** Ropinirole (n=131) daily, 1-3 hrs before bedtime Flexible dosing starting at 0.25mg/day up to a maximum of 4mg/day. **Comparator:** Placebo (n=136) **Outcomes reported:** A. **Change in Disease Status and Impact** IRLS Scale Score CGI-I scale Score **B. Quality of life**	**Assessment of Internal Validity** Sequence generation: adequate Allocation concealment: adequate Blinding of participants and personnel, outcome assessors yes Incomplete outcome data: yes, had to have received at least one dose of study drug and at least 1 post-baseline IRLS assessment Selective outcome reporting: no

Study Characteristics and Design	Inclusion/Exclusion criteria	Participant Characteristics	Intervention (daily dose) /Comparator (daily dose)	Risk of bias and Applicability
Duration: 12 weeks	symptoms that required treatment • experiencing augmentation or end of dose rebound with previous medication • secondary RLS (end stage renal disease, iron deficiency anaemia or pregnancy • other sleep disorders (e.g. narcolepsy, sleep terror disorder, sleep walking disorder, breathing related sleep disorder) • medical conditions that would affect assessment of RLS (e.g., rheumatoid arthritis, fibromyalgia syndrome) • known intolerance to ropinirole • abusing other substances	**Baseline Severity:** Moderate-Severe. Baseline mean IRLS score: 24.2 **Previous RLS medication history**: I:48.5%C: 43.4% **Iron Status**: NR	RLS QoL QoL by SF-36, a generic quality of life instrument **Subjective Sleep Quality** NR **Definition of clinically significant Improvement:** NR **Adverse Effects Reported:** yes	

CGI = Clinical Global Impression; IRLS = International RLS Study Group Rating Scale; NR = not reported; PGI = Patient Global Impression; PLMS = periodic leg movements during sleep; SF-36 = Short-Form 36-item Questionnaire

Appendix E. Table 2. Evidence Table for primary RLS: alpha-2-delta ligands trials

Study Characteristics and Design	Inclusion/Exclusion criteria	Participant Characteristics	Intervention (daily dose) /Comparator (daily dose)	Risk of bias and Applicability
Study ID Lee, 2011 [18] **Geographical Location**: US **Funding source**: Industry **Study Design**: parallel design **Duration**: 12 weeks	**Inclusion criteria**: • adults meeting diagnostic criteria of the IRLS for primary IRLS (IRLS score ≥15 points, RLS symptoms occurring ≥15 nights in the month prior to screening (or if on treatment, the same frequency of symptoms before treatment was started), documented RLS symptoms for ≥ 4 of the 7 consecutive evenings/nights during the baseline period • discontinued dopamine agonists, gabapentin and any other RLS treatments for ≥ 2 weeks prior to baseline. **Exclusion criteria**: • history of RLS symptom augmentation or end-of-dose rebound with previous dopamine agonist treatment • body mass index of > 34 kg/m2, an estimated • creatinine clearance of < 60 mL/min • serum ferritin level of < 20 ng/mLcurrently suffering from moderate or severe RLS • depression, a neurologic disease, a sleep disorder, or a movement disorder other than RLS • clinically significant or unstable medical conditions, or other medical conditions or drug therapy which could have affected RLS treatment efficacy • pregnant or lactating.	**N**=325 **Age** (mean yr): 49.0 **Gender** (Male %): 41.4 **Race/Ethnicity** (%): white 94.3 **Comorbidities**: NR **Criteria used to define RLS** *See inclusion criteria* **Baseline Severity**: moderate to severe. Baseline mean IRLS score: 23.3 **Previous RLS medication history**: 35.5% **Iron Status**: subjects with a serum ferritin level of < 20 ng/mL excluded	**Intervention 1:** Gabapentin enacarbil 1,200 mg (2 600 mg extended release tablets) (n=113) **Intervention 1:** Gabapentin enacarbil 600 mg (1 600 mg extended release tablet and 1 placebo) (n=115) **Comparator:** Placebo (n=108) **A. Change in Disease Status and Impact** IRLS Scale Score CGI Scale Score **Subjective Sleep Quality** MOS **Definition of clinically significant Improvement:** IRLS responders were patients with ≥50% improvement in IRLS total score **Adverse Effects Reported:** yes	**Assessment of Internal Validity** Sequence generation: unclear Allocation concealment: unclear Blinding: patients and investigators Incomplete outcome data: yes, modified intent-to-treat population (safety population who completed a baseline and at least one on-treatment IRLS assessment) Selective outcome reporting: no **Reviewer Comments** Research funding for design and conduct of this study, and collection, management, analysis, and interpretation of the data were sponsored by industry. Preparation, review, and approval of the manuscript was in part sponsored by industry.
Study ID Winkleman, 2011[19] **Geographical**	**Inclusion criteria**: • adults (≥18 years of age) meeting diagnostic criteria of the IRLS for primary IRLS	**N**=136 (demographic information on 131) **Age** (mean yr): 52.0	**Intervention 1:** Gabapentin enacarbil 1,200 mg (2 600 mg extended release tablets)	**Assessment of Internal Validity** Sequence generation: adequate Allocation concealment:

Study Characteristics and Design	Inclusion/Exclusion criteria	Participant Characteristics	Intervention (daily dose) /Comparator (daily dose)	Risk of bias and Applicability
Location: US **Funding source**: Industry **Study Design**: Crossover, fixed-dose **Duration**: 12 weeks	• documented RLS symptoms for ≥ 4 of the 7 evenings/ nights and 15 days in previous month prior to baseline (if untreated) • IRLS score ≥15 points • Significant sleep disturbance on item 4 of the IRLS • PLMS index (PLMS per hour) ≥15 on actigraphy (average over 5 nights using both legs) • Subjects receiving treatment for RLS were required to discontinue and wash out for a minimum of 5 half-lives or 7 consecutive nights **Exclusion criteria**: • history of sleep apnea or other sleep disorders • secondary RLS diagnosed by the investigator (eg, low ferritin, pregnancy) • neurologic disease or movement disorder • creatinine clearance < 60 mL/minute • serum ferritin < 20 lg/ • taking any medication that could affect sleep/wake, RLS, or periodic limb movements, including antidepressants • Previous treatment with gabapentin enacarbil	**Gender** (Male %): 42 **Race/Ethnicity** (%): white 92 **Comorbidities**: NR **Criteria used to define RLS** *See inclusion criteria* **Baseline Severity**: moderate to severe. Baseline mean IRLS score: 25.4. Severely ill 21% **Previous RLS medication history**: 42% **Iron Status**: subjects with a serum ferritin level of < 20 ng/mL excluded	**Comparator:** Placebo **A. Change in Disease Status and Impact** IRLS Scale Score CGI Scale Score PGI Scale Score **Subjective Sleep Quality** Subjective Post Sleep Diary **Definition of clinically significant Improvement:** NR **Adverse Effects Reported:** yes	adequate Blinding: patients and personnel Incomplete outcome data: yes, had to have received ≥1 dose of study drug and have ≥1 post-randomization assessment Selective outcome reporting: no **Reviewer Comments** Research funding for design and conduct of this study, and collection, management, analysis, and interpretation of the data were sponsored by industry. Preparation and review of the manuscript was sponsored by industry.
Study ID Allen, 2010[20] **Geographical Location**: multinational, Europe and US **Funding source**: Industry	**Inclusion criteria**: • adults, 18 to 65 years of age, meeting diagnostic criteria of the IRLS for idiopathic IRLS (IRLS score ≥15 points, RLS symptoms occurring ≥15 nights between 5 PM and 7 AM disturbing sleep for past 6 months). **Exclusion criteria**:	**N**=137 **Age** (mean yr): 50.8 **Gender** (Male %): 34.3 **Race/Ethnicity** (%): NR **Comorbidities**: NR	**Intervention:** Pregabalin (n=114 total), 5 arms. 50 mg (n=22), 100 mg (n=23), 150 mg (n=22), 300 mg (n=24), 450 mg (n=23) **Comparator:** Placebo (n=23) **A. Change in Disease Status and Impact**	**Assessment of Internal Validity** Sequence generation: adequate Allocation concealment: adequate Blinding: patients and personnel Incomplete outcome data: yes, had to have received ≥1 dose of study drug and have ≥1 post-randomization assessment

Study Characteristics and Design	Inclusion/Exclusion criteria	Participant Characteristics	Intervention (daily dose) /Comparator (daily dose)	Risk of bias and Applicability
Study Design: parallel design **Duration**: 12 weeks	• placebo responders (see reviewer comments), secondary RLS, severe daytime symptoms (requiring treatment), present or past history of another sleep disorder (e.g. sleep apnea) • history of failure to respond to gabapentin, serum ferritin <10 µg/L, failure to have appropriate washout periods for medicines that affect sleep • currently on shift work • clinically significant liver (bilirubin, aspartate aminotransferase, or alanine aminotransferase levels >3 x upper limit of normal) or renal disease (creatinine clearance <60 mL/min) • presence of symptomatic neuropathies, severe central nervous system degenerative disease, past or present history of lumbar radiculopathy or central spinal stenosis • pregnancy, lactating, or of child bearing potential and did not use or had inadequate contraception.	**Criteria used to define RLS** *See inclusion criteria* **Baseline Severity**: moderate to severe. Baseline mean IRLS score: 24.8 **Previous RLS medication history**: NR **Iron Status**: subjects with serum ferritin <10 µg/L excluded	IRLS Scale Score CGI Scale Score **B. Quality of life** RLS-QoL SF-36 **Subjective Sleep Quality** MOS **Definition of clinically significant Improvement:** IRLS responders were patients with ≥50% improvement in IRLS total score **Adverse Effects Reported:** yes	Selective outcome reporting: no **Reviewer Comments** Placebo responders, defined as having >50% improvement in IRLS total score between the beginning of the placebo run-in and baseline were excluded
Study ID Bogan, 2010[21] **Geographical Location**: US **Funding source**: Industry **Study Design**: parallel design, fixed dose **Duration:** 12 wks	**Inclusion criteria:** • adults, aged 18 years or older with a diagnosis of moderate to severe primary RLS using IRLS Study Group diagnostic criteria had RLS symptoms ≥15 night during the month prior to screening (or, if on treatment, similar symptom frequency before treatment initiation) and symptoms on ≥4 nights during the 7-day baseline period. Prior RLS treatment was discontinued at least 2 weeks prior to baseline. Patients also had an	**N**=194 (double-blind phase) **Age** (mean yr): 51.5 **Gender** (Male %): 41 **Race/Ethnicity** (%): white 95% **Comorbidities**: NR **Criteria used to define RLS** *See inclusion criteria*	**Intervention:** Gabapentin enacarbil 1,200 mg (2 600 mg tablets) (n=96) **Comparator:** Placebo (n=98) **A. Change in Disease Status and Impact** IRLS Scale Score CGI Scale Score **B. Quality of life** RLS-QoL	**Assessment of Internal Validity** Sequence generation: unclear Allocation concealment: unclear Blinding: patients and investigators Incomplete outcome data: yes, modified intent-to-treat population (1 dose required and one-post randomization visit) Selective outcome reporting: no

Study Characteristics and Design	Inclusion/Exclusion criteria	Participant Characteristics	Intervention (daily dose) /Comparator (daily dose)	Risk of bias and Applicability
(Trial consisted of 24-week single blind phase during which all patients received gabapentin enacarbil followed by 12 week double blind, placebo controlled phase for treatment responders defined as having an IRLS total score of less than 15 points at week 24 that had decreased by at least 6 points compared with baseline, an assessment of "much improved" or "very much improved" on the investigator-rated Clinical Global Impression Improvement (CGI-I) scale at week 24,and were stable while taking gabapentin enacarbil, 1200 mg, for at least 1 month before the DB phase.)	International Restless Legs Scale (IRLS) total score ≥15 at the beginning and end of the baseline period. • Creatinine clearance ≥60 mL/min. **Exclusion criteria:** • secondary RLS • body mass index >34 kg/m2 • currently experiencing moderate to severe depressive disorder • primary sleep disorders, neurologic disease, or movement diosroders other than RLS • history of RLS symptom augmentation or end-of-dose rebound with previous RLS treatment • pregnancy or breastfeeding	**Baseline Severity**: moderate to severe. Baseline mean IRLS score (single-blind phase): 24.7 **Previous RLS medication history**: 37% **Iron Status**: NR	**Subjective Sleep Quality** MOS **Definition of clinically significant Improvement** See duration, responders for single blind phase **Adverse Effects Reported:** yes	
Study ID Garcia-Borreguero, 2010[22] **Geographical Location**: Spain **Funding source**: Industry **Study Design**: parallel design, flexible dose	**Inclusion criteria:** • adults aged 18–80 years with idiopathic RLS (International Restless Legs Scale [IRLS] total score ≥15 points at baseline) that interfered with sleep onset or sleep maintenance on ≥4 nights/week for at least 6 months **Exclusion criteria:** • secondary RLS • coexistence of severe medical or psychiatric disorders	**N**=58 **Age** (mean yr): **Gender** (Male %): **Race/Ethnicity** (%): white **Comorbidities**: NR **Criteria used to define RLS:** *See inclusion criteria* **Baseline Severity**: moderate	**Intervention:** Pregabalin, starting at 150 mg (n=30). Study dose adjustments were performed weekly and were based on clinical judgment of their efficacy and tolerability. The mean daily dosage of pregabalin at the end of treatment was 337.50 mg **Comparator:** Placebo (n=28) **A. Change in Disease Status and Impact**	**Assessment of Internal Validity** Sequence generation: adequate Allocation concealment: adequate Blinding: patients and investigators Incomplete outcome data: no Selective outcome reporting: no **Reviewer Comments** A single-blind placebo run-in was performed. Patients who had a >40% improvement in

Study Characteristics and Design	Inclusion/Exclusion criteria	Participant Characteristics	Intervention (daily dose) /Comparator (daily dose)	Risk of bias and Applicability
Duration: 12 weeks	• previous treatment lasting >12 weeks with DAs, serum ferritin <10 µg/L • severe comorbid sleep disorders that might confound assessment • shift work.	to severe. Baseline mean IRLS score: 20.6 **Previous RLS medication history**: 12% **Iron Status** (baseline mean ferritin level, µg/L): 97	IRLS Scale Score CGI Scale Score **B. Quality of life** **Subjective Sleep Quality** MOS **Definition of clinically significant Improvement:** IRLS responders were patients with ≥50% improvement in IRLS total score **Adverse Effects Reported:** yes	their IRLS total score during this period were considered placebo responders and excluded from the study.
Study ID Kushida, 2009[23] **Geographical Location**: USA **Funding source**: Industry **Study Design**: parallel design, fixed-dose **Duration**: 12 weeks	**Inclusion criteria:** • adults, aged 18 years or older with a diagnosis of moderate to severe primary RLS using IRLS Study Group diagnostic criteria had RLS symptoms ≥15 days during the month prior to screening (or, if on treatment, similar symptom frequency before treatment initiation) and symptoms on ≥4 nights during the 7-day baseline period. Prior RLS treatment was discontinued at least 2 weeks prior to baseline. Patients also had an International Restless Legs Scale (IRLS) total score ≥15 at the beginning and end of the baseline period. **Exclusion criteria:** • secondary RLS • body mass index ≥34 kg/m2 • were currently experiencing or being treated for moderate to severe depression • other primary sleep disorders, or	**N**=222 **Age** (mean yr): 51.1 **Gender** (Male %): 40 **Race/Ethnicity** (%): white 97 **Comorbidities**: NR **Criteria used to define RLS** IRLSSG **Baseline Severity**: moderate to severe. Baseline mean IRLS score: 22.8 **Previous RLS medication history**: 32% **Iron Status**: NR (no secondary RLS)	**Intervention:** Gabapentin enacarbil (XP13512) starting at 1,200 mg (adjusted if AEs present) (n=114) **Comparator:** Placebo (n=108) **A. Change in Disease Status and Impact** IRLS Scale Score CGI Scale Score **B. Quality of life** Johns Hopkins RLS Quality of Life (RLSQoL) **Subjective Sleep Quality** MOS Pittsburgh Sleep Diary **Definition of clinically significant Improvement: For** IRLS total score, response was defined as a six-point decrease from baseline and a score <15. **Adverse Effects Reported:**	**Assessment of Internal Validity** Sequence generation: adequate Allocation concealment: unclear Blinding: patients and investigators Incomplete outcome data: yes, modified intent-to-treat population (all patients who took at least one dose of study medication and completed a baseline and at least one on-treatment IRLS assessment) Selective outcome reporting: no

Study Characteristics and Design	Inclusion/Exclusion criteria	Participant Characteristics	Intervention (daily dose) /Comparator (daily dose)	Risk of bias and Applicability
	neurologic disease or movement disorders • history of RLS symptom augmentation or end-of-dose rebound with previous dopaminergic treatment • pregnancy		yes	
Study ID Garcia-Borreguero 2002[24] **Geographical Location**: Spain **Funding source**: Industry (one author an employee of Pfizer) **Study Design**: cross-over, flexible dose **Duration**: two 6-week treatment periods with a 1-week washout period in between	**Inclusion criteria**: • criteria for RLS established by the International RLS Study Group **Exclusion criteria**: • ferritin levels below 20 mcg/mL	**N**=24 **Age** (mean yr): 55 **Gender** (Male %): 33 **Race/Ethnicity** (%): NR **Comorbidities**: NR **Criteria used to define RLS** Primary or secondary RLS: **Baseline Severity**: Baseline mean IRLS score: 20 **Previous RLS medication history**: None of the patients had been treated previously with gabapentin or dopaminergic medication. **Iron Status**: Patients with a ferritin value <45 mcg/mL were included in the study and classified as iron deficient. Iron was not administered orally until study completion.	**Intervention:** Gabapentin starting at 600 mg daily up to a maximal dose of 2,400 mg/day. The decision to modify the dosage was based on clinical criteria (i.e., therapeutic efficacy and tolerance). **Comparator:** Placebo **A. Change in Disease Status and Impact** IRLS Scale Score **B. Quality of life** **Subjective Sleep Quality** Pittsburgh Sleep Quality Index **Definition of clinically significant Improvement:** NR **Adverse Effects Reported:** yes	**Assessment of Internal Validity** Sequence generation: adequate Allocation concealment: adequate Blinding: patients and investigators Incomplete outcome data: no, treatment required Selective outcome reporting: no

CGI = Clinical Global Impression; IRLS = International RLS Study Group Rating Scale; MOS = Medical Outcomes Study Sleep Score; NR = not reported; PGI = Patient Global Impression; PLMS = periodic leg movements during sleep; SF-36 = Short-Form 36-item Questionnaire

Appendix E. Table 3. Evidence Table for primary RLS: Bupropion

Study Characteristics and Design	Inclusion/Exclusion criteria	Participant Characteristics	Intervention (daily dose) /Comparator (daily dose)	Risk of bias and Applicability
Study ID **Bayard, 2011**[25] **Geographical Location**: USA **Funding source**: Academic **Study Design**: parallel design, fixed-dose **Duration**: 6 weeks	**Inclusion criteria**: • Patients also had an International Restless Legs Scale (IRLS) total score ≥15 and meet diagnostic criteria based on 4 screening questions **Exclusion criteria**: • history of seizure disorder, alcoholism, suicidal history or ideation • inability to return for 3- and 6-week assessment, no telephone access • eating disorders • age younger than 18 • pregnancy • unwillingness or inability to discontinue current medications for the treatment of RLS.	**N**=60 **Age** (mean yr): 49.3 **Gender** (Male %): 23 **Race/Ethnicity** (%): NR **Comorbidities**: NR **Criteria used to define RLS** IRLSSG **Baseline Severity**: moderate to severe, baseline mean IRLS score: 26.1 **Previous RLS medication history**: NR but patients but had to complete a 2-week washout period off of the medication before becoming eligible **Iron Status**: NR	**Intervention:** Bupropion 150 mg **Comparator:** Placebo **A. Change in Disease Status and Impact** IRLS Scale Score **B. Quality of life** none **Subjective Sleep Quality** none **Definition of clinically significant Improvement:** NR **Adverse Effects Reported:** partially (withdrawals only)	**Assessment of Internal Validity** Sequence generation: adequate Allocation concealment: adequate Blinding of participants and personnel: yes Incomplete outcome data: no **Selective outcome reporting:** no **Reviewer Comments:** Improvement in IRLS Scale Score from baseline was significant (p=0.16) at week 3 but not week 6. Study was unable to recruit the target of 100 patients (leading possible type II error)

Appendix E. Table 4. Evidence Table for primary RLS: iron trials

Study Characteristics and Design	Inclusion/Exclusion criteria	Participant Characteristics	Intervention (daily dose) /Comparator (daily dose)	Risk of bias and Applicability
Study ID Allen, 2011[26] **Geographical Location**: US **Funding source**: none stated **Study Design**: parallel design, fixed-dose **Duration**: 28 days	**Inclusion criteria:** • aged 18 years or older • diagnosed with RLS based on IRLS criteria (independently confirmed by use of validated Hopkins Telephone Diagnostic Interview. • IRLS baseline score of ≥15 on the IRLS, RLS symptoms ≥5 nights per week, actigraph PLMS average for 3-5 nights ≥15 h^{-1}. **Exclusion criteria:** • baseline serum ferritin >300 mcg 1^{-1} • percentage transferrin saturation ≥45% • hemoglobin greater than normal • any other abnormal clinical evaluation • not on acceptable birth control (if at risk for pregnancy) • RLS secondary to central nervous system disease, CNS injury, or chronic kidney disease • had any pain or sleep disorders that would disturb clinical sleep measures or had any disease that would disrupt iron status or evaluations in this study	**N**=46 (demographic information for 43 patients) **Age** (mean yr): 51.8 **Gender** (Male %): 37 **Race/Ethnicity** (%): NR **Comorbidities**: NR **Criteria used to define RLS:** *see inclusion criteria* **Baseline Severity**: moderate to severe. Baseline mean IRLS score: 24.6 **Previous RLS medication history**: 81% (oral therapy) **Iron Status:** female 26.8 mcg/l male 63.6 mcg/l	**Intervention:** Intravenous ferric carboxymaltose 500 mg x 2 occasions on days 0 and 5 (n=24) **Comparator:** Placebo (intravenous saline) on days 0 and 5 (n=22) **A. Change in Disease Status and Impact** IRLS Scale Score **B. Quality of life** RLS-QoL **Subjective Sleep Quality** MOS sleep total score **Definition of clinically significant Improvement:** RLS remitters were defines as those with a day 28 IRLS score ≤ 10	**Assessment of Internal Validity** Sequence generation: adequate Allocation concealment: adequate Blinding: patients and investigators Incomplete outcome data: yes, 3 patients (7%, all placebo) were excluded from the analyses (one before first dose, and two prior to receiving the second dose) Selective outcome reporting: no **Reviewer Comments** Patients were not excluded due to iron deficiency

IRLS = International RLS Study Group Rating Scale; NR = not reported

Appendix E. Table 5. Evidence Table for primary RLS: Cabergoline trials

Study Characteristics and Design	Inclusion/Exclusion criteria	Participant Characteristics	Intervention /Comparator	Study Quality and Applicability
Study ID Trenkwalder, 2007[27] **Geographical Location** Europe (Multicenter) **Funding source:** Industry **Study Design:** RCT-parallel group **Duration:** 30 weeks	**Inclusion criteria:** • age 18 to 75 years • RLS diagnosed with IRLSSG criteria • RLS Severity; IRLS>10 and "severity at night" score ≥4 in the 11 point RLS-6 rating scale **Exclusion criteria:** • secondary RLS (end stage renal disease, iron deficiency anemia or pregnancy) • established or suspected hypersensitivity to ergot alkaloids or non-response or intolerability to previous cabergoline or L-dopa therapy • concomitant use of drugs with a probable influence on RLS	**N**=362 **Age** (mean, yr): 57.8 **Gender (Male %):** % **Race/Ethnicity (%):** white 100 **Comorbidities**: NR **Criteria used to define RLS** IRLSSG diagnostic criteria **Primary or secondary RLS:** Idiopathic **Baseline Severity:** Moderate-Severe. Baseline mean IRLS score: 25.7 **Previous RLS medication history**: NR **Iron Status**: NR	**Intervention:** Cabergoline 2-3 mg, 3 hours before bedtime (n=178) **Comparator:** Levodopa 200-300 mg, in 2 doses, the first one 3 hrs before bedtime and the second administered at bedtime (n=183) **Outcomes reported:** A. **Change in Disease Status and Impact** IRLS Scale Score CGI-I scale Score **B. Quality of life** RLS QoL **Subjective Sleep Quality** NR **Definition of clinically significant Improvement:** NR **Adverse Effects Reported:** yes Augmentation assessed using ASRS rating scale	**Assessment of Internal Validity** Sequence generation: adequate Allocation concealment: adequate Blinding of participants and personnel, outcome assessors yes Incomplete outcome data: yes, had to have received at least one dose of study drug and at least 1 post-baseline IRLS assessment **Selective outcome reporting:** no **Reviewer Comments** Patients had to pass a placebo run-in phase of 1 week prior to baseline. 19% of all subjects had augmentation/time shift during previous RLS treatment.
Study ID Oertel, 2006[28] **Geographical Location:** Europe (Austria, Germany, Norway, Sweden, Netherlands)	**Inclusion criteria:** • Age 18-80 yrs • Idiopathic RLS diagnosed with IRLS criteria • Moderate-severe RLS indicated by IRLS scale score>10 (AND) a RLS severity at night score of 4 or greater on a 11-point RLS-6 rating scale (AND) PLMS arousal index	**N**=40 **Age** (mean (SD), yr): 56.4 **Gender (Male %):** 27 **Race/Ethnicity (%):** NR	**Intervention** Cabergoline (n=20) 2mg/day, once daily, at least 3 hrs before bedtime. Starting dose of 0.5mg/day up titrated to 2.0mg/day over a period of 2 wks. **Comparator** Placebo (n=20)	**Assessment of Internal Validity** Sequence generation: adequate Allocation concealment: adequate Blinding of participants and personnel, outcome assessors yes Incomplete outcome data: yes,

Study Characteristics and Design	Inclusion/Exclusion criteria	Participant Characteristics	Intervention /Comparator	Study Quality and Applicability
Funding source: Industry **Study Design:** RCT-Parallel group **Duration:** 5 weeks	PLMS-AI >5per hour total sleep time **Exclusion criteria:** • Secondary RLS (iron deficiency, renal disease) or drugs suspected to cause such secondary forms • Patients who showed evidence of mimics of RLS • Idiopathic Parkinson disease, insulin-dependent diabetes mellitus, clinically relevant polyneuropathy, liver disease, history of sleep apnea or malignancy, pleural effusions or fibrosis • Established or suspected hypersensitivity to ergot alkaloids • Pretreatment with Cabergoline • Women who were pregnant, or lactating or at risk for pregnancy during course of study	**Comorbidities**: NR **Criteria used to define RLS** IRLSSG diagnostic criteria **Primary or secondary RLS:** Primary **Baseline Severity:** Severe-very severe. Baseline mean IRLS score: 31.5 **Previous RLS medication history**: Patients with previous RLS treatment I:95% C:80% **Iron Status**: NR	**Outcomes reported:** A. **Change in Disease Status and Impact** IRLS Scale Score **B. Quality of life** QoL RLS **Subjective Sleep Quality** NR (Study only reports a subscale of SF-A) **Definition of clinically significant Improvement:** Responders defined as patients with at least 50% reduction of their baseline IRLS score or those who assessed their condition at week 6 as "much better" or "very much better" on patient global impressions scale **Adverse Effects Reported:** yes	had to have received at least one dose of study drug, had a baseline IRLS score and at least 1 post-baseline IRLS assessment Selective outcome reporting: no **Applicability** Study participant had severe RLS, severe night time symptom scores and periodic limb movements of sleep **Reviewer Comments** 63% of all subjects had drug-related augmentation during previous RLS treatment.
Study ID Stiasny-Kolster, 2004[29] **Geographical Location:** Germany, Multicenter **Funding source:** Industry and Govt. **Study Design:** RCT-Parallel group Dose-ranging study with 3 different intervention arms	**Inclusion criteria:** • Age 18-75 yrs • Idiopathic RLS diagnosed with IRLS criteria • RLS Severity; IRLS>15 and a RLS severity at night≥4 on 11 point RLS-6 scale **Exclusion criteria:** • Patients with uremia, iron deficiency and rheumatoid arthritis • Patients with idiopathic Parkinson's syndrome, insulin-dependent diabetes, polyneuropathy, liver	**N**=86 **Age** (mean, yr): 56.1 **Gender (Male %):** 30% **Race/Ethnicity (%):** NR **Comorbidities**: NR **Criteria used to define RLS** IRLSSG diagnostic criteria	**Intervention:** Cabergoline in 3 different doses: 0.5 mg/day (n=21); 1.0 mg/day (n=20); and 2.0 mg/day (n=22) **Comparator:** Placebo (n=22) **Outcomes reported:** A. **Change in Disease Status and Impact** IRLS Scale Score **B. Quality of life** NR	**Assessment of Internal Validity** Sequence generation: adequate Allocation concealment: adequate Blinding of participants and personnel, outcome assessors yes Incomplete outcome data: yes, "7 withdrawn from study as they fulfilled definition of non-responders"; To be included in the analysis patients had to have at least 1 assessment.

Study Characteristics and Design	Inclusion/Exclusion criteria	Participant Characteristics	Intervention /Comparator	Study Quality and Applicability
Duration: 5 weeks	disease, history of sleep apnea, malignancy, pleural effusions or fibrosis, and established or suspected hypersensitivity to ergot alkaloids • Women who were pregnant, at risk for pregnancy or lactating • Concomitant medications that influence sleep architecture or motor manifestations during sleep within the last week before baseline visit and during the trial. These include: neuroleptics, dopamine agonists, L-dopa, hypnotics, antidepressants, anxiolytics, anticonvulsants, psychostimulant medications and opioids.	**Primary or secondary RLS:** Primary **Baseline Severity:** Moderate-Severe. Baseline mean IRLS score: 26.6 **Previous RLS medication history**: Patients with previous RLS treatment 63.5% **Iron Status**: NR	**Subjective Sleep Quality** NR (Sleep diaries were used to document quality and duration of sleep; but they did not use a validated sleep scale) **Definition of clinically significant Improvement:** Remitters defined as those IRLS scale score=0 **Adverse Effects Reported:** yes	**Selective outcome reporting:** no

IRLS = International RLS Study Group Rating Scale; NR = not reported

Appendix E. Table 6. Evidence Table for secondary RLS: iron trials

Study Characteristics and Design	Inclusion/Exclusion criteria	Participant Characteristics	Intervention (daily dose) /Comparator (daily dose)	Risk of bias and Applicability
Study ID Grote, 2009[30] **Geographical Location**: Sweden **Funding source**: Industry **Study Design**: parallel design, fixed dose **Duration**: 12 months	**Inclusion criteria:** • age between 18 and 70 years • 4 cardinal RLS diagnostic criteria* • score of ≥10 on the IRLS • S-ferritin concentration <30 µg/L. A study amendment issued after inclusion of 30 patients increased the threshold for S-ferritin to 45 µg/L according to previously published recommendations • normal folic acid/ B12 vitamin serum values. **Exclusion criteria:** • concomitant use of any drug treatment for RLS • clinical or laboratory findings suggestive of secondary RLS • any previously known clinically significant allergic reaction • use of drug treatment known to induce RLS • pregnancy • specific contraindication for iron sucrose	**N**=60 **Age** (mean yr): 46.5 **Gender** (Male %): 12 **Race/Ethnicity** (%): NR **Comorbidities**: NR **Criteria used to define RLS:** *see inclusion criteria* **Baseline Severity**: moderate to severe. Baseline mean IRLS score: 24.6 **Previous RLS medication history**: NR **Iron Status** (serum ferritin (µg/L)): 20.55	**Intervention:** Intravenous iron sucrose 200 mg x 5 occasions over 3 weeks (n=29) **Comparator:** Placebo (intravenous saline) (n=31) **A. Change in Disease Status and Impact** IRLS Scale Score **B. Quality of life** NR **Subjective Sleep Quality** Epworth Sleepiness Scale **Definition of clinically significant Improvement:** responders had ≥50% IRLS score reduction (A post-hoc analysis)	**Assessment of Internal Validity** Sequence generation: adequate Allocation concealment: adequate Blinding: patients and investigators Incomplete outcome data: no Selective outcome reporting: no
Study ID Wang, 2009[31] **Geographical Location:** Europe (43 hospitals and sleep clinics in: Austria, Belgium, France, Germany, Italy, Netherlands, Norway, Spain, Sweden, and the UK) **Funding source:** Industry	**Inclusion criteria:** • RLS diagnosed with IRLS criteria* • RLS Severity; IRLS ≥11 (AND) measured ferritin level of 15-7 5ng/ml **Exclusion criteria:** • pregnancy • hemochromatosis, or other significant liver disease, end-stage renal disease or significant sleep disturbance for reasons other than RLS • iron saturation less than 15% • iron sulphate allergy • hemoglobin levels less than 11.1	**N**=18 **Age** (mean (SD), yr): 59.2 **Gender (Male %):** 39% **Race/Ethnicity (%):** NR **Comorbidities**: NR **Criteria used to define RLS** IRLSS diagnostic criteria	**Intervention:** Oral ferrous sulfate 650 mg (n=11) **Comparator:** Placebo (n=7) All patients were also asked to take vitamin C 100 mg twice daily. **Outcomes reported:** A. **Change in Disease Status and Impact** IRLS Scale Score **B. Quality of life**	**Assessment of Internal Validity** Sequence generation: adequate Allocation concealment: adequate Blinding of participants and personnel, outcome assessors yes Incomplete outcome data: no Selective outcome reporting: no **Reviewer Comments** Performed at Veterans Affairs

Study Characteristics and Design	Inclusion/Exclusion criteria	Participant Characteristics	Intervention (daily dose) /Comparator (daily dose)	Risk of bias and Applicability
Study Design: Parallel group **Duration:** 12 weeks	g/dL for females and 14g/dL for male • current or recent treatment with iron sulfate as defined by more than 325 mg each day for at least half of the days in the past 2 months or any other potential medications for treatment of RLS.	**Baseline Severity:** moderate to severe. Baseline mean IRLS score: 24.1 **Previous RLS medication history**: NR **Iron Status**: NR	NR **Subjective Sleep Quality** NR **Definition of clinically significant Improvement:** NR **Adverse Effects Reported:** yes	Medical Center, included active duty personnel, retirees, or family members

IRLS = International RLS Study Group Rating Scale; NR = not reported; PGI = Patient Global Impression

* The 4 critical criteria are: 1) an urge to move the legs, usually accompanied or caused by uncomfortable and unpleasant sensations in the legs (sometimes the urge to move is present without the uncomfortable sensations and sometimes the arms or other body parts are involved in addition to the legs); 2) the urge to move or unpleasant sensations begin or worsen during periods of rest or inactivity such as lying or sitting; 3) the urge to move or unpleasant sensations are partially or totally relieved by movement, such as walking stretching, at least as long as the activity continues; 4) the urge to move or unpleasant sensations are worse in the evening or night than during the day or only occur in the evening or night (when symptoms are very severe, the worsening at night may not be noticeable but must have been previously present).

Appendix E. Table 7. Evidence Table for the nonpharmacologic studies

Study Characteristics and Design	Inclusion/Exclusion criteria	Participant Characteristics	Intervention (daily dose) /Comparator (daily dose)	Study Quality and Applicability
Study ID Mitchell, 2011 **Near-infrared light** **Geographical Location**: US **Funding source**: Academic **Study Design**: Prospective, randomized, single-blind, sham-controlled trial **Duration:** 4 weeks	**Inclusion criteria:** • Met the 4 minimal criteria established by the IRLS for the diagnosis of RLS • IRLS score 11-20 points • good skin integrity and no obvious signs of impaired circulation **Exclusion criteria:** • decreased sensation	**N**=34 **Age (mean yr)**: 55 **Gender (Male %):** 41 **Race/Ethnicity (%):** NR **Comorbidities:** NR **Baseline Severity:** IRLSS 24.1 **Previous RLS medication history:** 50% (n=17) were also taking RLS medication (dopamine agonist 82% (n=14), gabapentin 12% (n=2), hydrocodone 6% (n=1)) **Iron Status:** 18 patients had low ferritin levels. Means were 19.2 µg/L (range 3.4 to 42.6) for near-infrared group (n=9) and 20.12 µg/L (range 5.8 to 38.7) for sham group (n=9)	**Intervention:** monochromatic near- infrared light (n=17). Anodyne® Therapy System 480 which delivers pulsed light at 290 Hz with a wavelength of 890 nm. Active unit provides 62.4 Joules/cm^2 of energy density. 12 30-minute treatments over 4 weeks. **Comparator:** Sham therapy (n=17) **A. Change in Disease Status and Impact** IRLS Scale Score **B. Quality of life** None **Subjective Sleep Quality** None **Definition of clinically significant Improvement:** none provided	**Assessment of Internal Validity** Sequence generation: Allocation concealment: unclear Blinding: patients Incomplete outcome data: no Selective outcome reporting: no **Applicability** Some patients may have had secondary RLS as over one half of the subjects (53%, n=18) had low ferritin levels (see iron status).
Study ID Cuellar, 2009[32] **Botanical preparation** **Geographical Location**: US **Funding source**: NR **Study Design**:	**Inclusion criteria**: • Met diagnostic criteria based on the IRLS criteria including akathisia brought on by rest, relieved with moving or walking, and worsening at night or in the evening • at least 21 years old; not satisfied with current treatment outcomes • willing to use valerian as treatment with possibility of being in control group; have symptoms of RLS 3 nights a week or more; commitment	**N**=48 **Age (mean yr)**: 49.5 **Gender (Male %)**: 25 **Race/Ethnicity (%)**: white 68 **Comorbidities**: NR **Baseline Severity**: IRLSS 23.5	**Intervention:** Valerian 800 mg (n=24) **Comparator:** Placebo (identical in taste, color, etc.) (n=24) **A. Change in Disease Status and Impact** IRLS Scale Score **B. Quality of life** None	**Assessment of Internal Validity** Sequence generation: adequate Allocation concealment: adequate, pharmacy controlled Blinding: patients, personnel, data enterer, outcome assessment Incomplete outcome data: yes, needed to take at least one dose of study medication Selective outcome reporting: No

Study Characteristics and Design	Inclusion/Exclusion criteria	Participant Characteristics	Intervention (daily dose) /Comparator (daily dose)	Study Quality and Applicability
parallel design **Duration**: 8 weeks	to treatment fidelity. **Exclusion criteria:** • Positive toxicology report, liver function profile abnormal, and 3 *yes* answers on CAGE 2 • participation in a clinical study with an investigation drug within 3 months • current use of vitamins or minerals beyond the recommended RDA requirements • current use of any herbs or natural products; current use of benzodiazepines or barbiturates • sleep disorder other than RLS • use of valerian within 120 days of baseline visit • history of liver disease including cirrhosis, alcoholism, and hepatitis • pregnant, nursing, or intending to become pregnant in 3 months.	**Previous RLS medication history**: yes **Iron Status**: NR	**Subjective Sleep Quality** Pittsburgh Sleep Quality Index (PSQI) Epworth Sleepiness Scale (ESS) **Definition of clinically significant Improvement:** none provided **Adverse Effects Reported:** Yes	**Applicability** Yes
Study ID Lettieri, 2009[33] **Compression device** **Geographical Location**: US **Funding source**: NR **Study Design**: Prospective, randomized, double-blind, sham-controlled trial **Duration**: 28 days	**Inclusion criteria**: • Subjects >17 years of age with a reliable diagnosis of RLS in accordance with the *International Classification of Sleep Disorders, Revised Diagnostic and Coding Manual* of the American Academy of Sleep Medicine **Exclusion criteria**: • Individuals <17 years old • Mental/physical limitations that would preclude data collection on questionnaires • medical conditions that would preclude the use of PCDs, such as known or suspected deep vein thrombosis, active skin infections, recent vein ligation or skin graft, or	N=35 Age (mean yr): 51.0 Gender (Male %): 60 Race/Ethnicity (%): NR Comorbidities: NR **Criteria used to define RLS** see inclusion criteria Baseline Severity: IRLS 19.8 Previous RLS medication history: Subjects taking iron or prescription medications for RLS were offered	**Intervention:** Compression device (n=21) **Comparator:** Control (n=14) **A. Change in Disease Status and Impact** IRLS Scale Score **B. Quality of life** Yes **Subjective Sleep Quality** Yes **Definition of clinically significant Improvement:** No **Adverse Effects Reported:**	**Assessment of Internal Validity** Sequence generation: adequate Allocation concealment: adequate Blinding: patients, physicians, investigators Incomplete outcome data: adequate Selective outcome reporting: no

Study Characteristics and Design	Inclusion/Exclusion criteria	Participant Characteristics	Intervention (daily dose) /Comparator (daily dose)	Study Quality and Applicability
	extreme deformity of the legs. We also excluded individuals if they had previously used PCDs for deep vein thrombosis prophylaxis, as this would have potentially unblinded subjects randomized to sham devices.	enrollment only if they had been on a stable dose of medications for more than two months and reported persistent symptoms. Iron Status: Current iron therapy 17.1%	Yes	
Study ID Aukerman, 2006[34] **Exercise** **Geographical Location**: US **Funding source**: non-industry **Study Design**: parallel design **Duration**: 12 weeks	**Inclusion criteria**: • Meeting diagnostic criteria for RLS **Exclusion criteria**: • Secondary causes of RLS • orthopedic condition that limited ambulation on a treadmill or ability to perform prescribed resistance exercises • recent coronary event in the preceding six months • uncontrolled hypertension, renal dysfunction (serum creatinine >1.5 mg/dL) or anemia (hemoglobin <13 g/dL in males and <11 g/dL in females).	N=41, demographic data for 28 subjects who completed trial (9 exercise and 4 controls dropped out) Age (mean yr): 53.7 Gender (Male %): 39 Race/Ethnicity (%): white 96 Comorbidities: NR **Criteria used to define RLS** Primary or secondary RLS: primary Baseline Severity: NR Previous RLS medication history: NR Iron Status: NR	**Intervention:** Exercise (lower body resistance exercises performed 3 times/week for 12 weeks and treadmill walking for aerobic exercise) (n=11) **Comparator:** Control (n=17) Both groups were instructed in lifestyle interventions that are thought to improve RLS, including cigarette and alcohol cessation, avoidance of excessive caffeine, and proper sleep hygiene. **A. Change in Disease Status and Impact** IRLS Scale Score **B. Quality of life** None **Subjective Sleep Quality** No **Definition of clinically significant Improvement:** none provided **Adverse Effects Reported:** yes	**Assessment of Internal Validity** Sequence generation: adequate Allocation concealment: unclear Blinding: study personnel blinded to allocation called participants at 3 and 9 weeks to complete the questionnaire over the phone Incomplete outcome data: yes Selective outcome reporting: no

IRLS = International RLS Study Group Rating Scale; NR = not reported

Appendix F. Outcomes Tables

Appendix F. Table 1. IRLS responders (≥ 50% score reduction) at end of treatment for the dopamine agonist studies

Study, year	Duration (weeks)	Drug and daily dosage / control	Positive response % (n/N)	Risk ratio [95% CI]
Montagna, 2011[4]	12	Pramipexole 0.125-0.75 mg	75.9 (154/203)	1.32 [1.15 to 1.53]
		Placebo	57.3 (114/199)	
Oertel, 2007[11]	6	Pramipexole 0.125-0.75 mg	52.2 (117/224)	1.80 [1.32 to 2.47]
		Placebo	28.9 (33/114)	
Winkelman, 2006[15]	12	Pramipexole 0.125-0.75 mg	61.8 (157/254)	1.46 [1.12 to 1.90]
		Placebo	42.4 (36/85)	
Hening, 2010[5]	26	Rotigotine 1,2,3 mg	60.0 (177/297)	1.59 [1.22 to 2.09]
		Placebo	37.4 (37/99)	
Oertel, 2010[35]	7	Rotigotine 1-3 mg	76.1 (35/46)	2.17 [1.17 to 4.04]
		Placebo	35.0 (7/20)	
Oertel, 2008[9]	6	Rotigotine 1,2,3 mg	63.2 (112/177)	1.52 [1.09 to 2.14]
		Placebo	41.5 (22/53)	
Trenkwalder, 2008[10]	27	Rotigotine 1,2,3 mg	55.0 (183/333)	2.16 [1.55 to 3.00]
		Placebo	25.4 (29/114)	

CI = confidence intervals; IRLS = International Restless Legs Study Group Rating Scale.

Appendix F. Table 2. International Restless Legs Study Group Rating Scale (IRLS) scores for the dopamine agonist studies

Author year	Study Duration (weeks)	Intervention/ Comparator (daily dose) (n)	IRLS score (SD) Baseline	IRLS score (SD), After treatment	Before/After Difference (SE)	Treatment versus Control, Difference [95% CI]	p-value
Bassetti, 2011[1]	4x2 (crossover)	Pramipexole (0.25-0.75 mg) (39)	20.8 (8.2)	13.6 (8.0)	-7.2 (9.5)	-3.0	0.054
		Levodopa/ benserazide 100	21.1 (6.9)	17.1 (7.8)	-4.2 (7.5)		
Benes, 2011[2]	12	Ropinirole (0.25-4.0 mg) (171)	28.5 (4.5)	–	-14.7 (9.0)	-4.8 [-7.5 to -2.1]	< 0.001
		Placebo (60)	29.0 (4.6)	–	-9.9 (8.9)		
Högl, 2011[3]	26	Pramipexole (0.125-0.75 mg) (166)	23.9 (5.3)	10.2	-13.7 (0.8)	-3.7	0.0077
		Placebo (163)	23.5 (5.4)	12.4	-11.1 (0.8)		
Montagna, 2011[4]	12	Pramipexole (0.125-0.75 mg) (203)	25.9 (5.2)	11.4 (9.2)	-14.2 (0.7)	-6.1 [-4.3 to -7.9]	< 0.0001
		Placebo (200)	25.9 (5.5)	17.4 (10.4)	-8.1 (0.7)		
Hening, 2010[5]	28	Rotigotine (0.5 mg) (98)	23.1 (5.0)	12.2 (8.2)	-10.9 (8.9)	-2.2 (1.2)	0.068
		Rotigotine (1 mg) (99)	23.2 (5.3)	12.1 (8.7)	-11.1 (9.3)	-2.3 (1.2)	0.054
		Rotigotine (2 mg) (95)	23.3 (4.6)	9.9 (8.8)	-13.4 (9.2)	-4.5 (1.2)	0.0002
		Rotigotine (3 mg) (103)	23.6 (5.0)	9.3 (8.5)	-14.3 (9.4)	-5.2 (1.2)	<0.0001
		Placebo (99)	23.5 (5.1)	14.5 (8.0)	-9.0 (7.7)		
Oertel, 2010[35]	6	Rotigotine (1-3 mg) (46)	26.3 (6.4)	9.7 (9.1)	-16.5 (9.3)	-6.09 [-10.71 to 1.47]	0.0107
		Placebo (21)	25.4 (6.3)	–	-9.9 (9.9)		
Ferini-Stambi, 2008[7]	12	Pramipexole (0.25-0.75 mg) (182)	24.3 (5.1)	10.8 (9.1)	-13.4 (0.7)	-3.8	< 0.0001
		Placebo (187)	24.6 (5.8)	15.0 (10.9)	-9.6 (0.7)		
Oertel, 2008[9]	6	Rotigotine (0.5 mg) (50)	27.8 (6.0)	17.3 (9.7)	-10.5 (9.2)	-1.3 (1.8)	0.23
		Rotigotine (1 mg) (64)	28.2 (5.4)	13.0 (10.1)	-15.3 (10.0)	-5.8 (1.7)	0.0004
		Rotigotine (2 mg) (49)	28.0 (5.4)	12.2 (9.1)	-15.7 (9.5)	-6.5 (1.9)	0.0003
		Rotigotine (3 mg) (64)	27.4 (6.1)	10.1 (8.6)	-17.3 (10.5)	-8.3 (1.7)	<0.0001
		Rotigotine (4 mg) (53)	28.2 (6.6)	13.3 (10.1)	-14.9 (10.3)	-5.5 (1.8)	0.0013
		Placebo (53)	28.0(6.3)	18.7 (10.6)	-9.3 (9.6)		

Author year	Study Duration (weeks)	Intervention/ Comparator (daily dose) (n)	IRLS score (SD) Baseline	IRLS score (SD), After treatment	Before/After Difference (SE)	Treatment versus Control, Difference [95% CI]	p-value
Kushida, 2008[8]	12	Ropinirole (0.5-6.0 mg) (176)	–	–	~ -11 (3)*	-4.11 [-6.08 to -2.14]	0.001
		Placebo (186)	–	–	~ -15.5 (3)*		
Trenkwalder, 2008[10]	27	Rotigotine (1 mg) (115)	28.1 (6.3)	–	-13.7 (0.9)	-5.1 [-7.6 to -2.7]	< 0.0001
		Rotigotine (2 mg) (112)	28.2 (6.1)	–	-16.2 (0.9)	-7.5 [-10.0 to -5.1]	< 0.0001
		Rotigotine (3 mg) (114)	28.0 (5.9)	–	-16.8 (0.9)	-8.2 [-10.6 to -5.7]	< 0.0001
		Placebo (117)	28.1 (6.3)	–	-8.6 (0.9)		
Oertel, 2007[11]	6	Pramipexole (0.125-0.750 mg) (230)	24.7 (5.2)	12.3 (9.3)	-12.3 (0.6)	-6.6 [-8.6 to -4.5]	< 0.0001
		Placebo (115)	24.9 (5.4)	18.8 (10.0)	-5.7 (0.9)		
Bogan, 2006[13]	12	Ropinirole (0.25-4.00 mg) (187)	22.0 (4.99)	8.4 (7.32)	-13.5 (1.2)	-3.7 [-5.4 to -2.0]	< 0.001
		Placebo (194)	21.6 (4.79)	11.9 (9.20)	-9.8 (1.2)		
Montplaisir, 2006[14]	12	Ropinirole (mean 2.05 mg) (45)	8.9 (7.41)**	–	4.1	-4.6 [-8.6 to -0.6]	0.0246
		Placebo (47)	10.4 (7.30)**	–	8.2		
Winkelman, 2006[15]	12	Pramipexole (0.25 mg) (88)	23.4 (4.9)	–	-12.8 (1.0)	–	0.0086
		Pramipexole (0.50 mg) (80)	22.9 (5.1)	–	-13.8 (1.0)	–	0.0011
		Pramipexole (0.75 mg) (90)	24.1 (5.2)	–	-14.0 (1.0)	–	0.0005
		Placebo (86)	23.5 (5.2)	–	-9.3 (1.0)		
Adler, 2004[12]	5	Ropinirole (0.5-6.0 mg) (11)	(overall) 25.0 (7.0)	13.0 (12.0)	-12.0 (12.0)	-12.0 [-17.0 to -6.3]	< 0.001
		Placebo (11)		24.7 (7.2)	–		
Trenkwalder, 2004[16]	12	Ropinirole (0.25-4.00 mg) (147)	24.4 (5.75)	13.5 (9.3)	-11.04 (0.72)	-3.01 [-5.03 to -0.99]	0.0036
		Placebo (139)	25.2 (5.63)	17.1 (9.4)	-8.03 (0.74)		
Walters, 2004[17]	12	Ropinirole (0.25-4.0 mg) (131)	23.6 (5.9)	–	-11.2 (0.76)	-2.5 [-4.6 to -0.4]	0.0197
		Placebo (136)	24.8 (5.4)	–	-8.7 (0.75)		

CI = confidence interval; SE = standard error; SD = standard deviation; mg = milligrams. *estimated from table; ** Double-blind phase, trial consisted of 24-week single blind phase during which all patients received ropinirole followed by 12 week double blind, placebo controlled phase for treatment responders

Appendix F. Table 3. International Restless Legs Study Group Rating Scale (IRLS) scores for alpha-2-delta ligands studies

Author year	Study Duration (weeks)	Intervention/ Comparator, daily dose (n)	IRLS score (SD), Baseline	IRLS score (SD), After treatment	Before/After Difference (SD)	Treatment versus Control, Difference [95% CI]	p-value vs. control
Lee, 2011[18]	12	Gabapentin enacarbil 1200 mg (111)	23.2 (5.3)	10.2 (8.3)	-13.0 (9.1)	-3.5 [-5.6 to -1.3]*	0.0015
		Gabapentin enacarbil 600 mg (114)	23.1 (4.9)	9.3 (7.7)	-13.8 (8.1)	-4.3 [-6.4 to -2.3]*	<0.0001
		Placebo (96)	23.8 (4.6)	14.0 (7.9)	-9.8 (7.7)		
Winkelman, 2011[19]	4x2	Gabapentin enacarbil 1200 mg (123)	25.4 (all subjects) (crossover study)	-	-14.99 (SE 0.73)	-6.57 [-8.58 to -4.57]	<0.0001
		Placebo (127)		-	-8.42 (SE 0.71)		
Allen, 2010[20]	6	Pregabalin 50 mg (22)	24.6 (6.7)	-	-11.9 (10.9)	-4.20 [-9.75 to 1.35]	NS**
		Pregabalin 100 mg (23)	25.3 (6.4)	-	-12.3 (9.0)	-4.60 [-9.30 to 0.10]	NS**
		Pregabalin 150 mg (22)	26.2 (7.4)	-	-17.2 (10.3)	-9.50 [-15.03 to -3.79]	<0.05**
		Pregabalin 300 mg (24)	25.0 (7.4)	-	-12.6 (8.6)	-4.90 [-9.41 to -0.39]	<0.05**
		Pregabalin 450 mg (23)	24.1 (7.8)	-	-15.6 (9.0)	-7.90 [-12.75 to -3.05]	<0.05**
		Placebo (23)	23.8 (7.2)	-	-7.7 (6.6)		-
Bogan, 2010[21]†	12	Gabapentin enacarbil 1200 mg (96)	24.7 (5.5)		-1.9 (7.0) ††	-2.1	0.03
		Placebo (98)	Single-blind phase		-3.9 (6.5) ††		
Garcia-Borreguero, 2010[22]	12	Pregabalin 150-450 mg (30)	19.80 (4.16)	6.85 (6.87)		-4.92 [0.73 to 9.12]*	0.005
		Placebo (28)	21.46 (3.81)	11.2 (8.60)			-
Kushida, 2009[23]	12	Gabapentin enacarbil (XP13512/ GSK1838262) 1200 mg (114)	23.1 (4.9)	-	-13.2 (9.2)	-4.0 [-6.2 to -1.9]*	0.0003
		Placebo (108)	22.6 (4.9)	-	-8.8 (8.6)		
Garcia-Borreguero,	6	Gabapentin 600-2400 mg (22)	20.0 (all subjects)	9.5 (1.35)	-		

Author year	Study Duration (weeks)	Intervention/ Comparator, daily dose (n)	IRLS score (SD), Baseline	IRLS score (SD), After treatment	Before/After Difference (SD)	Treatment versus Control, Difference [95% CI]	p-value vs. control
2002[24]			(crossover study)				
						-8.40 [-12.06 to -4.74]	< 0.001
		Placebo (22)		17.9 (1.35)	-		

CI = confidence intervals; SE = standard error; SD = standard deviation.

* adjusted**;** ** Based on confidence intervals; † Double-blind phase, trial consisted of 24-week single blind phase during which all patients received gabapentin enacarbil followed by 12 week double blind, placebo controlled phase for treatment responders; †† mean change in scores after randomization following single blind phase during which all patients received gabapentin enacarbil.

Appendix F. Table 4. International Restless Legs Study Group Rating Scale (IRLS) scores for the cabergoline studies

Author year	Study Duration (weeks)	Intervention/ Comparator (daily dose) (n)	IRLS score (SD) Baseline	IRLS score (SD), After treatment	Before/After Difference (SD/SE)	Treatment versus Control, Difference [95% CI]	p-value
Trenkwalder, 2007[27]	30	Cabergoline (2/3 mg) (178)	25.6 (7.2)	–	-15.6 (10.8)	-7.0 [-9.1 to -4.9]	<0.001
		Levodopa (200/300 mg) (183)	25.8 (6.2)	–	-8.8 (10.7)		
Oertel, 2006[28]	5	Cabergoline (2 mg) (20)	31.2 (5.4)	–	-23.7 (11.2)	-15.8 [-22.68 to -8.92]	<0.001
		Placebo (20)	31.8 (4.0)	–	-7.9 (11.0)		
Stiasny-Kolster, 2004[29]	47	Cabergoline (0.5 mg) (21)	27.2 (5.1)	–	-13.1 (10.3)	-9.8 [-15.33 to 4.27]	<0.001
		Cabergoline (1.0 mg) (20)	25.2 (4.5)	–	-13.5 (9.9)	-10.2 [-15.77 to 4.63]	<0.001
		Cabergoline (2.0 mg) (22)	27.7 (5.7)	–	-15.7 (11.9)	-12.4 [-18.39 to 6.41]	<0.001
		Placebo (22)	26.0 (5.5)	–	-3.3 (8.0)		

CI = confidence interval; SE = standard error; SD = standard deviation; mg = milligrams; *estimated from table.

Appendix F. Table 5. International Restless Legs Study Group Rating (IRLS) scores for miscellaneous pharmacologic studies

Author, year	Study Duration (weeks)	Intervention/ Comparator (daily dose) (n)	IRLS score (SD) Baseline	IRLS score (SD), After treatment	Before/After Difference (SD/SE)	Treatment versus Control, Difference [95% CI]	p-value
Allen, 2011[26]	4	Iron (ferric carboxy-maltose) 1000 mg (n=24)	25.0 (5.8)	-	-8.9 (8.5)	-4.90 [-9.27 to -0.53]	0.049 (non-parametric)
		Placebo	24.2 (5.5)	-	-4.0 (6.1)		
Bayard, 2011[25]	6	Bupropion 150 mg (29)	26.3 (5.4)	15.9 (9.1)	-10.4 (10.1)		
		Placebo (31)	25.9 (5.3)	18.3 (8.7)	-7.6 (7.1)	-2.80 [-7.25 to 1.65]	0.22

Appendix F. Table 6. International Restless Legs Study Group Rating (IRLS) scores for nonpharmacologic studies

Author, year	Study Duration (weeks)	Intervention/ Comparator (daily dose) (n)	IRLS score (SD) Baseline	IRLS score (SD), After treatment	Before/After Difference (SD/SE)	Treatment versus Control, Difference [95% CI]	p-value
Mitchell, 2011[36]	4	Near-infrared (17)	24.5 (5.3)	--	-13.4 (8.1)		
		Sham (17)	23.6 (6.9)	--	-4.4 (3.6)	-9.00 [-13.21 to -4.79]	0.001
Cuellar, 2009[37]	8	Valerian (800 mg) (24)	23.0 (5.9)	--	3.4 (9.4)		
		Placebo (NR) (24)	24.0 (8.0)	--	4.7 (10.4)	-1.30 [-7.68, 5.08]	0.69
Lettieri, 2008[33]	4	Compression (21)	20.3 (5.9)	8.4 (3.4)	--		
		Sham (14)	19.0 (5.2)	14.1 (3.9)	--	-5.70 [-8.21, -3.19]	< 0.05
Aukerman, 2006[34]	12	Exercise (11)	20.6 (6.4)	12.1 (5.6)	--		
		Control (17)	22.5 (6.4)	21.5 (6.3)	--	-9.40 [-13.86, -4.94]	< 0.05

Appendix F. Table 7. International Restless Legs Study Group Rating Scale (IRLS) scores for iron studies

Author year	Study Duration (weeks)	Intervention (n) / Comparator (n)	IRLS score (SD), Baseline	IRLS score (SD), After treatment	Before/After Difference (SE)	Treatment versus Control, Difference [95% CI]	p-value vs. control
Grote, 2009[30]	52	Iron sucrose 200 mg x 5 times over three months I.V. (29)	23.2 (6.6)	14.6 (10.6)	-8.7 (9.4)	-1.80 [-6.63 to 3.03]	0.47
		Placebo (31)	25.9 (5.6)	19.0 (9.4)	-6.9 (9.7)		
Wang, 2009[31]	12	Oral iron 650 mg (7)	24.8 (5.72)	-	-10.3 (7.40)	-9.16 [-15.21 to -3.11]	0.01
		Placebo (11)	23.0 (5.03)	-	-1.14 (5.64)		

CI = confidence intervals; IV = intravenously; SE = standard error; SD = standard deviation; mU = mouse units; *10-item IRLS.

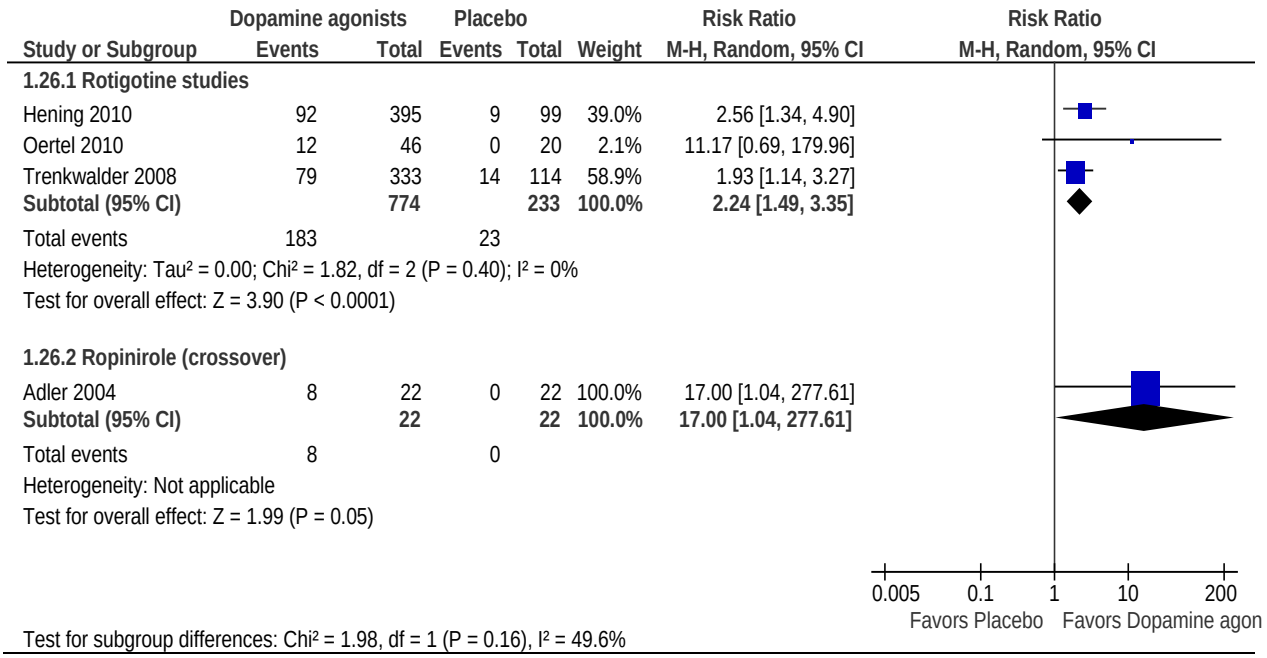
Appendix F. Table 8. IRLS Remitters (score = 0): Absolute effect per 100 patients

Study	Number of studies	Dopamine Agonist % (n/N)	Placebo % (n/N)	RR [95% CI]	Absolute effect [95% CI]
Rotigotine	3	23.6 (183/774)	9.9 (23/233)	2.24 [1.49 to 3.35]	12 more per 100 [5 more to 23 more]
Gabapentin enacarbil	1	24.4 (55/225)	11.5 (11/96)	2.13 [1.17 to 3.89]	13 more per 100 [2 more to 33 more]

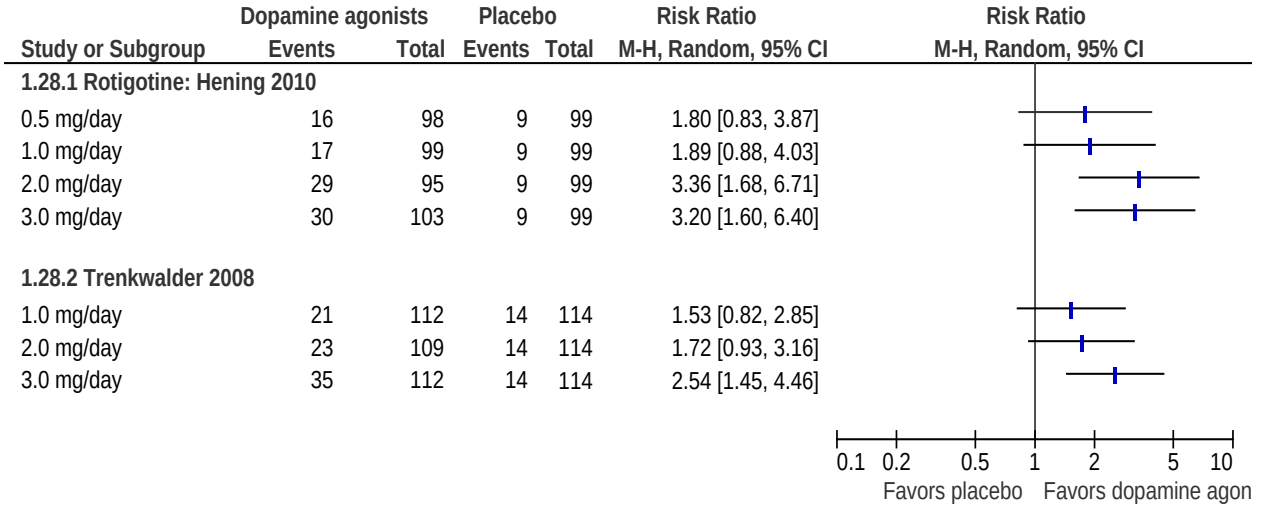
CI = confidence intervals.

Appendix F. Figure 1. IRLS Remitters analyses

IRLS Remitters (International Restless Legs Scale (IRLS) score = 0)



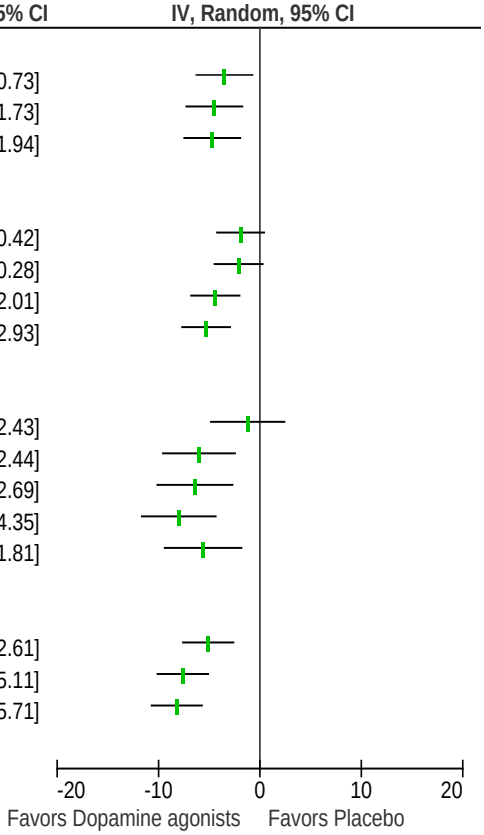
IRLS Remitters (score = 0): Fixed dose analyses



Appendix F. Figure 2. Efficacy and Harms data for double-blind dopamine agonist trials

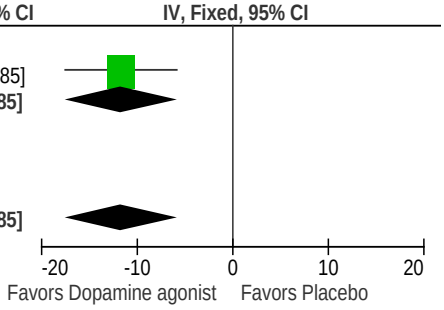
Mean change in International Restless Legs Scale (IRLS) total score from baseline – fixed-dose studies

Study or Subgroup	Dopamine agonists Mean	SD	Total	Placebo Mean	SD	Total	Mean Difference IV, Random, 95% CI
1.2.1 Pramipexole studies - Winkelman 2006							
0.25 mg/day	-12.8	9.4	88	-9.3	9.2	85	-3.50 [-6.27, -0.73]
0.5 mg/day	-13.8	8.9	79	-9.3	9.2	85	-4.50 [-7.27, -1.73]
0.75 mg/day	-14	9.3	87	-9.3	9.2	85	-4.70 [-7.46, -1.94]
1.2.2 Rotigotine studies - Hening 2010							
0.5 mg/day	-10.9	8.9	98	-9	7.7	99	-1.90 [-4.22, 0.42]
1.0 mg/day	-11.1	9.3	99	-9	7.7	99	-2.10 [-4.48, 0.28]
2.0 mg/day	-13.4	9.2	95	-9	7.7	99	-4.40 [-6.79, -2.01]
3.0 mg/day	-14.3	9.4	103	-9	7.7	99	-5.30 [-7.67, -2.93]
1.2.3 Rotigotine studies - Oertel 2008							
0.5 mg/day	-10.5	9.2	50	-9.3	9.6	53	-1.20 [-4.83, 2.43]
1.0 mg/day	-15.3	10	64	-9.3	9.6	53	-6.00 [-9.56, -2.44]
2.0 mg/day	-15.7	9.5	49	-9.3	9.6	53	-6.40 [-10.11, -2.69]
3.0 mg/day	-17.3	10.5	64	-9.3	9.6	53	-8.00 [-11.65, -4.35]
4.0 mg/day	-14.9	10.3	53	-9.3	9.6	53	-5.60 [-9.39, -1.81]
1.2.4 Rotigotine studies - Trenkwalder 2008							
1.0 mg/day	-13.7	9.5	112	-8.6	9.6	114	-5.10 [-7.59, -2.61]
2.0 mg/day	-16.2	9.4	109	-8.6	9.6	114	-7.60 [-10.09, -5.11]
3.0 mg/day	-16.8	9.5	112	-8.6	9.6	114	-8.20 [-10.69, -5.71]



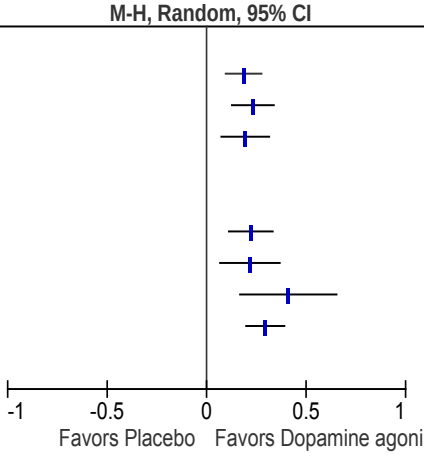
IRLS total score: mean score at end of treatment

Study or Subgroup	Dopamine agonists Mean	SD	Total	Placebo Mean	SD	Total	Weight	Mean Difference IV, Fixed, 95% CI
1.4.1 Ropinirole studies (crossover)								
Adler 2004	13	12	22	24.7	7.2	22	100.0%	-11.70 [-17.55, -5.85]
Subtotal (95% CI)			**22**			**22**	**100.0%**	**-11.70 [-17.55, -5.85]**
Heterogeneity: Not applicable								
Test for overall effect: Z = 3.92 (P < 0.0001)								
Total (95% CI)			**22**			**22**	**100.0%**	**-11.70 [-17.55, -5.85]**
Heterogeneity: Not applicable								
Test for overall effect: Z = 3.92 (P < 0.0001)								
Test for subgroup differences: Not applicable								



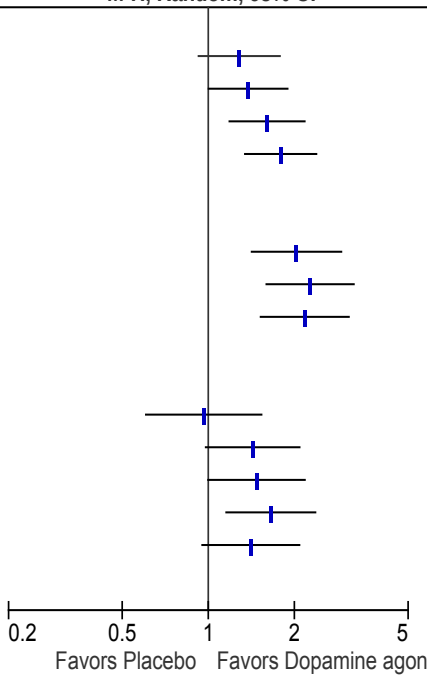
IRLS Responders (≥50% score reduction): Absolute risk differences

Study or Subgroup	Dopamine agonists Events	Total	Placebo Events	Total	Risk Difference M-H, Random, 95% CI
1.3.1 Pramipexole studies					
Montagna 2011	154	203	114	199	0.19 [0.10, 0.28]
Oertel 2007	117	224	33	114	0.23 [0.13, 0.34]
Winkelman 2006	157	254	36	85	0.19 [0.07, 0.32]
1.3.2 Rotigotine studies					
Hening (1,2,3 mg) 2010	177	297	37	99	0.22 [0.11, 0.33]
Oertel (1,2,3 mg) 2008	112	177	22	53	0.22 [0.07, 0.37]
Oertel 2010	35	46	7	20	0.41 [0.17, 0.65]
Trenkwalder 2008	183	333	29	114	0.30 [0.20, 0.39]

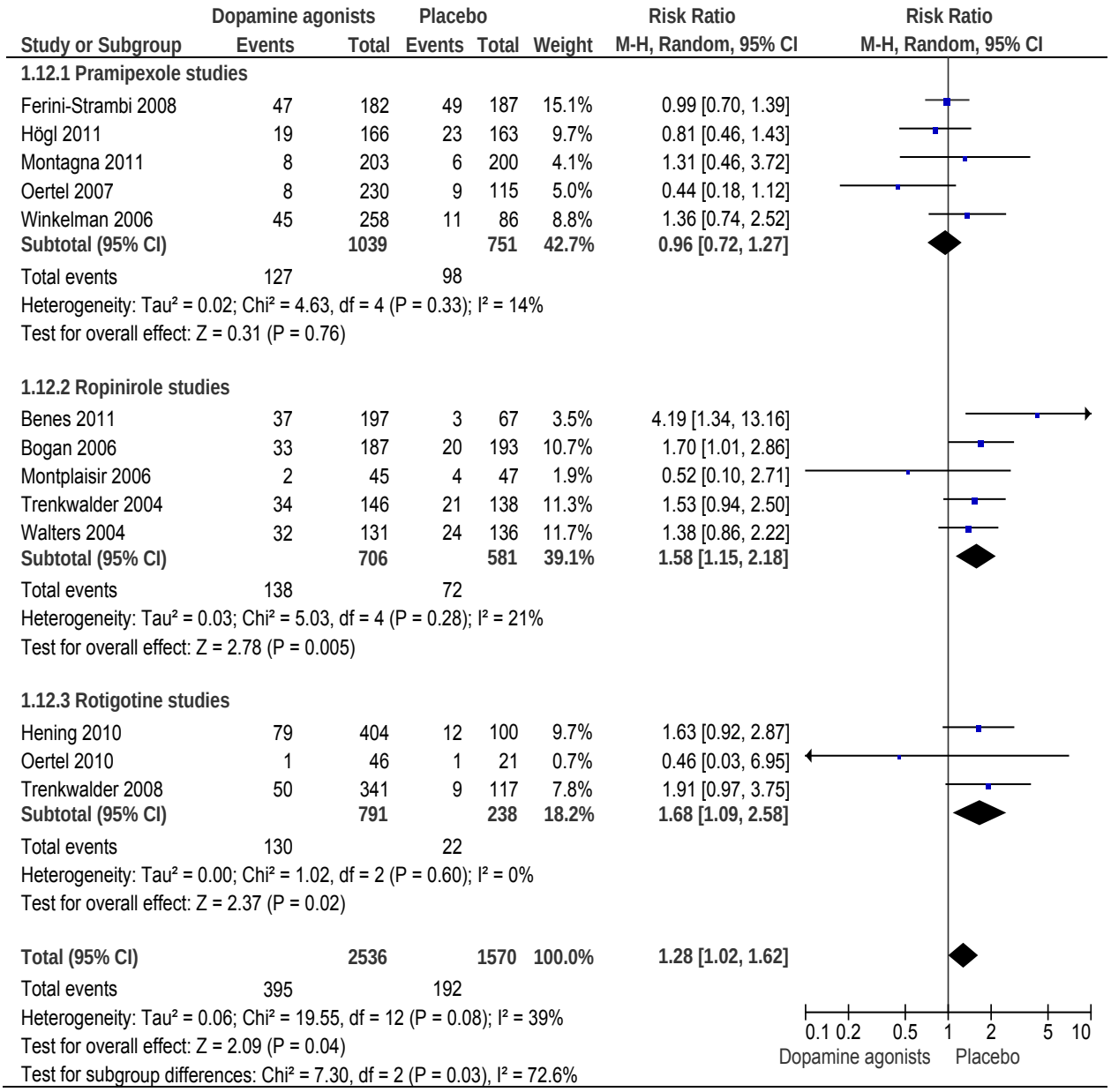


IRLS Responders (≥50% score reduction) – fixed-dose studies

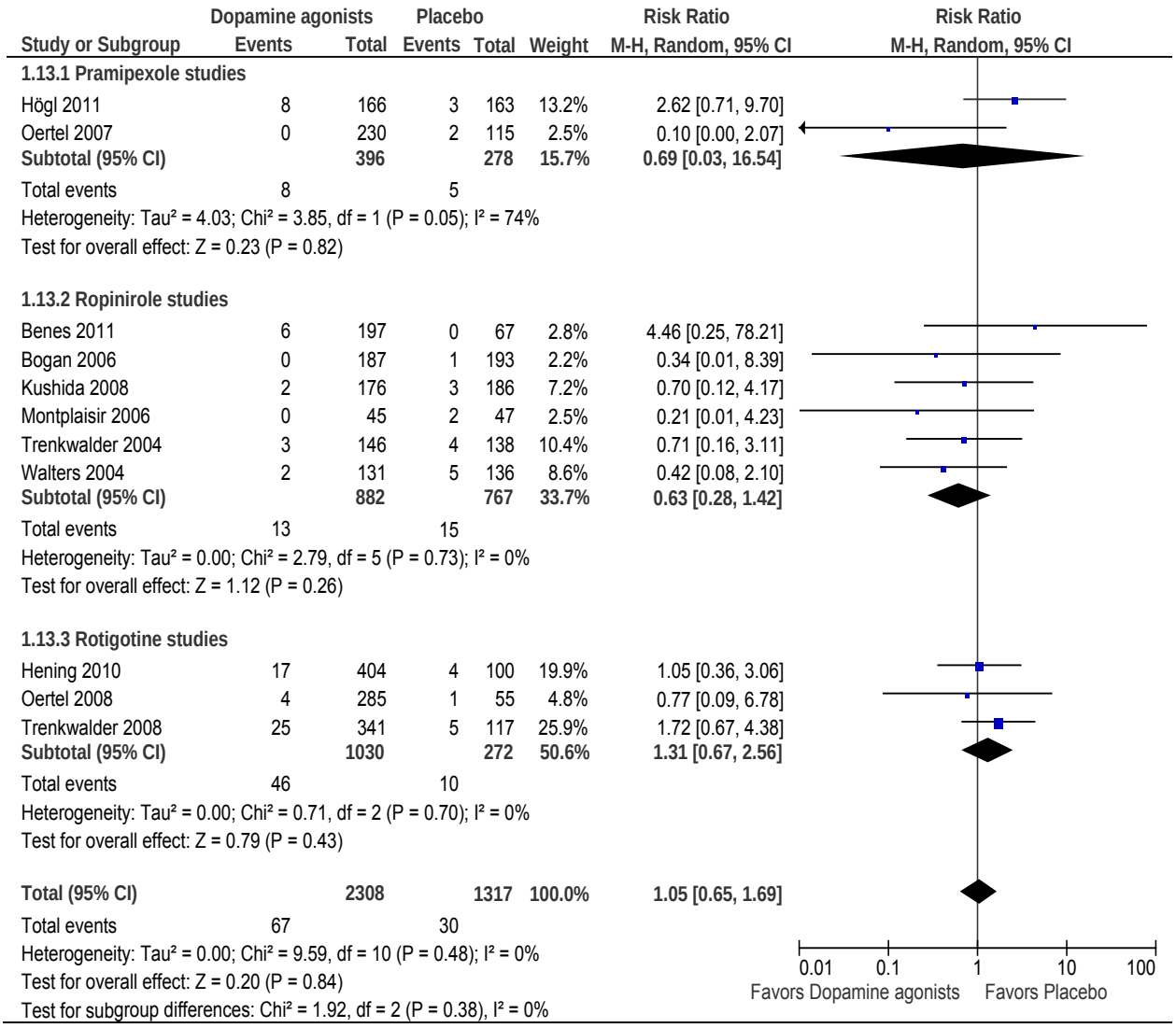
Study or Subgroup	Dopamine agonists Events	Total	Placebo Events	Total	Risk Ratio M-H, Random, 95% CI
1.4.1 Rotigotine studies - Hening 2010					
0.5 mg/day	47	98	37	99	1.28 [0.92, 1.78]
1.0 mg/day	51	99	37	99	1.38 [1.00, 1.90]
2.0 mg/day	57	95	37	99	1.61 [1.19, 2.17]
3.0 mg/day	69	103	37	99	1.79 [1.34, 2.39]
1.4.2 Rotigotine studies - Trenkwalder 2008					
1.0 mg/day	58	112	29	114	2.04 [1.42, 2.92]
2.0 mg/day	63	109	29	114	2.27 [1.60, 3.23]
3.0 mg/day	62	112	29	114	2.18 [1.52, 3.11]
1.4.3 Rotigotine studies - Oertel 2008					
0.5 mg/day	20	50	22	53	0.96 [0.60, 1.54]
1.0 mg/day	38	64	22	53	1.43 [0.98, 2.09]
2.0 mg/day	30	49	22	53	1.47 [1.00, 2.18]
3.0 mg/day	44	64	22	53	1.66 [1.16, 2.37]
4.0 mg/day	31	53	22	53	1.41 [0.95, 2.09]



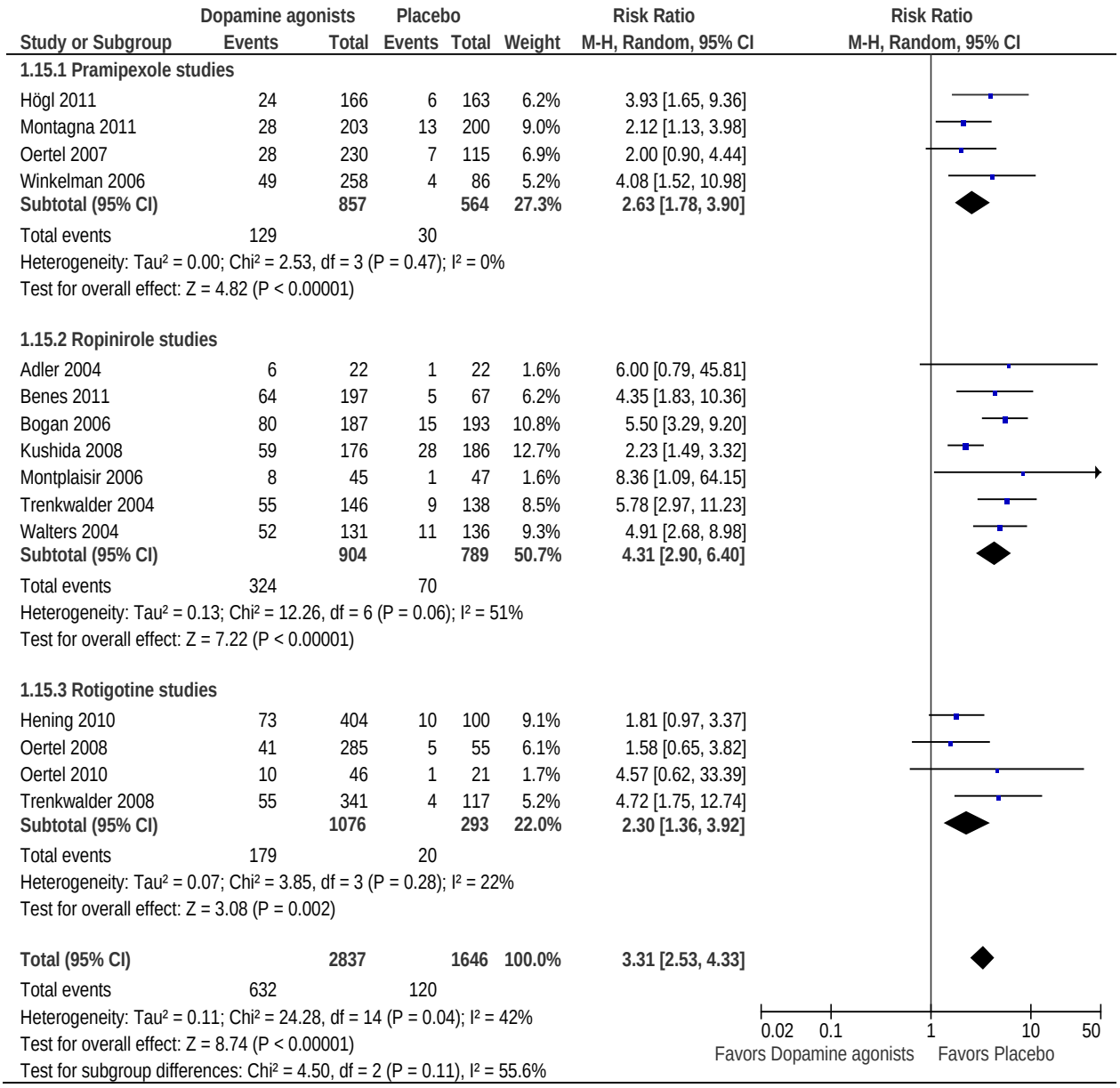
Patients with ≥1 severe adverse event



Patients with ≥1 serious adverse event

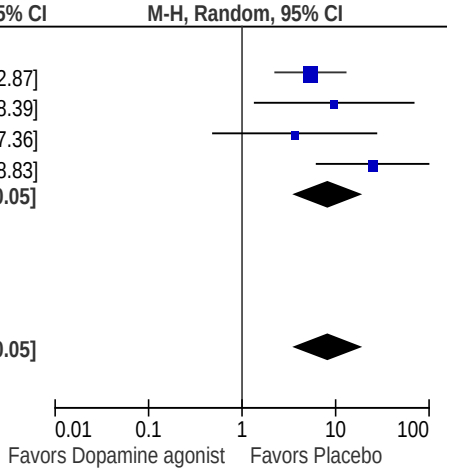


Nausea


Dopamine agonists
Placebo
Risk Ratio
Risk Ratio
Study or Subgroup Events Total Events Total Weight M-H, Random, 95% CI
M-H, Random, 95% CI
1.15.1 Pramipexole studies
Högl 2011 24 166 6 163 6.2% 3.93 [1.65, 9.36]
Montagna 2011 28 203 13 200 9.0% 2.12 [1.13, 3.98]
Oertel 2007 28 230 7 115 6.9% 2.00 [0.90, 4.44]
Winkelman 2006 49 258 4 86 5.2% 4.08 [1.52, 10.98]
Subtotal (95% CI) 857 564 27.3% 2.63 [1.78, 3.90]
Total events 129 30
Heterogeneity: Tau² = 0.00; Chi² = 2.53, df = 3 (P = 0.47); I² = 0%
Test for overall effect: Z = 4.82 (P < 0.00001)
1.15.2 Ropinirole studies
Adler 2004 6 22 1 22 1.6% 6.00 [0.79, 45.81]
Benes 2011 64 197 5 67 6.2% 4.35 [1.83, 10.36]
Bogan 2006 80 187 15 193 10.8% 5.50 [3.29, 9.20]
Kushida 2008 59 176 28 186 12.7% 2.23 [1.49, 3.32]
Montplaisir 2006 8 45 1 47 1.6% 8.36 [1.09, 64.15]
Trenkwalder 2004 55 146 9 138 8.5% 5.78 [2.97, 11.23]
Walters 2004 52 131 11 136 9.3% 4.91 [2.68, 8.98]
Subtotal (95% CI) 904 789 50.7% 4.31 [2.90, 6.40]
Total events 324 70
Heterogeneity: Tau² = 0.13; Chi² = 12.26, df = 6 (P = 0.06); I² = 51%
Test for overall effect: Z = 7.22 (P < 0.00001)
1.15.3 Rotigotine studies
Hening 2010 73 404 10 100 9.1% 1.81 [0.97, 3.37]
Oertel 2008 41 285 5 55 6.1% 1.58 [0.65, 3.82]
Oertel 2010 10 46 1 21 1.7% 4.57 [0.62, 33.39]
Trenkwalder 2008 55 341 4 117 5.2% 4.72 [1.75, 12.74]
Subtotal (95% CI) 1076 293 22.0% 2.30 [1.36, 3.92]
Total events 179 20
Heterogeneity: Tau² = 0.07; Chi² = 3.85, df = 3 (P = 0.28); I² = 22%
Test for overall effect: Z = 3.08 (P = 0.002)
Total (95% CI) 2837 1646 100.0% 3.31 [2.53, 4.33]
Total events 632 120
Heterogeneity: Tau² = 0.11; Chi² = 24.28, df = 14 (P = 0.04); I² = 42%
Test for overall effect: Z = 8.74 (P < 0.00001)
Test for subgroup differences: Chi² = 4.50, df = 2 (P = 0.11), I² = 55.6%
0.02 0.1 1 10 50
Favors Dopamine agonists
Favors Placebo

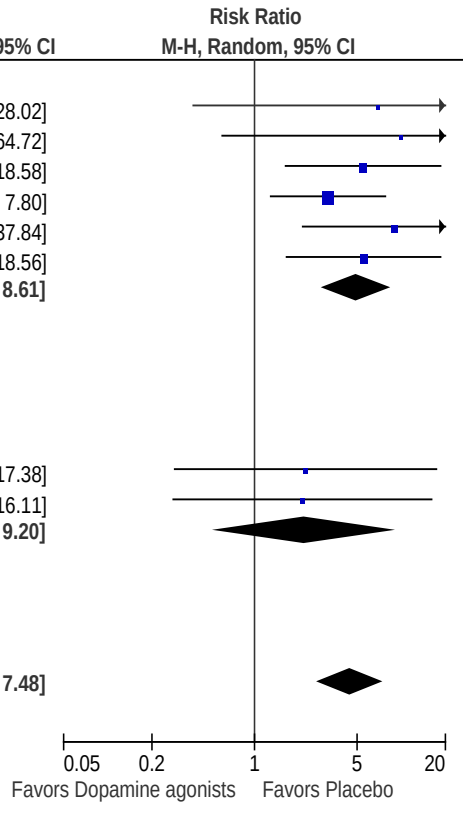
Application site reactions (Rotigotine transdermal patch)

Study or Subgroup	Dopamine agonists Events	Total	Placebo Events	Total	Weight	Risk Ratio M-H, Random, 95% CI
1.19.1 Rotigotine studies						
Hening 2010	109	404	5	100	42.8%	5.40 [2.26, 12.87]
Oertel 2008	50	285	1	55	15.8%	9.65 [1.36, 68.39]
Oertel 2010	8	46	1	21	15.1%	3.65 [0.49, 27.36]
Trenkwalder 2008	145	341	2	117	26.2%	24.88 [6.26, 98.83]
Subtotal (95% CI)		**1076**		**293**	**100.0%**	**8.32 [3.45, 20.05]**
Total events	312		9			
Heterogeneity: Tau² = 0.27; Chi² = 4.51, df = 3 (P = 0.21); I² = 34%						
Test for overall effect: Z = 4.72 (P < 0.00001)						
Total (95% CI)		**1076**		**293**	**100.0%**	**8.32 [3.45, 20.05]**
Total events	312		9			
Heterogeneity: Tau² = 0.27; Chi² = 4.51, df = 3 (P = 0.21); I² = 34%						
Test for overall effect: Z = 4.72 (P < 0.00001)						
Test for subgroup differences: Not applicable						



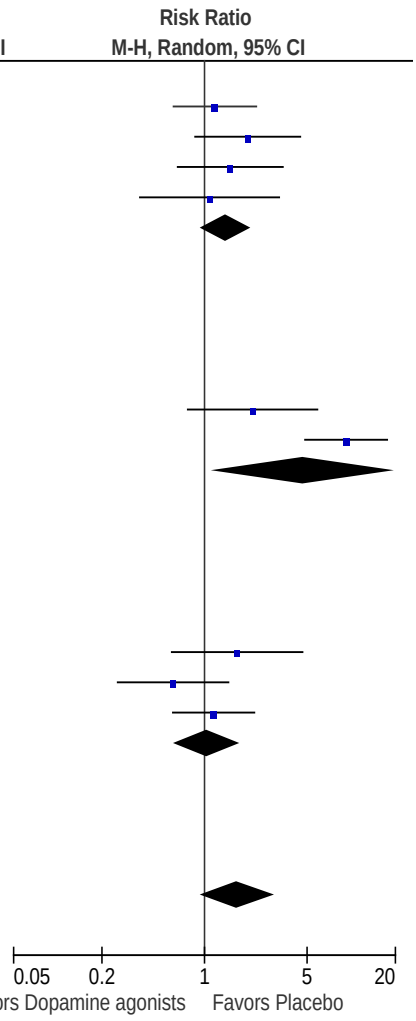
Vomiting

Study or Subgroup	Dopamine agonists Events	Total	Placebo Events	Total	Weight	Risk Ratio M-H, Random, 95% CI
1.16.1 Ropinirole studies						
Adler 2004	3	22	0	22	3.1%	7.00 [0.38, 128.02]
Benes 2011	14	197	0	67	3.3%	9.96 [0.60, 164.72]
Bogan 2006	16	187	3	193	17.8%	5.50 [1.63, 18.58]
Kushida 2008	18	176	6	186	32.4%	3.17 [1.29, 7.80]
Trenkwalder 2004	19	146	2	138	12.7%	8.98 [2.13, 37.84]
Walters 2004	16	131	3	136	18.0%	5.54 [1.65, 18.56]
Subtotal (95% CI)		**859**		**742**	**87.4%**	**4.98 [2.87, 8.61]**
Total events	86		14			
Heterogeneity: Tau² = 0.00; Chi² = 2.02, df = 5 (P = 0.85); I² = 0%						
Test for overall effect: Z = 5.73 (P < 0.00001)						
1.16.2 Rotigotine studies						
Hening 2010	9	404	1	100	6.2%	2.23 [0.29, 17.38]
Oertel 2008	11	285	1	55	6.4%	2.12 [0.28, 16.11]
Subtotal (95% CI)		**689**		**155**	**12.6%**	**2.17 [0.51, 9.20]**
Total events	20		2			
Heterogeneity: Tau² = 0.00; Chi² = 0.00, df = 1 (P = 0.97); I² = 0%						
Test for overall effect: Z = 1.05 (P = 0.29)						
Total (95% CI)		**1548**		**897**	**100.0%**	**4.48 [2.68, 7.48]**
Total events	106		16			
Heterogeneity: Tau² = 0.00; Chi² = 3.12, df = 7 (P = 0.87); I² = 0%						
Test for overall effect: Z = 5.73 (P < 0.00001)						
Test for subgroup differences: Chi² = 1.11, df = 1 (P = 0.29), I² = 9.5%						

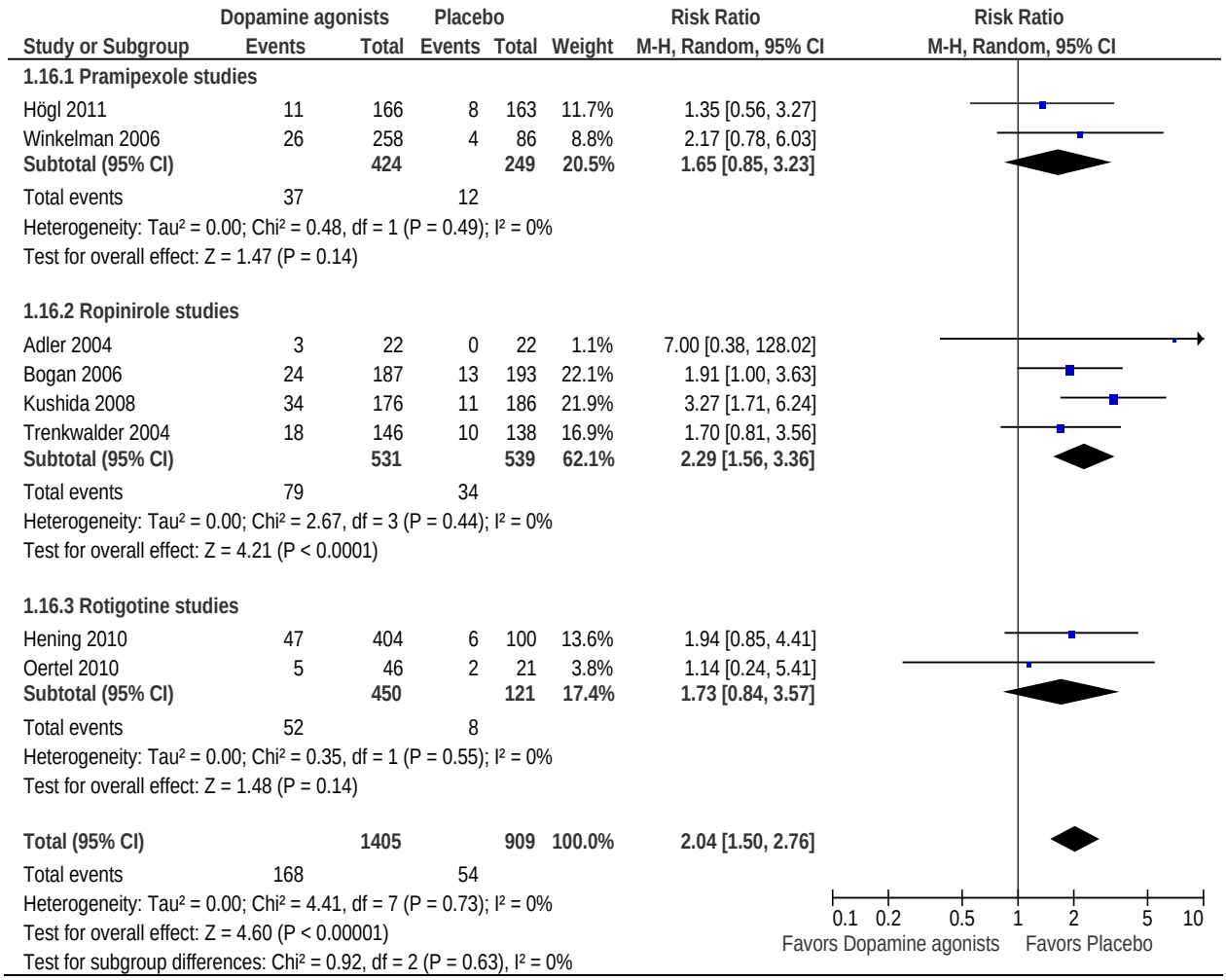


Fatigue

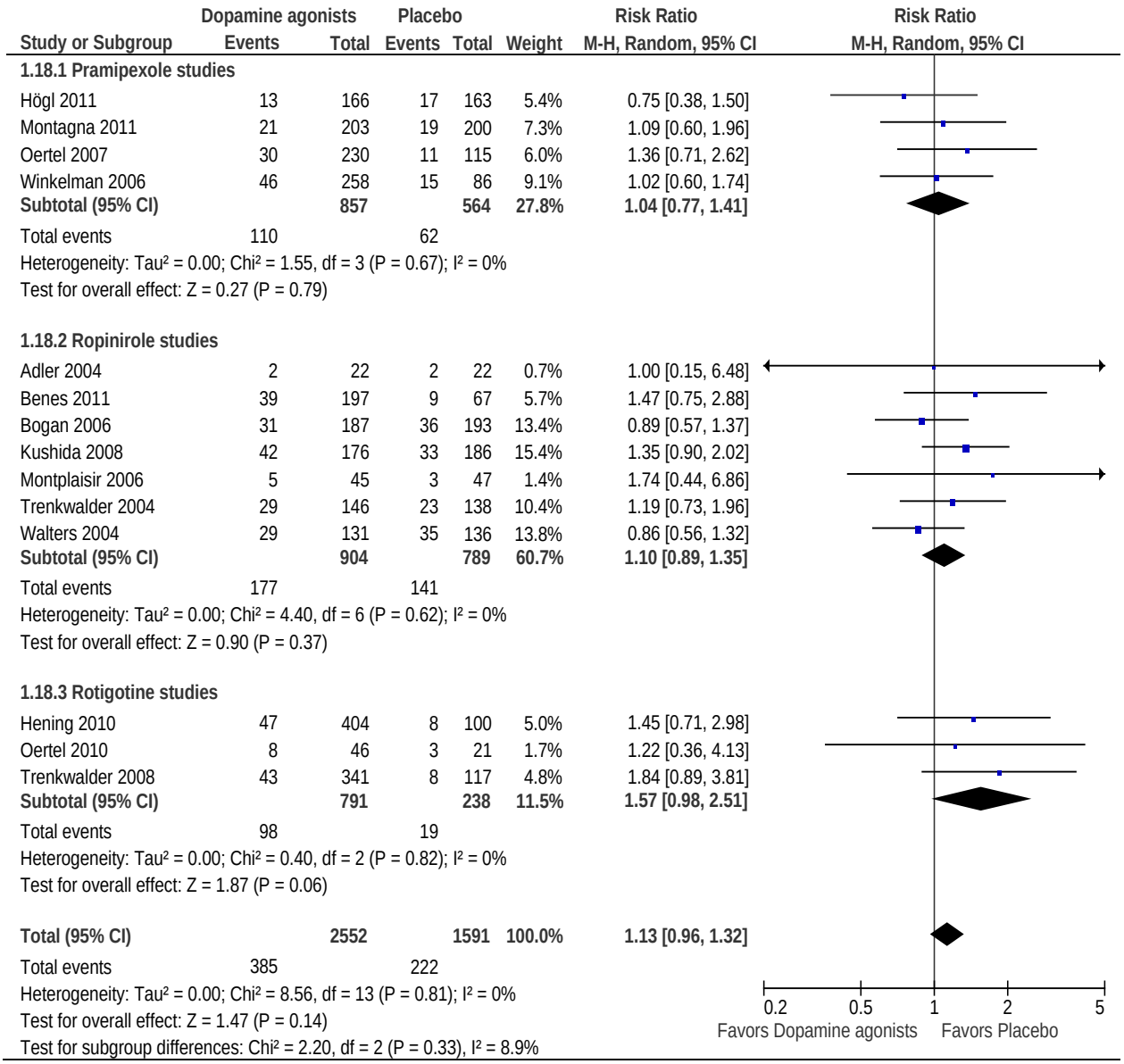
Study or Subgroup	Dopamine agonists Events	Total	Placebo Events	Total	Weight	Risk Ratio M-H, Random, 95% CI
1.14.1 Pramipexole studies						
Högl 2011	18	166	15	163	12.3%	1.18 [0.61, 2.26]
Montagna 2011	16	203	8	200	11.2%	1.97 [0.86, 4.50]
Oertel 2007	21	230	7	115	11.2%	1.50 [0.66, 3.42]
Winkelman 2006	13	258	4	86	9.6%	1.08 [0.36, 3.23]
Subtotal (95% CI)		**857**		**564**	**44.3%**	**1.40 [0.93, 2.09]**
Total events	68		34			
Heterogeneity: Tau² = 0.00; Chi² = 1.17, df = 3 (P = 0.76); I² = 0%						
Test for overall effect: Z = 1.62 (P = 0.11)						
1.14.2 Ropinirole studies						
Benes 2011	25	197	4	67	10.0%	2.13 [0.77, 5.89]
Walters 2004	80	131	9	136	12.3%	9.23 [4.84, 17.61]
Subtotal (95% CI)		**328**		**203**	**22.4%**	**4.68 [1.11, 19.72]**
Total events	105		13			
Heterogeneity: Tau² = 0.89; Chi² = 5.72, df = 1 (P = 0.02); I² = 83%						
Test for overall effect: Z = 2.10 (P = 0.04)						
1.14.3 Rotigotine studies						
Hening 2010	27	404	4	100	10.0%	1.67 [0.60, 4.67]
Oertel 2008	19	285	6	55	11.0%	0.61 [0.26, 1.46]
Trenkwalder 2008	37	341	11	117	12.4%	1.15 [0.61, 2.19]
Subtotal (95% CI)		**1030**		**272**	**33.3%**	**1.04 [0.62, 1.73]**
Total events	83		21			
Heterogeneity: Tau² = 0.04; Chi² = 2.39, df = 2 (P = 0.30); I² = 16%						
Test for overall effect: Z = 0.15 (P = 0.88)						
Total (95% CI)		**2215**		**1039**	**100.0%**	**1.67 [0.93, 2.99]**
Total events	256		68			
Heterogeneity: Tau² = 0.61; Chi² = 36.86, df = 8 (P < 0.0001); I² = 78%						
Test for overall effect: Z = 1.73 (P = 0.08)						
Test for subgroup differences: Chi² = 3.88, df = 2 (P = 0.14), I² = 48.5%						



Somnolence

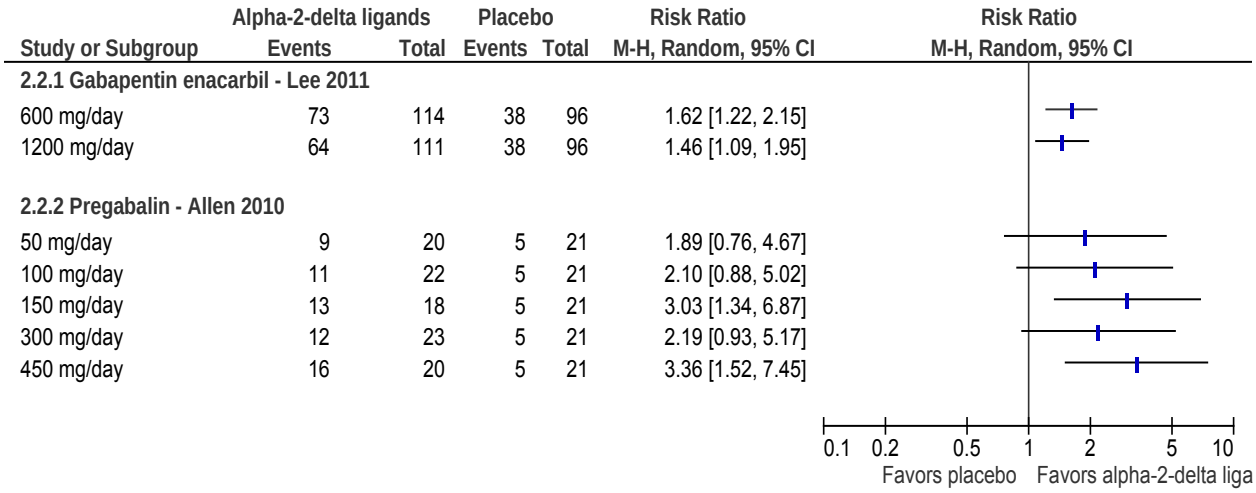

Dopamine agonists
Placebo
Risk Ratio
Risk Ratio
Study or Subgroup Events Total Events Total Weight M-H, Random, 95% CI
M-H, Random, 95% CI
1.16.1 Pramipexole studies
Högl 2011 11 166 8 163 11.7% 1.35 [0.56, 3.27]
Winkelman 2006 26 258 4 86 8.8% 2.17 [0.78, 6.03]
Subtotal (95% CI) 424 249 20.5% 1.65 [0.85, 3.23]
Total events 37 12
Heterogeneity: Tau² = 0.00; Chi² = 0.48, df = 1 (P = 0.49); I² = 0%
Test for overall effect: Z = 1.47 (P = 0.14)
1.16.2 Ropinirole studies
Adler 2004 3 22 0 22 1.1% 7.00 [0.38, 128.02]
Bogan 2006 24 187 13 193 22.1% 1.91 [1.00, 3.63]
Kushida 2008 34 176 11 186 21.9% 3.27 [1.71, 6.24]
Trenkwalder 2004 18 146 10 138 16.9% 1.70 [0.81, 3.56]
Subtotal (95% CI) 531 539 62.1% 2.29 [1.56, 3.36]
Total events 79 34
Heterogeneity: Tau² = 0.00; Chi² = 2.67, df = 3 (P = 0.44); I² = 0%
Test for overall effect: Z = 4.21 (P < 0.0001)
1.16.3 Rotigotine studies
Hening 2010 47 404 6 100 13.6% 1.94 [0.85, 4.41]
Oertel 2010 5 46 2 21 3.8% 1.14 [0.24, 5.41]
Subtotal (95% CI) 450 121 17.4% 1.73 [0.84, 3.57]
Total events 52 8
Heterogeneity: Tau² = 0.00; Chi² = 0.35, df = 1 (P = 0.55); I² = 0%
Test for overall effect: Z = 1.48 (P = 0.14)
Total (95% CI) 1405 909 100.0% 2.04 [1.50, 2.76]
Total events 168 54
Heterogeneity: Tau² = 0.00; Chi² = 4.41, df = 7 (P = 0.73); I² = 0%
Test for overall effect: Z = 4.60 (P < 0.00001)
Test for subgroup differences: Chi² = 0.92, df = 2 (P = 0.63), I² = 0%
0.1 0.2 0.5 1 2 5 10
Favors Dopamine agonists
Favors Placebo

Headache

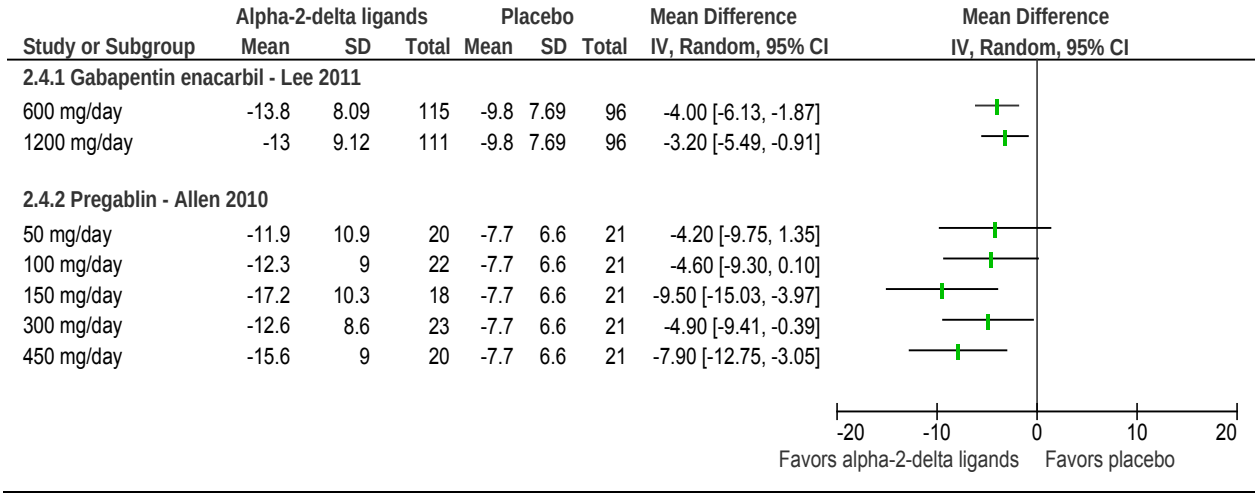

Dopamine agonists
Placebo
Risk Ratio
Risk Ratio
Study or Subgroup Events Total Events Total Weight M-H, Random, 95% CI
M-H, Random, 95% CI
1.18.1 Pramipexole studies
Högl 2011 13 166 17 163 5.4% 0.75 [0.38, 1.50]
Montagna 2011 21 203 19 200 7.3% 1.09 [0.60, 1.96]
Oertel 2007 30 230 11 115 6.0% 1.36 [0.71, 2.62]
Winkelman 2006 46 258 15 86 9.1% 1.02 [0.60, 1.74]
Subtotal (95% CI) 857 564 27.8% 1.04 [0.77, 1.41]
Total events 110 62
Heterogeneity: Tau² = 0.00; Chi² = 1.55, df = 3 (P = 0.67); I² = 0%
Test for overall effect: Z = 0.27 (P = 0.79)
1.18.2 Ropinirole studies
Adler 2004 2 22 2 22 0.7% 1.00 [0.15, 6.48]
Benes 2011 39 197 9 67 5.7% 1.47 [0.75, 2.88]
Bogan 2006 31 187 36 193 13.4% 0.89 [0.57, 1.37]
Kushida 2008 42 176 33 186 15.4% 1.35 [0.90, 2.02]
Montplaisir 2006 5 45 3 47 1.4% 1.74 [0.44, 6.86]
Trenkwalder 2004 29 146 23 138 10.4% 1.19 [0.73, 1.96]
Walters 2004 29 131 35 136 13.8% 0.86 [0.56, 1.32]
Subtotal (95% CI) 904 789 60.7% 1.10 [0.89, 1.35]
Total events 177 141
Heterogeneity: Tau² = 0.00; Chi² = 4.40, df = 6 (P = 0.62); I² = 0%
Test for overall effect: Z = 0.90 (P = 0.37)
1.18.3 Rotigotine studies
Hening 2010 47 404 8 100 5.0% 1.45 [0.71, 2.98]
Oertel 2010 8 46 3 21 1.7% 1.22 [0.36, 4.13]
Trenkwalder 2008 43 341 8 117 4.8% 1.84 [0.89, 3.81]
Subtotal (95% CI) 791 238 11.5% 1.57 [0.98, 2.51]
Total events 98 19
Heterogeneity: Tau² = 0.00; Chi² = 0.40, df = 2 (P = 0.82); I² = 0%
Test for overall effect: Z = 1.87 (P = 0.06)
Total (95% CI) 2552 1591 100.0% 1.13 [0.96, 1.32]
Total events 385 222
Heterogeneity: Tau² = 0.00; Chi² = 8.56, df = 13 (P = 0.81); I² = 0%
Test for overall effect: Z = 1.47 (P = 0.14)
Test for subgroup differences: Chi² = 2.20, df = 2 (P = 0.33), I² = 8.9%
0.2
0.5
1
2
5
Favors Dopamine agonists
Favors Placebo

Appendix. F. Figure3. Efficacy and Harms data for double-blind alpha-2-delta ligands trials

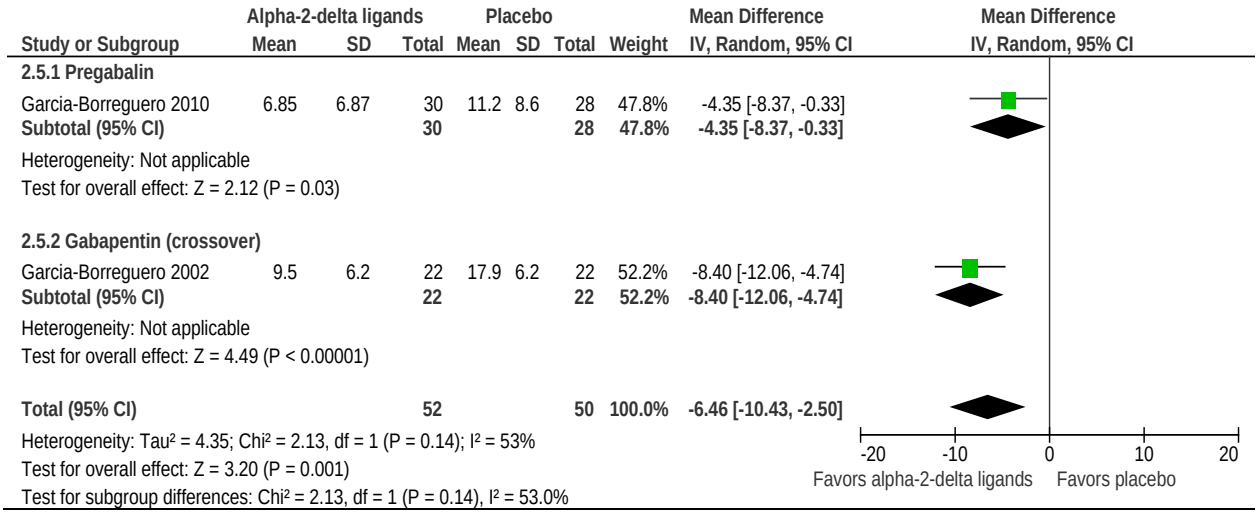
IRLS Responders (≥50% score reduction) - fixed-dose study analyses



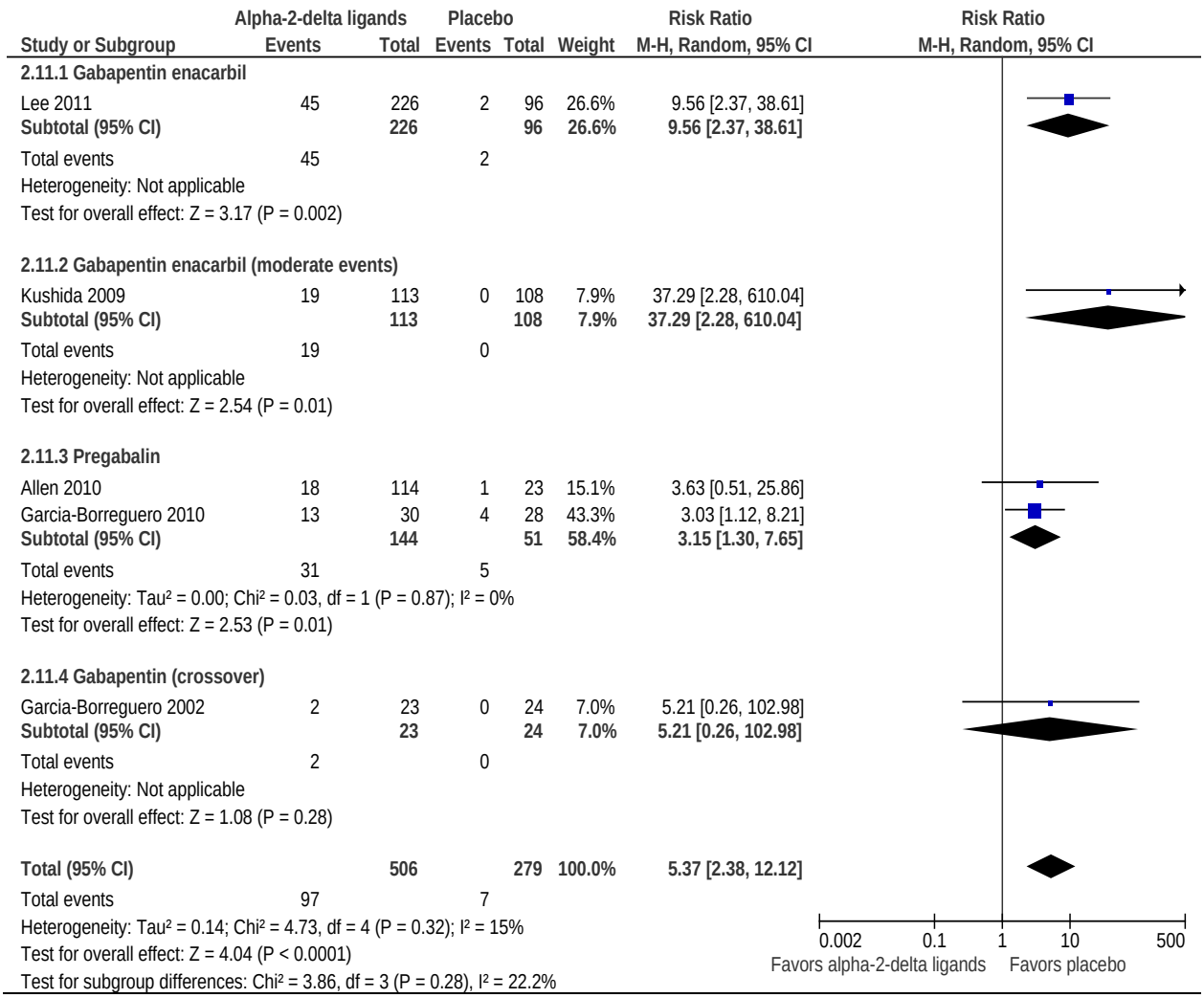
IRLS total score: Mean change from baseline - fixed-dose study analyses



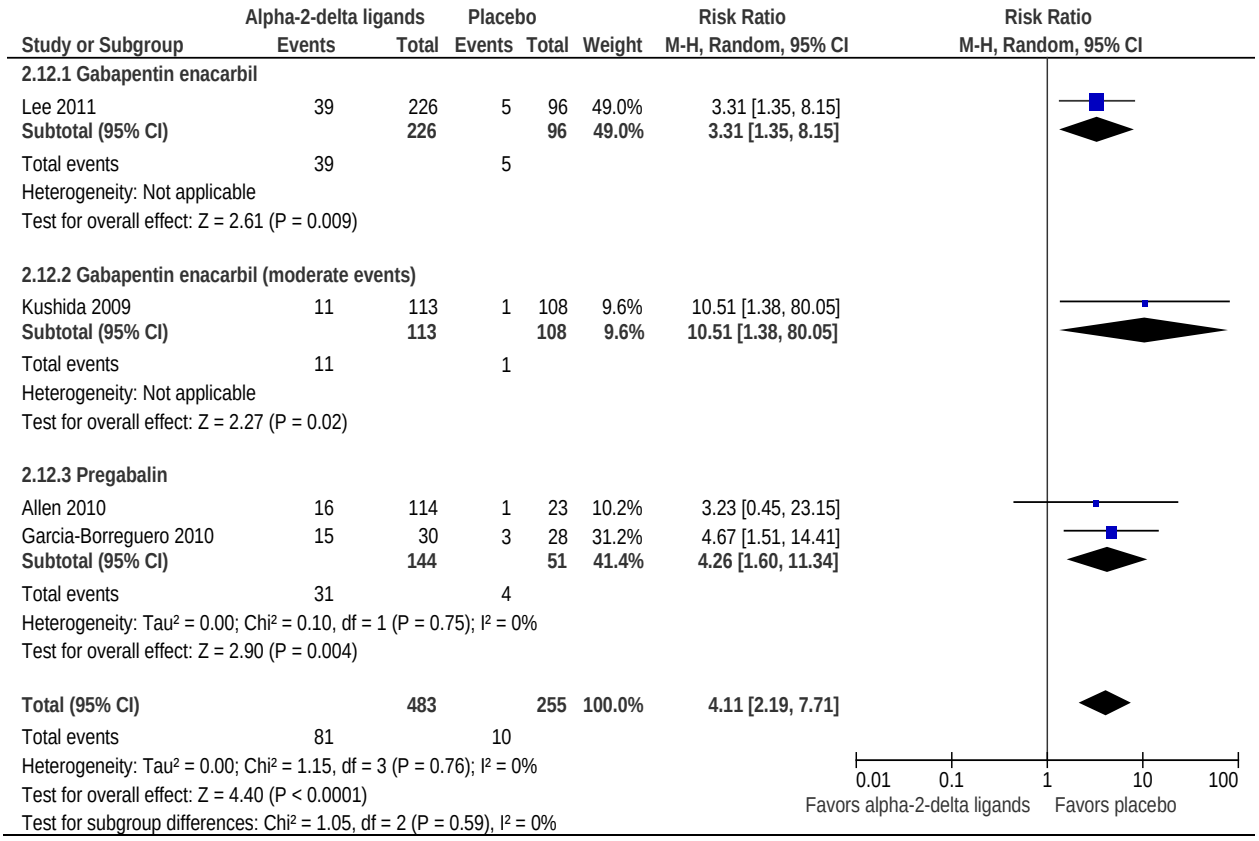
IRLS total score: mean score at end of treatment



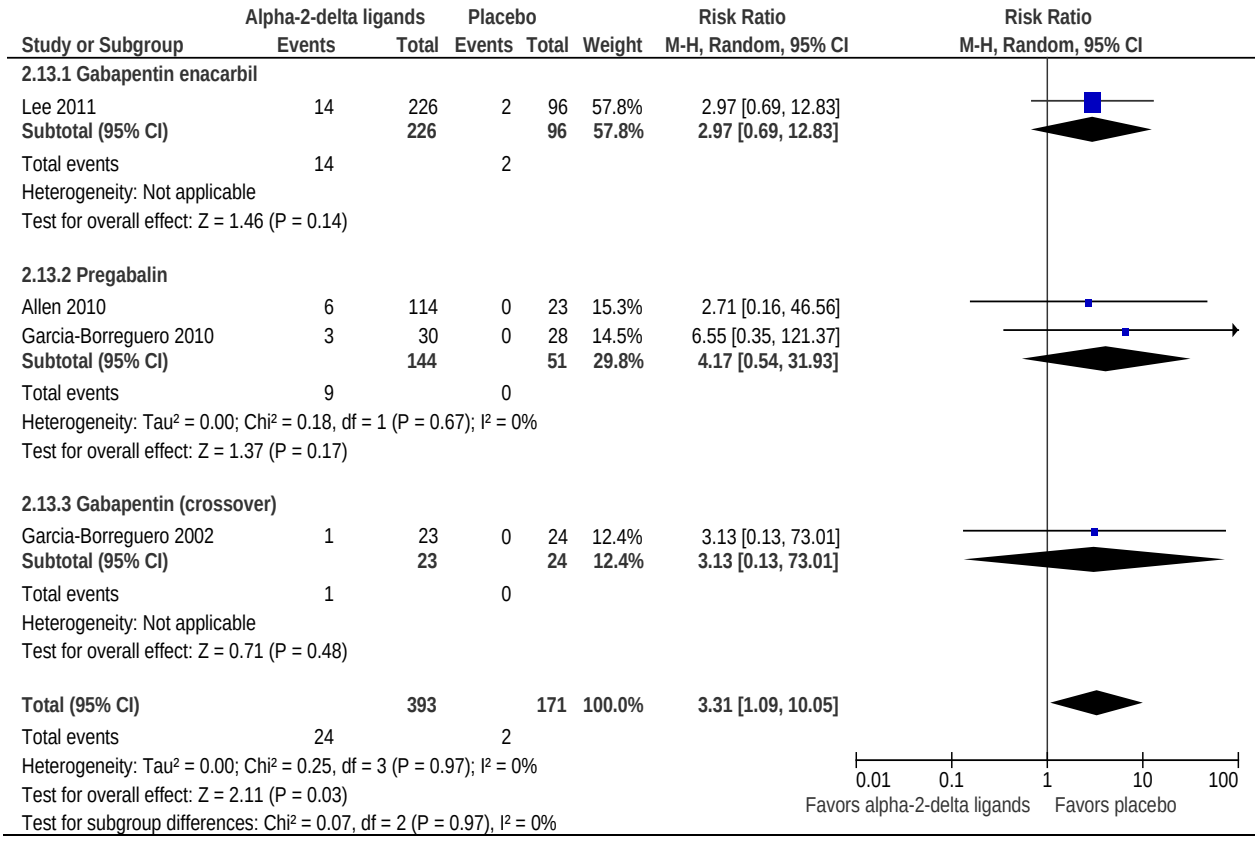
Daytime sleepiness/somnolence



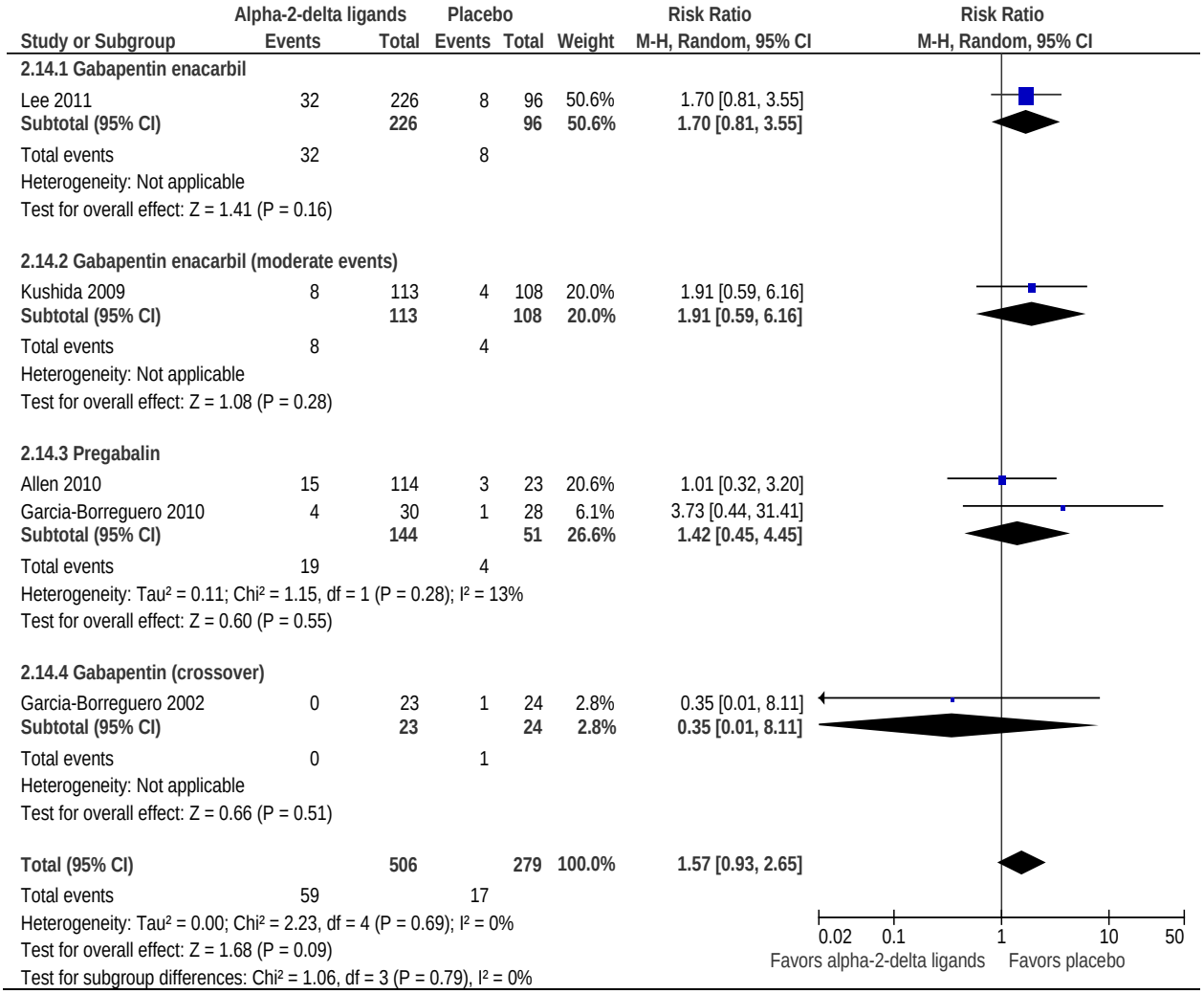
Unsteadiness/dizziness



Dry mouth

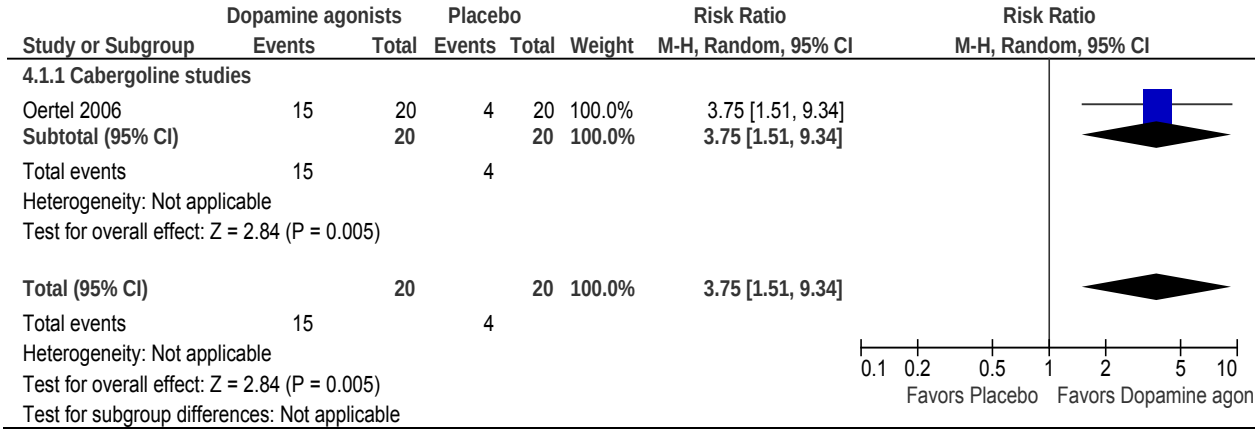

Alpha-2-delta ligands
Placebo
Risk Ratio
Risk Ratio
Study or Subgroup
Events
Total
Events
Total
Weight
M-H, Random, 95% CI
M-H, Random, 95% CI
2.13.1 Gabapentin enacarbil
Lee 2011 14 226 2 96 57.8% 2.97 [0.69, 12.83]
Subtotal (95% CI) 226 96 57.8% 2.97 [0.69, 12.83]
Total events 14 2
Heterogeneity: Not applicable
Test for overall effect: Z = 1.46 (P = 0.14)
2.13.2 Pregabalin
Allen 2010 6 114 0 23 15.3% 2.71 [0.16, 46.56]
Garcia-Borreguero 2010 3 30 0 28 14.5% 6.55 [0.35, 121.37]
Subtotal (95% CI) 144 51 29.8% 4.17 [0.54, 31.93]
Total events 9 0
Heterogeneity: Tau² = 0.00; Chi² = 0.18, df = 1 (P = 0.67); I² = 0%
Test for overall effect: Z = 1.37 (P = 0.17)
2.13.3 Gabapentin (crossover)
Garcia-Borreguero 2002 1 23 0 24 12.4% 3.13 [0.13, 73.01]
Subtotal (95% CI) 23 24 12.4% 3.13 [0.13, 73.01]
Total events 1 0
Heterogeneity: Not applicable
Test for overall effect: Z = 0.71 (P = 0.48)
Total (95% CI) 393 171 100.0% 3.31 [1.09, 10.05]
Total events 24 2
Heterogeneity: Tau² = 0.00; Chi² = 0.25, df = 3 (P = 0.97); I² = 0%
Test for overall effect: Z = 2.11 (P = 0.03)
Test for subgroup differences: Chi² = 0.07, df = 2 (P = 0.97), I² = 0%
0.01
0.1
1
10
100
Favors alpha-2-delta ligands
Favors placebo

Headache

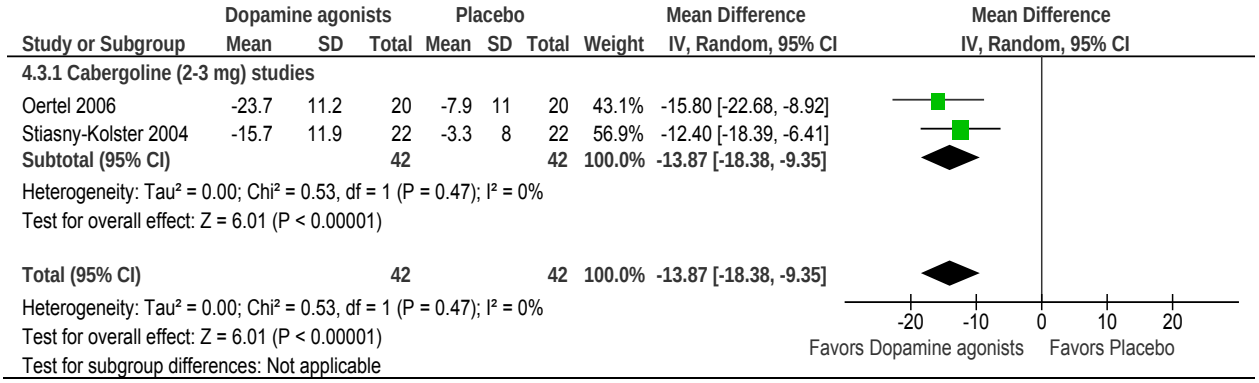

Alpha-2-delta ligands
Placebo
Risk Ratio
Risk Ratio
Study or Subgroup Events Total Events Total Weight M-H, Random, 95% CI
M-H, Random, 95% CI
2.14.1 Gabapentin enacarbil
Lee 2011 32 226 8 96 50.6% 1.70 [0.81, 3.55]
Subtotal (95% CI) 226 96 50.6% 1.70 [0.81, 3.55]
Total events 32 8
Heterogeneity: Not applicable
Test for overall effect: Z = 1.41 (P = 0.16)
2.14.2 Gabapentin enacarbil (moderate events)
Kushida 2009 8 113 4 108 20.0% 1.91 [0.59, 6.16]
Subtotal (95% CI) 113 108 20.0% 1.91 [0.59, 6.16]
Total events 8 4
Heterogeneity: Not applicable
Test for overall effect: Z = 1.08 (P = 0.28)
2.14.3 Pregabalin
Allen 2010 15 114 3 23 20.6% 1.01 [0.32, 3.20]
Garcia-Borreguero 2010 4 30 1 28 6.1% 3.73 [0.44, 31.41]
Subtotal (95% CI) 144 51 26.6% 1.42 [0.45, 4.45]
Total events 19 4
Heterogeneity: Tau² = 0.11; Chi² = 1.15, df = 1 (P = 0.28); I² = 13%
Test for overall effect: Z = 0.60 (P = 0.55)
2.14.4 Gabapentin (crossover)
Garcia-Borreguero 2002 0 23 1 24 2.8% 0.35 [0.01, 8.11]
Subtotal (95% CI) 23 24 2.8% 0.35 [0.01, 8.11]
Total events 0 1
Heterogeneity: Not applicable
Test for overall effect: Z = 0.66 (P = 0.51)
Total (95% CI) 506 279 100.0% 1.57 [0.93, 2.65]
Total events 59 17
Heterogeneity: Tau² = 0.00; Chi² = 2.23, df = 4 (P = 0.69); I² = 0%
Test for overall effect: Z = 1.68 (P = 0.09)
Test for subgroup differences: Chi² = 1.06, df = 3 (P = 0.79), I² = 0%
0.02 0.1 1 10 50
Favors alpha-2-delta ligands
Favors placebo

Appendix F. Figure 4. Efficacy and Harms data for double-blind Cabergoline trials

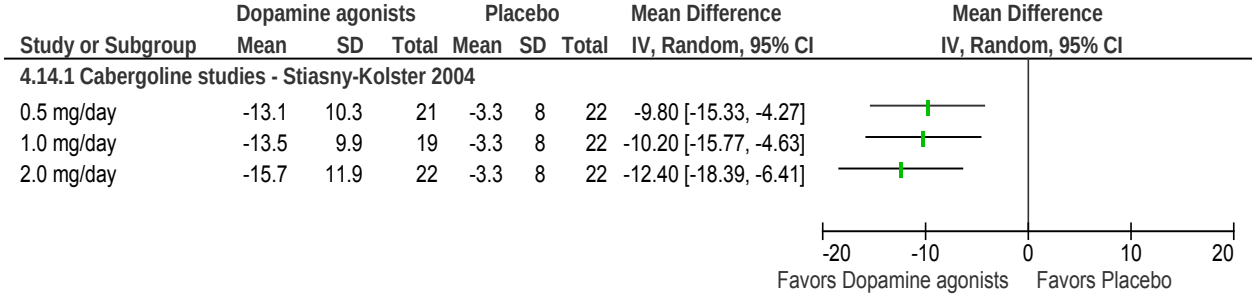
International Restless Legs Scale (IRLS) Responders (≥50% score reduction)



Mean change in IRLS total score from baseline

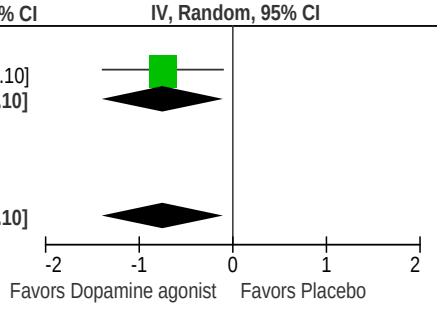


Mean change in IRLS total score from baseline: Fixed-dose studies



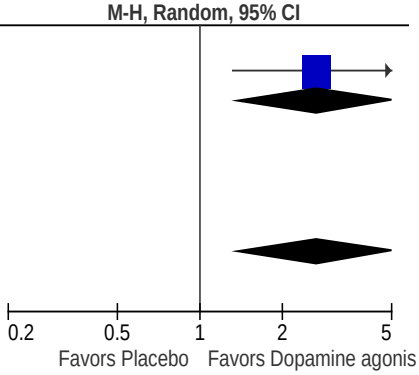
RSL-QoL

Study or Subgroup	Dopamine agonists Mean	SD	Total	Placebo Mean	SD	Total	Weight	Std. Mean Difference IV, Random, 95% CI
4.19.1 Cabergoline (2-3 mg) studies								
Oertel 2006	-23.7	14.5	20	-11.4	17.6	20	100.0%	-0.75 [-1.39, -0.10]
Subtotal (95% CI)			**20**			**20**	**100.0%**	**-0.75 [-1.39, -0.10]**
Heterogeneity: Not applicable								
Test for overall effect: Z = 2.28 (P = 0.02)								
Total (95% CI)			**20**			**20**	**100.0%**	**-0.75 [-1.39, -0.10]**
Heterogeneity: Not applicable								
Test for overall effect: Z = 2.28 (P = 0.02)								
Test for subgroup differences: Not applicable								



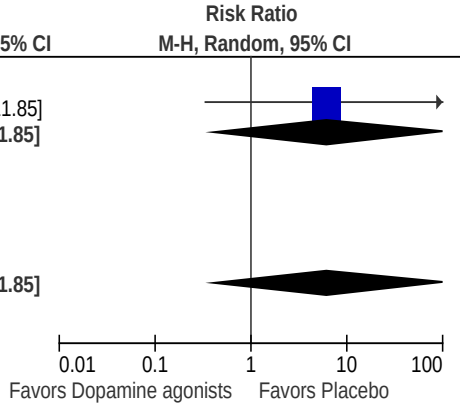
Clinical Global Impression: Responders (much-very much improved)

Study or Subgroup	Dopamine agonists Events	Total	Placebo Events	Total	Weight	Risk Ratio M-H, Random, 95% CI
4.6.1 Cabergoline studies						
Oertel 2006	16	20	6	20	100.0%	2.67 [1.32, 5.39]
Subtotal (95% CI)		**20**		**20**	**100.0%**	**2.67 [1.32, 5.39]**
Total events	16		6			
Heterogeneity: Not applicable						
Test for overall effect: Z = 2.73 (P = 0.006)						
Total (95% CI)		**20**		**20**	**100.0%**	**2.67 [1.32, 5.39]**
Total events	16		6			
Heterogeneity: Not applicable						
Test for overall effect: Z = 2.73 (P = 0.006)						
Test for subgroup differences: Not applicable						



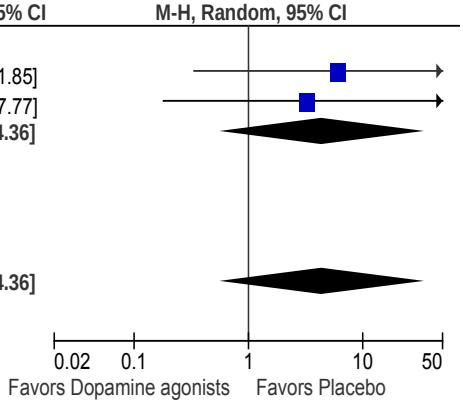
Any study withdrawal

Study or Subgroup	Dopamine agonists Events	Total	Placebo Events	Total	Weight	Risk Ratio M-H, Random, 95% CI
4.8.1 Cabergoline studies						
Oertel 2006	3	23	0	20	100.0%	6.13 [0.34, 111.85]
Subtotal (95% CI)		**23**		**20**	**100.0%**	**6.12 [0.34, 111.85]**
Total events	3		0			
Heterogeneity: Not applicable						
Test for overall effect: Z = 1.22 (P = 0.22)						
Total (95% CI)		**23**		**20**	**100.0%**	**6.12 [0.34, 111.85]**
Total events	3		0			
Heterogeneity: Not applicable						
Test for overall effect: Z = 1.22 (P = 0.22)						
Test for subgroup differences: Not applicable						



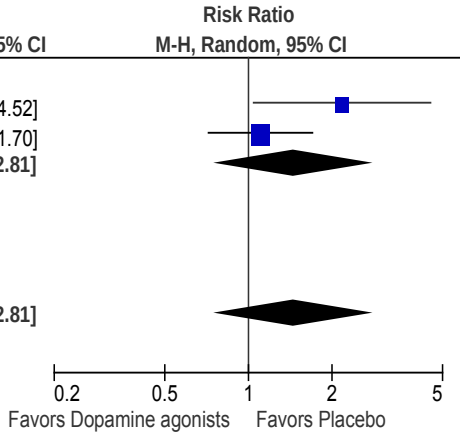
Study withdrawals due to adverse effects

Study or Subgroup	Dopamine agonists Events	Total	Placebo Events	Total	Weight	Risk Ratio M-H, Random, 95% CI
4.9.1 Cabergoline studies						
Oertel 2006	3	23	0	20	49.6%	6.13 [0.34, 111.85]
Stiasny-Kolster 2004	4	63	0	22	50.4%	3.23 [0.18, 57.77]
Subtotal (95% CI)		**86**		**42**	**100.0%**	**4.44 [0.57, 34.36]**
Total events	7		0			
Heterogeneity: Tau² = 0.00; Chi² = 0.09, df = 1 (P = 0.76); I² = 0%						
Test for overall effect: Z = 1.43 (P = 0.15)						
Total (95% CI)		**86**		**42**	**100.0%**	**4.44 [0.57, 34.36]**
Total events	7		0			
Heterogeneity: Tau² = 0.00; Chi² = 0.09, df = 1 (P = 0.76); I² = 0%						
Test for overall effect: Z = 1.43 (P = 0.15)						
Test for subgroup differences: Not applicable						



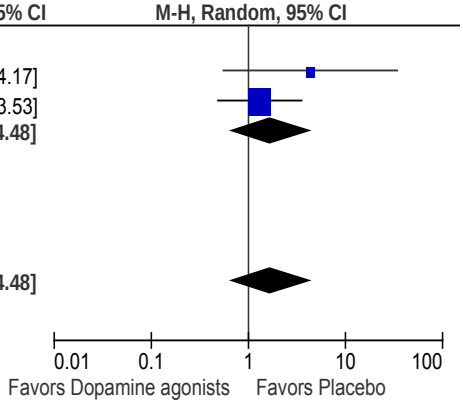
Patients with ≥1 adverse event

Study or Subgroup	Dopamine agonists Events	Total	Placebo Events	Total	Weight	Risk Ratio M-H, Random, 95% CI
4.10.1 Cabergoline studies						
Oertel 2006	15	23	6	20	40.3%	2.17 [1.04, 4.52]
Stiasny-Kolster 2004	38	63	12	22	59.7%	1.11 [0.72, 1.70]
Subtotal (95% CI)		**86**		**42**	**100.0%**	**1.45 [0.75, 2.81]**
Total events	53		18			
Heterogeneity: Tau² = 0.14; Chi² = 2.51, df = 1 (P = 0.11); I² = 60%						
Test for overall effect: Z = 1.11 (P = 0.27)						
Total (95% CI)		**86**		**42**	**100.0%**	**1.45 [0.75, 2.81]**
Total events	53		18			
Heterogeneity: Tau² = 0.14; Chi² = 2.51, df = 1 (P = 0.11); I² = 60%						
Test for overall effect: Z = 1.11 (P = 0.27)						
Test for subgroup differences: Not applicable						



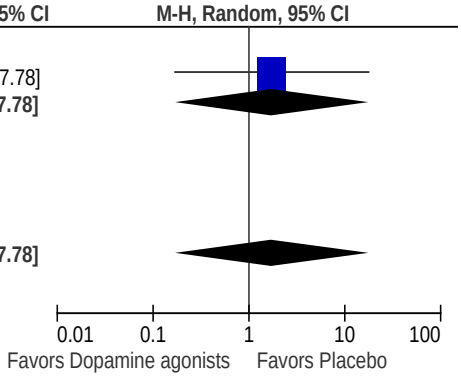
Nausea

Study or Subgroup	Dopamine agonists Events	Total	Placebo Events	Total	Weight	Risk Ratio M-H, Random, 95% CI
4.9.1 Cabergoline studies						
Oertel 2006	5	23	1	20	21.3%	4.35 [0.55, 34.17]
Stiasny-Kolster 2004	15	63	4	22	78.7%	1.31 [0.49, 3.53]
Subtotal (95% CI)		**86**		**42**	**100.0%**	**1.69 [0.64, 4.48]**
Total events	20		5			
Heterogeneity: Tau² = 0.06; Chi² = 1.09, df = 1 (P = 0.30); I² = 8%						
Test for overall effect: Z = 1.05 (P = 0.29)						
Total (95% CI)		**86**		**42**	**100.0%**	**1.69 [0.64, 4.48]**
Total events	20		5			
Heterogeneity: Tau² = 0.06; Chi² = 1.09, df = 1 (P = 0.30); I² = 8%						
Test for overall effect: Z = 1.05 (P = 0.29)						
Test for subgroup differences: Not applicable						



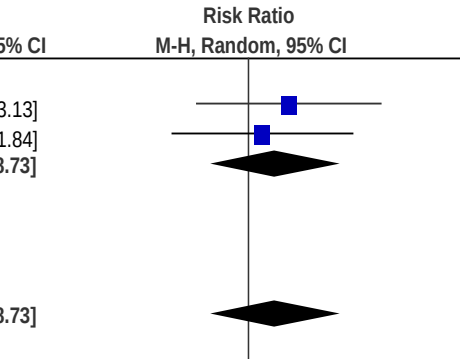
Vomiting

Study or Subgroup	Dopamine agonists Events	Total	Placebo Events	Total	Weight	Risk Ratio M-H, Random, 95% CI
4.10.1 Cabergoline studies						
Oertel 2006	2	23	1	20	100.0%	1.74 [0.17, 17.78]
Subtotal (95% CI)		**23**		**20**	**100.0%**	**1.74 [0.17, 17.78]**
Total events	2		1			
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.47 (P = 0.64)						
Total (95% CI)		**23**		**20**	**100.0%**	**1.74 [0.17, 17.78]**
Total events	2		1			
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.47 (P = 0.64)						
Test for subgroup differences: Not applicable						



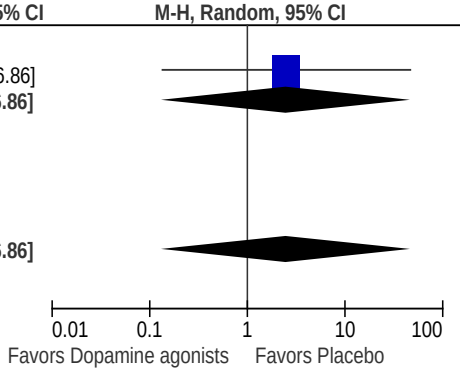
Fatigue

Study or Subgroup	Dopamine agonists Events	Total	Placebo Events	Total	Weight	Risk Ratio M-H, Random, 95% CI
4.8.1 Cabergoline studies						
Oertel 2006	3	23	1	20	48.9%	2.61 [0.29, 23.13]
Stiasny-Kolster 2004	4	63	1	22	51.1%	1.40 [0.16, 11.84]
Subtotal (95% CI)		**86**		**42**	**100.0%**	**1.90 [0.41, 8.73]**
Total events	7		2			
Heterogeneity: $Tau^2 = 0.00$; $Chi^2 = 0.16$, df = 1 (P = 0.69); $I^2 = 0\%$						
Test for overall effect: Z = 0.82 (P = 0.41)						
Total (95% CI)		**86**		**42**	**100.0%**	**1.90 [0.41, 8.73]**
Total events	7		2			
Heterogeneity: $Tau^2 = 0.00$; $Chi^2 = 0.16$, df = 1 (P = 0.69); $I^2 = 0\%$						
Test for overall effect: Z = 0.82 (P = 0.41)						
Test for subgroup differences: Not applicable						

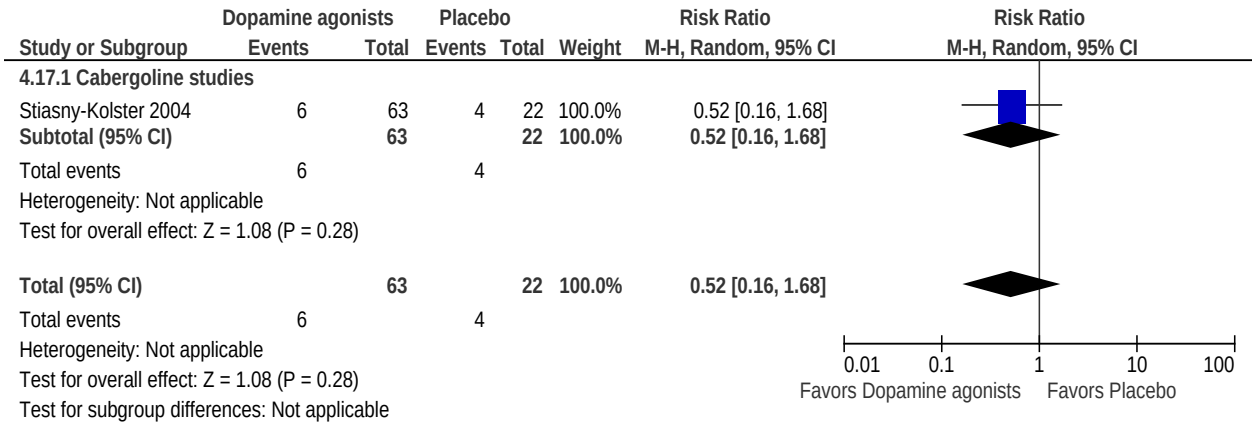


Somnolence

Study or Subgroup	Dopamine agonists Events	Total	Placebo Events	Total	Weight	Risk Ratio M-H, Random, 95% CI
4.11.1 Cabergoline studies						
Stiasny-Kolster 2004	3	63	0	22	100.0%	2.52 [0.14, 46.86]
Subtotal (95% CI)		**63**		**22**	**100.0%**	**2.52 [0.14, 46.86]**
Total events	3		0			
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.62 (P = 0.54)						
Total (95% CI)		**63**		**22**	**100.0%**	**2.52 [0.14, 46.86]**
Total events	3		0			
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.62 (P = 0.54)						
Test for subgroup differences: Not applicable						

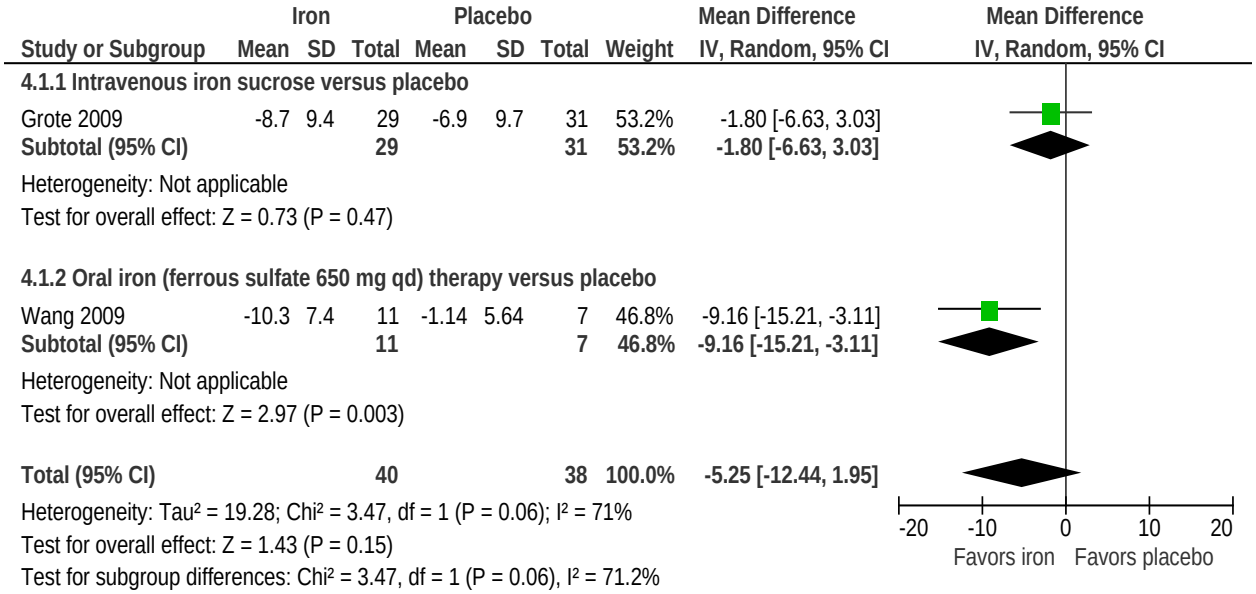


Headache


Dopamine agonists
Placebo
Risk Ratio
Risk Ratio
Study or Subgroup Events Total Events Total Weight M-H, Random, 95% CI
M-H, Random, 95% CI
4.17.1 Cabergoline studies
Stiasny-Kolster 2004 6 63 4 22 100.0% 0.52 [0.16, 1.68]
Subtotal (95% CI) 63 22 100.0% 0.52 [0.16, 1.68]
Total events 6 4
Heterogeneity: Not applicable
Test for overall effect: Z = 1.08 (P = 0.28)
Total (95% CI) 63 22 100.0% 0.52 [0.16, 1.68]
Total events 6 4
Heterogeneity: Not applicable
Test for overall effect: Z = 1.08 (P = 0.28)
Test for subgroup differences: Not applicable
0.01
0.1
1
10
100
Favors Dopamine agonists
Favors Placebo

Appendix F. Figure 5. Efficacy and Harms data for double-blind Iron therapy trials

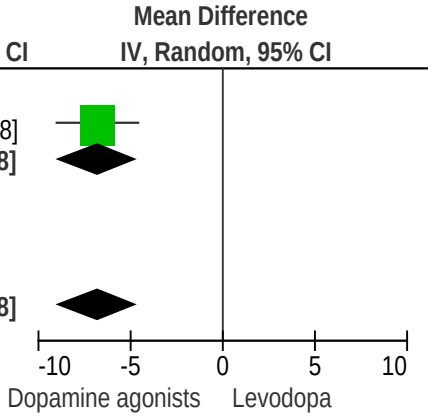
IRLS total score: Mean change from baseline



Appendix F. Figure 6. Efficacy and Harms data for double-blind Cabergoline (dopamine agonists) vs. levodopa

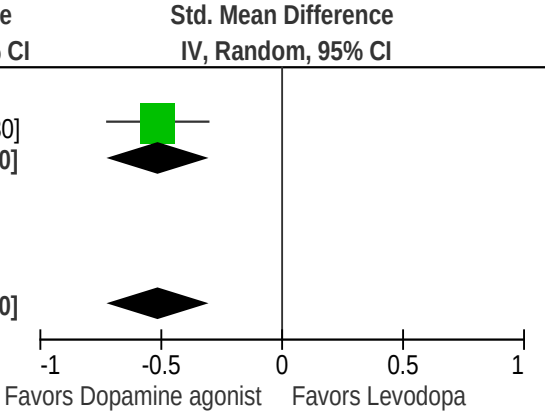
Mean change in International Restless Legs Scale (IRLS) from baseline

Study or Subgroup	Dopamine agonists Mean	SD	Total	Levodopa Mean	SD	Total	Weight	Mean Difference IV, Random, 95% CI
2.1.1 Cabergoline studies								
Trenkwalder 2007	-15.6	10.8	178	-8.8	10.7	183	100.0%	-6.80 [-9.02, -4.58]
Subtotal (95% CI)			**178**			**183**	**100.0%**	**-6.80 [-9.02, -4.58]**
Heterogeneity: Not applicable								
Test for overall effect: Z = 6.01 (P < 0.00001)								
Total (95% CI)			**178**			**183**	**100.0%**	**-6.80 [-9.02, -4.58]**
Heterogeneity: Not applicable								
Test for overall effect: Z = 6.01 (P < 0.00001)								
Test for subgroup differences: Not applicable								



RSL-QoL

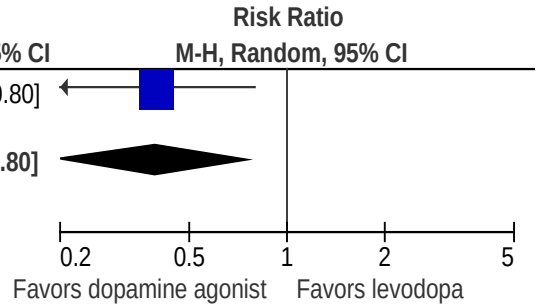
Study or Subgroup	Dopamine agonists Mean	SD	Total	Levodopa Mean	SD	Total	Weight	Std. Mean Difference IV, Random, 95% CI
2.2.1 Cabergoline studies								
Trenkwalder 2007	-17.7	13	178	-10.6	14.5	183	100.0%	-0.51 [-0.72, -0.30]
Subtotal (95% CI)			**178**			**183**	**100.0%**	**-0.51 [-0.72, -0.30]**
Heterogeneity: Not applicable								
Test for overall effect: Z = 4.80 (P < 0.00001)								
Total (95% CI)			**178**			**183**	**100.0%**	**-0.51 [-0.72, -0.30]**
Heterogeneity: Not applicable								
Test for overall effect: Z = 4.80 (P < 0.00001)								
Test for subgroup differences: Not applicable								



Augmentation

Study or Subgroup	Dopamine agonists Events	Total	Levodopa Events	Total	Weight	Risk Ratio M-H, Random, 95% CI
Trenkwalder 2007	10	178	26	183	100.0%	0.40 [0.20, 0.80]
Total (95% CI)		**178**		**183**	**100.0%**	**0.40 [0.20, 0.80]**
Total events	10		26			

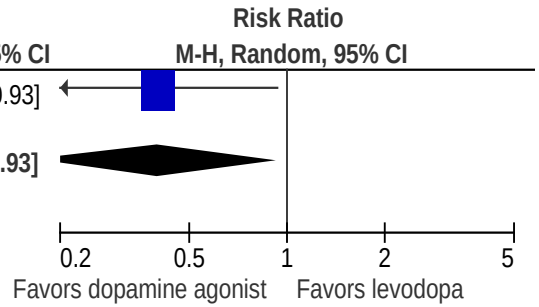
Heterogeneity: Not applicable
Test for overall effect: Z = 2.60 (P = 0.009)



Augmentation leading to study withdrawal

Study or Subgroup	Dopamine agonists Events	Total	Levodopa Events	Total	Weight	Risk Ratio M-H, Random, 95% CI
Trenkwalder 2007	7	178	18	183	100.0%	0.40 [0.17, 0.93]
Total (95% CI)		**178**		**183**	**100.0%**	**0.40 [0.17, 0.93]**
Total events	7		18			

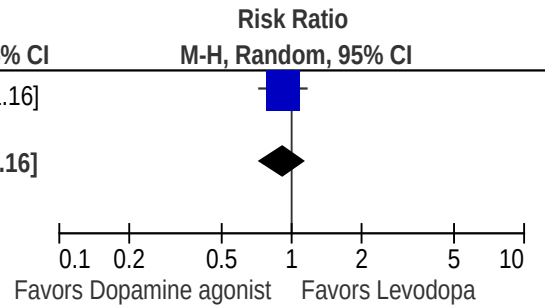
Heterogeneity: Not applicable
Test for overall effect: Z = 2.12 (P = 0.03)



Any study withdrawals

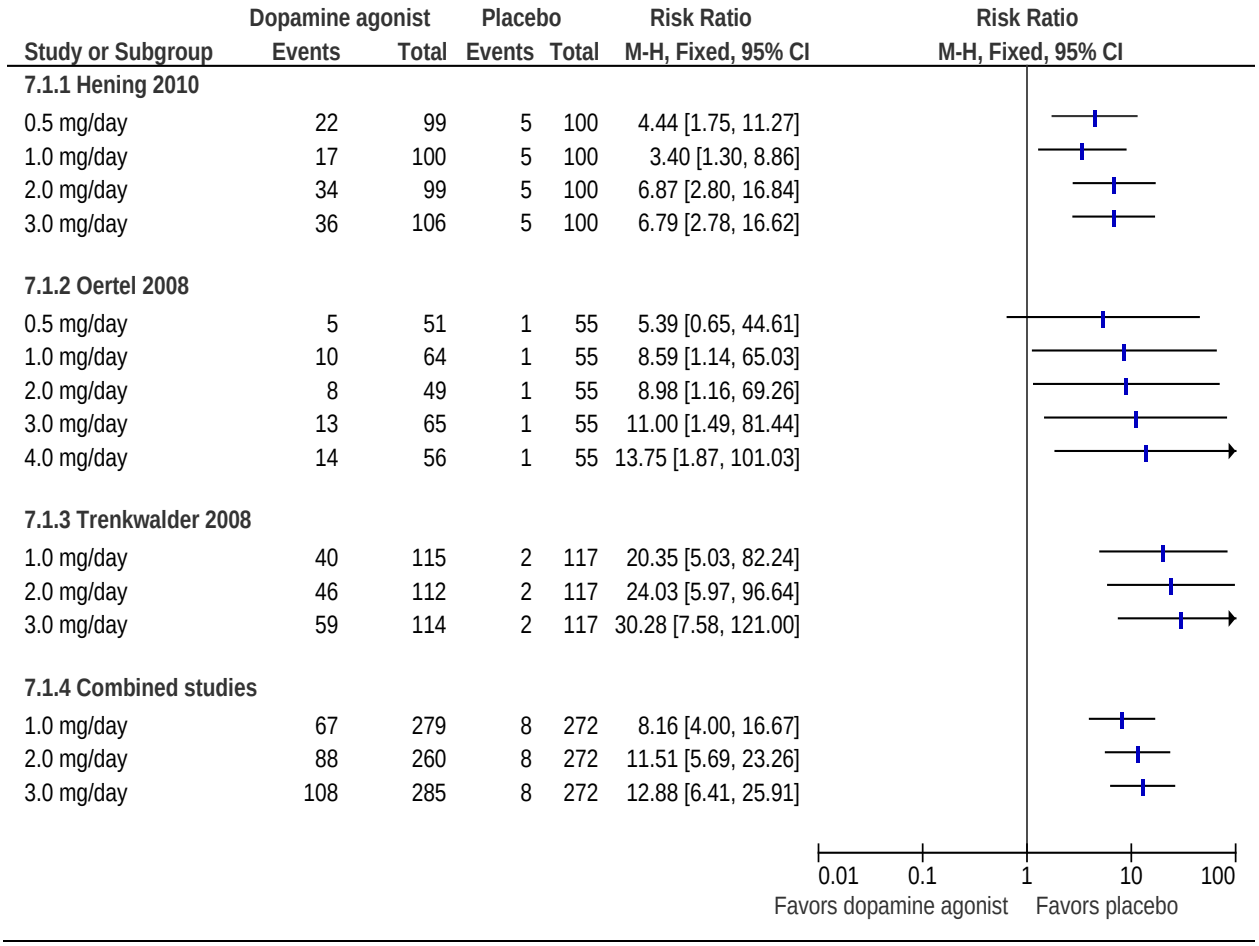
Study or Subgroup	Dopamine agonists Events	Total	Levodopa Events	Total	Weight	Risk Ratio M-H, Random, 95% CI
Trenkwalder 2007	74	178	83	183	100.0%	0.92 [0.72, 1.16]
Total (95% CI)		**178**		**183**	**100.0%**	**0.92 [0.72, 1.16]**
Total events	74		83			

Heterogeneity: Not applicable
Test for overall effect: Z = 0.72 (P = 0.47)



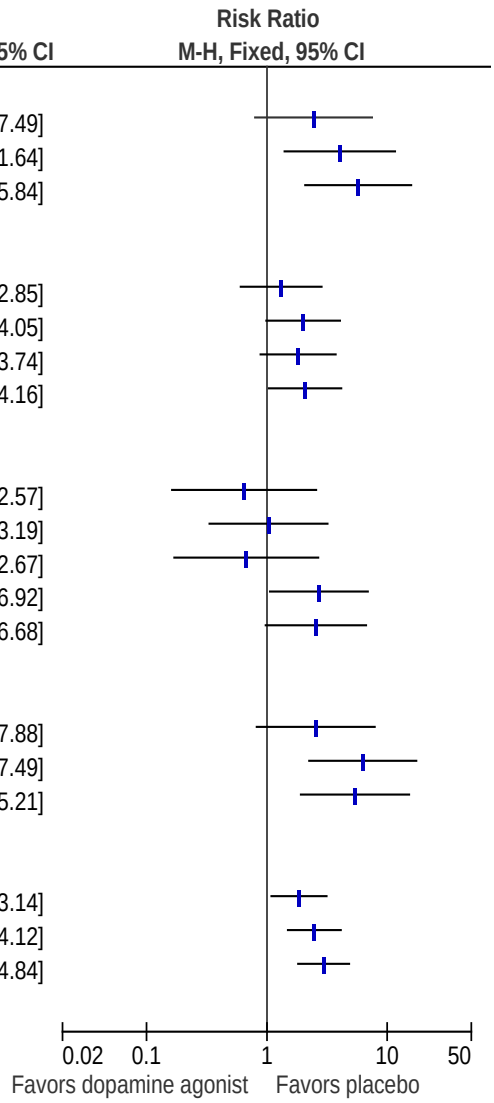
Appendix F. Figure 7. Fixed-dose analyses of harms: Dopamine agonists

Application site reactions (rotigotine only)



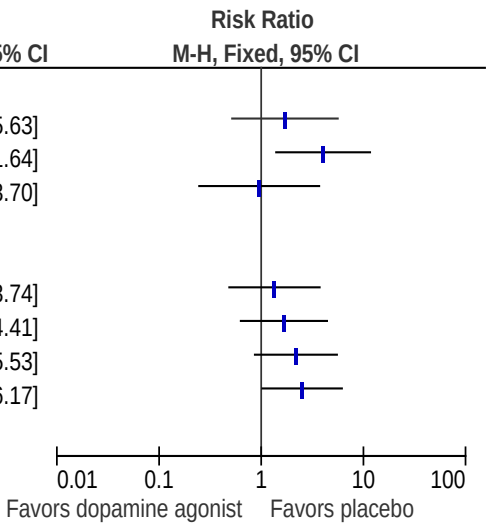
Nausea

Study or Subgroup	Dopamine agonist Events	Total	Placebo Events	Total	Risk Ratio M-H, Fixed, 95% CI
7.2.1 Pramipexole - Winkelman 2006					
0.25 mg/day	10	88	4	86	2.44 [0.80, 7.49]
0.5 mg/day	15	80	4	86	4.03 [1.40, 11.64]
0.75 mg/day	24	90	4	86	5.73 [2.07, 15.84]
7.2.2 Rotigotine - Hening 2010					
0.5 mg/day	13	99	10	100	1.31 [0.60, 2.85]
1.0 mg/day	20	100	10	100	2.00 [0.99, 4.05]
2.0 mg/day	18	99	10	100	1.82 [0.88, 3.74]
3.0 mg/day	22	106	10	100	2.08 [1.04, 4.16]
7.2.3 Rotigotine - Oertel 2008					
0.5 mg/day	3	51	5	55	0.65 [0.16, 2.57]
1.0 mg/day	6	64	5	55	1.03 [0.33, 3.19]
2.0 mg/day	3	49	5	55	0.67 [0.17, 2.67]
3.0 mg/day	16	65	5	55	2.71 [1.06, 6.92]
4.0 mg/day	13	56	5	55	2.55 [0.98, 6.68]
7.2.4 Rotigotine - Trenkwalder 2008					
1.0 mg/day	10	115	4	117	2.54 [0.82, 7.88]
2.0 mg/day	24	112	4	117	6.27 [2.25, 17.49]
3.0 mg/day	21	114	4	117	5.39 [1.91, 15.21]
7.2.5 Combined rotigotine studies					
1.0 mg/day	36	279	19	272	1.85 [1.09, 3.14]
2.0 mg/day	45	260	19	272	2.48 [1.49, 4.12]
3.0 mg/day	59	285	19	272	2.96 [1.82, 4.84]



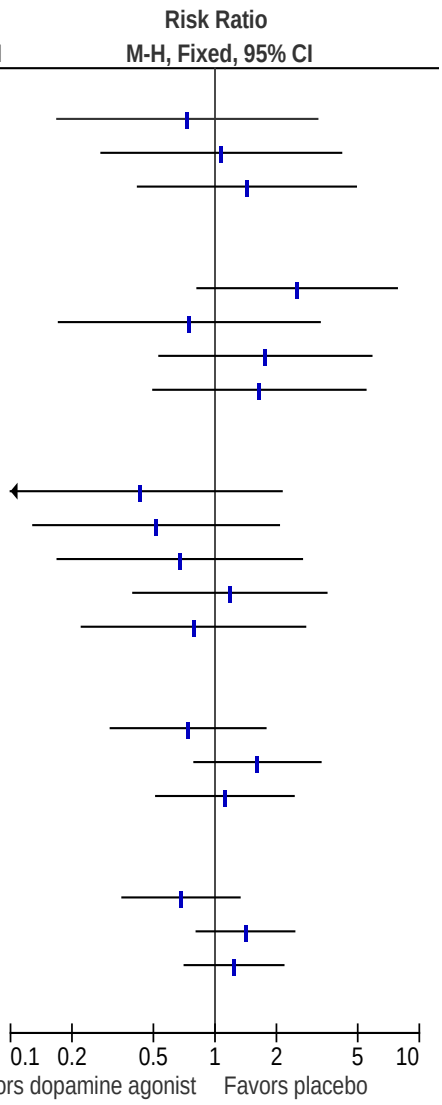
Somnolence

Study or Subgroup	Dopamine agonist Events	Total	Placebo Events	Total	Risk Ratio M-H, Fixed, 95% CI
7.4.1 Pramipexole - Winkelman 2006					
0.25 mg/day	7	88	4	86	1.71 [0.52, 5.63]
0.5 mg/day	15	80	4	86	4.03 [1.40, 11.64]
0.75 mg/day	4	90	4	86	0.96 [0.25, 3.70]
7.4.2 Rotigotine - Hening 2010					
0.5 mg/day	8	99	6	100	1.35 [0.48, 3.74]
1.0 mg/day	10	100	6	100	1.67 [0.63, 4.41]
2.0 mg/day	13	99	6	100	2.19 [0.87, 5.53]
3.0 mg/day	16	106	6	100	2.52 [1.03, 6.17]



Fatigue

Study or Subgroup	Dopamine agonist Events	Total	Placebo Events	Total	Risk Ratio M-H, Fixed, 95% CI
7.3.1 Pramipexole - Winkelman 2006					
0.25 mg/day	3	88	4	86	0.73 [0.17, 3.18]
0.5 mg/day	4	80	4	86	1.07 [0.28, 4.16]
0.75 mg/day	6	90	4	86	1.43 [0.42, 4.90]
7.3.2 Rotigotine - Hening 2010					
0.5 mg/day	10	99	4	100	2.53 [0.82, 7.78]
1.0 mg/day	3	100	4	100	0.75 [0.17, 3.27]
2.0 mg/day	7	99	4	100	1.77 [0.53, 5.85]
3.0 mg/day	7	106	4	100	1.65 [0.50, 5.47]
7.3.3 Rotigotine - Oertel 2008					
0.5 mg/day	2	51	5	55	0.43 [0.09, 2.13]
1.0 mg/day	3	64	5	55	0.52 [0.13, 2.06]
2.0 mg/day	3	49	5	55	0.67 [0.17, 2.67]
3.0 mg/day	7	65	5	55	1.18 [0.40, 3.52]
4.0 mg/day	4	56	5	55	0.79 [0.22, 2.77]
7.3.4 Rotigotine - Trenkwalder 2008					
1.0 mg/day	8	115	11	117	0.74 [0.31, 1.77]
2.0 mg/day	17	112	11	117	1.61 [0.79, 3.29]
3.0 mg/day	12	114	11	117	1.12 [0.52, 2.43]
7.3.5 Combined rotigotine studies					
1.0 mg/day	14	279	20	272	0.68 [0.35, 1.32]
2.0 mg/day	27	260	20	272	1.41 [0.81, 2.45]
3.0 mg/day	26	285	20	272	1.24 [0.71, 2.17]



Appendix F. Table 9a. Self-rated quality of sleep for dopamine agonist trials: Medical Outcomes Scale- Sleep Problems Index II

Study/ Duration (wks)	Treatment/ control	Baseline Score (±SD)*	Mean change from baseline (±SD)*	SMD [95%CI] between placebo
Hening, 2010[5]	Rotigotine (2 mg ** n=95)	NR	-21.5 (20.0)	0.35 [0.07 to 0.57]
(26)	Placebo (n=99)	NR	-14.8 (18.1)	
Oertel, 2010[35]	Rotigotine (n=46)	53.3 (19.9)	-20.5 (21.4)	0.30 [-0.22 to 0.82]
(7)	Placebo (n=21)	49.5 (20.8)	-14.1 (21.0)	
Trenkwalder, 2008[10]	Rotigotine (2 mg ** n=99)	NR	-20.1 (20.5)	0.54 [0.25 to 0.82]
(29)	Placebo (n=99)	NR	-10.0 (16.7)	
Ferini-Strambi, 2008†[7]	Pramipexole(n=178)	NR	-19.5 (19.2)	0.36 [0.15 to 0.57]
(12)	Placebo (n=178)	NR	-12.9 (17.8)	
Kushida, 2008†[8]	Ropinirole (n=174)	NR	-22.4 (23.5)	0.24 [0.04 to 0.45]
(12)	Placebo (n=183)	NR	-16.8 (22.4)	
Bogan, 2006[13]	Ropinirole (n=176)	52.0 (16.6)	-22.8 (18.0)	0.45 [0.24 to 0.66]
(12)	Placebo (n=182)	50.4 (15.6)	-14.6 (18.0)	
Trenkwalder, 2004†[16]	Ropinirole (n=140)	NR	-14.8 (22.0)	0.29 [0.05 to 0.53]
(12)	Placebo (n=130)	NR	-9.0 (18.2)	
Walters, 2004†[17]	Ropinirole (n=123)	NR	-16.5 (20.0)	0.50 [0.25 to 0.75]
(12)	Placebo (n=129)	NR	-7.0 (18.1)	

SD = standard deviation; SMD = standardized mean difference * If provided. ** Fixed-dose study (range 0.5-3mg), 2 mg dose used for analysis. † Data not reported in publication but was obtained from a prior systematic review (Scholz H,Trenkwalder C,Kohnen R,Kriston L, Riemann D,Hornyak M. Dopamine agonists for the treatment of restless legs syndrome. *Cochrane Database of Systematic Reviews* 2011, Issue 3. Art. No.: CD006009. DOI: 10.1002/14651858.CD006009.pub2).

Appendix F. Table 9b. Self-rated quality of daytime sleepiness for dopamine agonist trials: Epworth Sleepiness Scale

Study/ Duration (wks)	Treatment/ control	Baseline Score (±SD)*	Mean change from baseline (±SD)*	Mean difference [95%CI] between control
Bassetti 2011{Bassetti, 2011 #4}	Pramipexole (n=39)	8.2 (4.0)	7.9 (3.4) †	No statistical
(4 x 2)**	Levopdopa/benserazide (n=39)_	8.7 (3.7)	8.2 (3.7) †	significance reported
Winkelman, 2006[15]	Pramipexole (n=253)	7.5 (4.5)	-1.8 (0.2)	P=0.30††
(12)	Placebo (n=85)	8.1 (4.4)	-1.4 (0.4)	
Adler, 2004[12]	Ropinirole (n=22)	NR	6.9 (7.2) ††	-1.2 [-3.7 to 1.2] ‡
(4 x 2)**	Placebo (n=22)	NR	8.1 (6.3) ††	

SD = standard deviation; SMD = standardized mean difference * If provided. ** Crossover trial, two 4 week treatment periods † Scores at end of treatment †† MD not calculated, unclear if mean reduction represents all fixed doses of pramipexole combined.

Appendix F. Table 10a. Self-rated quality of sleep for alpha-2-delta ligands trials: Medical Outcomes Scale- Sleep Problems Index II or Pittsburgh Sleep Quality Index

Study/ Duration (wks)	Treatment/ control	Instrument	Baseline Score (±SD)*	Mean change from baseline (±SD)*	SMD [95%CI] or P-value between placebo
Lee, 2011[18]	Gabapentin enacarbil 600 mg (n=115)	MOS-sleep adequacy	30.5 (24.08)	29.1 (29.91)	0.0003
	Gabapentin enacarbil 1200 mg (n=111)		34.7 (24.86)	27.7 (29.1)	<0.0001
	Placebo (n=96)		34.8 (24.62)	13.6 (24.59)	
Allen, 2011[38] (6)	Pregabalin (300 mg ** n=24)	MOS-SPI-II, 9-item	NR	-22.3 (19.1)	-0.29 [-0.29 to 0.86]
	Placebo (n=23)		NR	-16.8 (18.2)	
Garcia-Borreguero, 2010[22] (12)	Pregabalin (n=30)	MOS-sleep adequacy	NR	NR	NR, P=0.001
	Placebo (n=23)		NR	NR	
Kushida, 2009[23] (12)	Gabapentin enacarbil (XP13515)(n=112)	MOS-sleep adequacy	NR	27.7 (29.9)	0.50 [0.23 to 0.76]
	Placebo (n=108)		NR	13.4 (27.4)	
	Gabapentin enacarbil (XP13515)(n=112)	PSQI	NR	NR	NR, "all PSQ outcomes significantly improved with XP13515 at week 12"
	Placebo (n=108)		NR	NR	
Garcia-Borreguero, 2002[24] (6 x 2) †	Gabapentin (n=22)	PSQI	9.7 (all patients)	6.4 (1.9) ††	P<0.001
	Placebo (n=22)			9.4 (1.9) ††	

Medical Outcomes Scale- Sleep Problems Index II; PSQI = Pittsburgh Sleep Quality Index; SD = standard deviation; SMD = standardized mean difference
* If provided.
** Fixed dose study (range 50-400 mg), 300 mg dose used for analysis.
† Crossover trial, two 6 week treatment periods
†† Scores at end of treatment

Appendix F. Table 10b. Self-rated quality of daytime sleepiness for alpha-2-delta ligands trials: Epworth Sleepiness

Study/ Duration (wks)	Treatment/ control	Baseline Score (±SD)*	Mean change from baseline (±SD)*	SMD [95%CI] between placebo
Kushida, 2009[23] (12)	Gabapentin enacarbil (XP13515)(n=112)	9.8 (4.9)	6.1 (4.1) **	-0.21 [-0.47 to 0.06]
	Placebo (n=108)	9.2 (4.5)	7.0 (4.6) **	

SD = standard deviation; SMD = standardized mean difference
* If provided.
** Scores at end of treatment

Appendix F. Table 11. Self-rated quality of life and of quality sleep for the miscellaneous pharmacologic trials

Study/ Duration (wks)	Treatment/ control	Instrument	Baseline Score (±SD)*	Mean change from baseline (±SD)*	P-value between placebo
Allen, 2011{Allen, 2011 #756}	Iron (ferric carboxymaltose) 1000 mg (n=24)	RLS-QoL	NR	56.5 (49.1)	0.024
	Placebo (n=19)		NR	19.5 (51.7)	
	Iron (ferric carboxymaltose) 1000 mg (n=24)	MOS total	NR	75.8 (79.0)	0.094
	Placebo (n=19)		NR	35.1 (75.2)	

Medical Outcomes Sleep Scale; SD = standard deviation; SMD = standardized mean difference.

Appendix F. Table 12. Self-rated quality of sleep for the non-pharmacologic trials

Study/ Duration (wks)	Treatment/ control	Instrument	Baseline Score (±SD)*	Mean change from baseline (±SD)*	P-value between placebo
Cuellar, 2009[32] (8)	Valerian (n = 17)	PSQ	14.4 (3.7)	4.5 (5.3)	0.94
	Placebo (n = 20)		12.4 (5.0)	4.4 (4.8)	
Cuellar, 2009[32] (8)	Valerian (n = 17)	ESS	11.7 (5.4)	3.4 (4.4)	0.64
	Placebo (n = 20)		10.4 (6.1)	2.8 (3.7)	
Lettieri, 2009[33] (4)	Compression device (n = 21)	ESS	11.2 (4.4)	6.5 (4.0)	0.04
	Sham device (n = 14)		11.3 (3.9)	10.6 (3.8)	

ESS = Epworth Sleepiness Scale; PSQ = Pittsburgh Sleep Quality Index; SD = standard deviation.

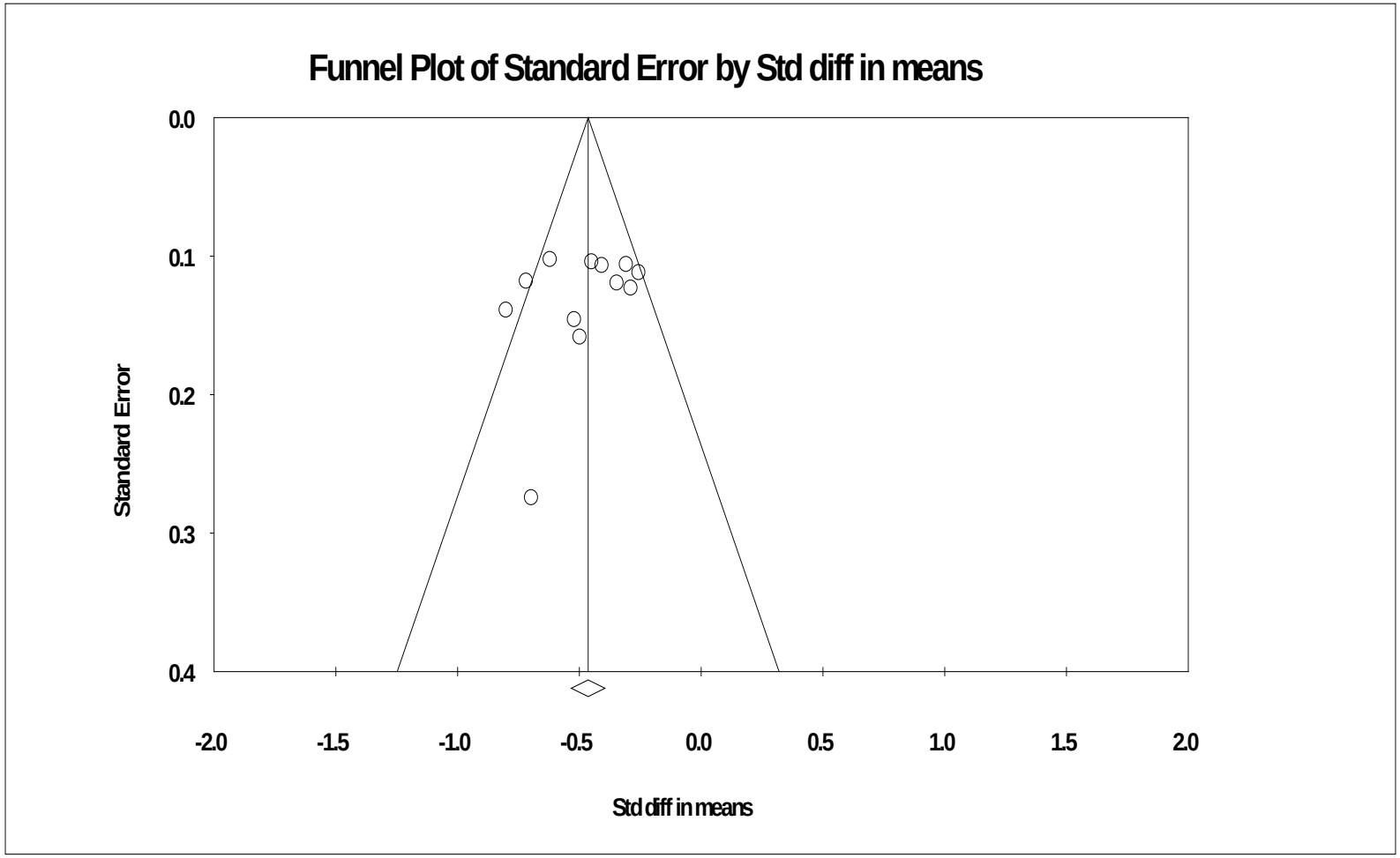
Appendix F. Table 13. Self-rated quality of life and of sleep for iron trials

Study/ Duration (wks)	Treatment/ control	Instrument	Baseline Score	Mean change from baseline	P-value between placebo
Grote, 2009[30] (52)	Intravenous iron 200 mg x 5 occasions (1000 mg) (n=29)	ESS	Median 9.0 (2-18)	NR	NR "no statistical difference between treatment groups at any point of the study"
	Placebo (n=31)		Median 9.5 (1-18)	NR	
Wang, 2009[31] (12)	Oral iron 650 mg daily (n=11)	Overall Quality of life		Improved 7 (64%)	P=0.07
	Placebo (n=7)			Improved 1 (14%)	

ESS = Epworth Sleepiness Scale. SD = standard deviation

* Proportion of participants reporting "Improved" versus "stayed the same or worsened."

Appendix F. Figure 8. Funnel plot for Mean change in IRLS total score from baseline



Appendix F. Table 14. Patient global impressions responders (PGI) at end of treatment for dopamine agonist studies

Study, year	Duration (weeks)	Drug and daily dosage / control	Positive response % (n/N)	Risk ratio [95% CI]
Högl, 2011[3]	26	Pramipexole 0.125-0.75 mg Placebo	62.3 (101/162) 44.0 (70/159)	1.42 [1.15 to 1.75]
Montagna, 2011[4]	12	Pramipexole 0.125-0.75 mg Placebo	62.9 (112/178) 38.0 (68/179)	1.66 [1.33 to 2.06]
Ferini-Strambi, 2008[7]	12	Pramipexole 0.125-0.75 mg Placebo	62.9 (112/178) 38.0 (68/179)	1.66 [1.33 to 2.06]
Oertel, 2007[11]	6	Pramipexole 0.125-0.75 mg Placebo	61.6 (138/224) 31.6 (36/114)	1.95 [1.46 to 2.61]
Winkelman, 2006[15]	12	Pramipexole 0.125-0.75 mg Placebo	42.5 (108/224) 14.1 (12/85)	3.01 [1.75 to 5.19]
Kushida, 2008[8]	12	Ropinirole 0.5-6 mg Placebo	78.2 (136/174) 51.4 (94/183)	1.52 [1.29 to 1.79]

CI = confidence intervals

Appendix F. Table 15. Clinical global impressions (CGI) responders (much-very much improved) at end of treatment for the dopamine agonist studies

Study, year	Duration (weeks)	Drug and daily dosage / control	Positive response % (n/N)	Risk ratio [95% CI]
Ferini-Strambi, 2008[7]	12	Pramipexole 0.125-0.75 mg	66.3 (118/178)	1.65 [1.34 to 2.03]
		Placebo	40.2 (72/179)	
Högl, 2011[3]	26	Pramipexole 0.125-0.75 mg	68.5 (111/162)	1.36 [1.13 to 1.64]
		Placebo	50.3 (80/159)	
Montagna, 2011[4]	12	Pramipexole 0.125-0.75 mg	69.3 (140/202)	1.88 [1.53 to 2.30]
		Placebo	36.9 (72/195)	
Oertel, 2007[11]	6	Pramipexole 0.125-0.75 mg	62.9 (141/224)	1.94 [1.46 to 2.57]
		Placebo	32.5 (37/114)	
Winkelman, 2006[15]	12	Pramipexole 0.125-0.75 mg	72.0 (180/250)	1.41 [1.13 to 1.76]
		Placebo	51.2 (43/84)	
Benes, 2011[2]	12	Ropinirole 0.25-4 mg	64.3 (110/171)	1.38 [1.03 to 1.85]
		Placebo	46.7 (28/60)	
Bogan, 2006[13]	12	Ropinirole 0.25-4 mg	73.3 (137/187)	1.30 [1.12 to 1.51]
		Placebo	56.5 (109/193)	
Kushida, 2008[8]	12	Ropinirole 0.5-6 mg	70.9 (124/175)	1.42 [1.19 to 1.68]
		Placebo	50.0 (92/184)	
Montplaisir, 2006[14]-	12	Ropinirole 2.05 mg (mean)	68.9 (31/45)	1.48 [1.02 to 2.13]
		Placebo	46.7 (21/45)	
Trenkwalder, 2004[16]	12	Ropinirole 0.25-4 mg	53.4 (78/146)	1.31 [1.02 to 1.68]
		Placebo	40.9 (56/137)	
Walters, 2004[17]	12	Ropinirole 0.25-4 mg	59.5 (78/131)	1.51 [1.17 to 1.94]
		Placebo	39.6 (53/134)	
Hening, 2010[5]	26	Rotigotine 1,2,3 mg	69.5 (264/380)	1.26 [1.05 to 1.52]
		Placebo	57.1 (56/98)	
Oertel, 2010[35]	7	Rotigotine 1-3 mg	84.1 (37/44)	1.40 [0.96 to 2.05]
		Placebo	60.0 (12/20)	
Oertel, 2008[9]	6	Rotigotine 1,2,3 mg	75.7 (134/177)	1.38 [1.07 to 1.79]

		Placebo	54.7 (29/53)	
Trenkwalder, 2008[10]	29	Rotigotine 1-3 mg	69.4 (213/307)	1.52 [1.22 to 1.91]
		Placebo	45.5 (46/101)	

Appendix G. Withdrawals and Adverse Events Tables

Appendix G. Table 1. Withdrawals and adverse effects for the dopamine agonist trials Part A

Study	Any study withdrawals n/N (%)		Withdrawals due to adverse effects n/N (%)		Patients with ≥ 1 adverse event n/N (%)		Patients with ≥ 1 severe adverse effects n/N (%)		Patients with ≥ 1 serious adverse effects n/N (%)	
	Treatment	Placebo	Treatment	Placebo	Treatment	Placebo	Treatment	Placebo	Treatment	Placebo
Pramipexole										
Bassetti 2011[1]	28/67* (41.8)				38/67 (56.7)	39/67** (58.2)				
Ferini-Stamb, 2008[7]	27/182 (14.8)	52/187 (27.8)	17/182 (9.3)	16/187 (8.6)	106/182 (58.2)	86/187 (46.0)	47/182 (25.8)	49/187 (26.2)		
Högl, 2011[3]	35/166 (21.1)	60/163 (36.8)	19/166 (11.4)	23/163 (14.1)	120/166 (72.3)	106/163 (65.0)	17/166 (10.2)	15/163 (9.2)	8/166 (4.8)	3/163 (1.8)
Montagna, 2011[4]	26/203 (12.8)	41/201 (20.4)	9/203 (4.4)	11/201 (5.5)	124/203 (61.1)	103/200 (51.5)	8/203 (3.9)	6/200 (3.0)		
Oertel, 2007[11]	12/230 (5.2)	8/115 (7.0)	6/230 (2.6)	5/115 (4.3)	150/230 (65.2)	55/115 (47.8)	8/230 (3.5)	9/115 (7.8)	0/230 (0)	2/115 (1.7)
Winkelman, 2006[15]	53/259 (20.5)	11/86 (12.8)	32/258 (12.4)	6/86 (7.0)	209/258 (81.0)	69/86 (80.2)	45/258 (17.4)	11/86 (12.8)		
Ropinirole										
Adler, 2004[12]	2/22 (9.1)	1/22 (4.5)	1/22 (4.5)	1/22 (4.5)						
Benes, 2011[2]	54/199 (27.1)	29/67 (43.3)	31/199 (15.6)	6/67 (9.0)	123/199 (61.8)	26/67 (38.8)	37/197 (18.8)	3/67 (4.5)	6/197 (3.0)	0/67 (0)
Bogan, 2006[13]	23/187 (12.3)	26/194 (13.4)	7/187 (3.7)	9/194 (4.6)	155/187 (82.9)	129/193 (66.8)	33/187 (17.6)	20/193 (10.4)	0/187 (0)	1/193 (0.5)
Kushida, 2008[8]	25/176 (14.2)	27/186 (14.5)	8/176 (4.5)	6/186 (3.2)	138/176 (78.4)	119/186 (64.0)			2/176 (1.1)	3/186 (1.6)
Montplaisir, 2006[14]	15/45 (33.3)	28/47 (59.6)	1/45 (2.2)	0/47 (0)	26/45 (57.8)	24/47 (51.1)	6/45 (13.3)	6/47 (12.8)	0/45 (0)	2/47 (4.3)
Trenkwalder, 2004[16]	35/147 (23.8)	30/139 (21.6)	16/147 (10.9)	6/139 (4.3)	120/146 (82.2)	103/138 (74.6)	34/146 (23.3)	21/138 (15.2)	3/146 (2.1)	4/138 (2.9)
Walters, 2004[17]	29/131 (22.1)	29/136 (21.3)	11/131 (8.4)	9/136 (6.6)	112/131 (85.5)	102/136 (75.0)	32/131 (24.4)	24/136 (17.6)	2/131 (1.5)	5/136 (3.7)
Rotigotine										
Hening, 2010[5]	152/404 (37.6)	33/100 (33.0)	82/404 (20.3)	4/100 (4.0)	355/404 (87.9)	84/100 (84.0)	79/404 (19.6)	12/100 (12.0)	17/404 (4.2)	4/100 (4.0)
Oertel, 2010[35]	5/46 (10.9)	1/21 (4.8)	2/46 (4.3)	1/21 (4.8)	34/46 (73.9)	12/21 (57.1)	1/46 (2.2)	1/21 (4.8)		
Oertel, 2008[9]	23/286 (8.0)	8/55 (14.5)	13/286 (4.5)	2/55 (3.6)	177/285 (62.1)	25/55 (45.5)			4/285 (1.4)	1/55 (1.8)

Trenkwalder, 2008[10]	96/341 (28.2)	49/117 (41.9)	54/341 (15.8)	8/117 (6.8)	265/341 (77.7)	64/117 (54.7)	50/341 (14.7)	9/117 (7.7)	25/341 (7.3)	5/117 (4.3)

* All subjects, crossover trial

**Versus levodopa/benserazide

Appendix G. Table 2 Adverse effects for the dopamine agonist trials Part B

Study	Fatigue n/N (%)		Nausea n/N (%)		Vomiting n/N (%)		Headache n/N (%)		Somnolence n/N (%)	
	Treatment	Placebo	Treatment	Placebo	Treatment	Placebo	Treatment	Placebo	Treatment	Placebo
Pramipexole										
Bassetti 2011[1]			31%*	17%*	8%*	3%*	17%*	11%*		
Ferini-Stamb, 2008[7]	16/182 (8.8)	4/187 (2.1)	32/182 (17.6)	11/187 (5.9)			27/182 (14.8)	24/187 (12.8)		
Högl, 2011[3]	18/166 (10.8)	15/163 (9.2)	24/166 (14.5)	6/163 (3.7)			13/166 (7.8)	17/163 (10.4)	11/166 (6.6)	8/163 (4.9)
Montagna, 2011[4]	16/203 (7.9)	8/200 (4.0)	28/203 (13.8)	13/200 (6.5)			21/203 (10.3)	19/200 (9.5)		
Oertel, 2007[11]	21/230 (9.1)	7/115 (6.1)	28/230 (12.2)	7/115 (6.1)			30/230 (13.0)	11/115 (9.6)		
Winkelman, 2006[15]	13/258 (5.0)	4/86 (4.7)	49/258 (19.0)	4/86 (4.7)			46/258 (17.8)	15/86 (17.4)	26/258 (10.1)	4/86 (4.7)
Ropinirole										
Adler, 2004[12]			6/22 (27.3)	1/22 (4.5)	3/22 (13.6)	0/22 (0)	2/22 (9.1)	2/22 (9.1)	3/22 (13.6)	0/22 (0)
Benes, 2011[2]	25/197 (12.7)	4/67 (6.0)	64/197 (32.5)	5/67 (7.5)	14/197 (7.1)	0/67 (0)	38/197 (19.8)	9/67 (13.4)		
Bogan, 2006[13]			80/187 (42.8)	15/193 (7.8)	16/187 (8.6)	3/193 (1.6)	31/187 (16.6)	36/193 (18.7)	24/187 (12.8)	13/193 (6.7)
Kushida, 2008[8]			59/176 (33.5)	28/186 (15.1)	18/176 (10.2)	6/186 (3.2)	42/176 (23.9)	33/186 (17.7)	34/176 (19.3)	11/186 (5.9)
Montplaisir, 2006[14]	38/202** (18.8)		8/45 (17.8); 101/202** (50.0)	1/47 (2.1)	31/202* (15.3)		5/45 (11.1); 44/202** (21.8)	3/47 (6.4)		
Trenkwalder, 2004[16]			55/146 (37.7)	9/138 (6.5)	19/146 (13.0)	2/138 (1.4)	29/146 (19.9)	23/138 (16.7)	18/146 (12.3)	10/138 (7.2)
Walters, 2004[17]	80/131 (61.1)	9/136 (6.6)	52/131 (39.7)	11/136 (8.1)	16/131 (12.2)	3/136 (2.2)	29/131 (22.1)	35/136 (25.7)		
Rotigotine										
Hening, 2010[5]	27/404 (6.7)	4/100 (4.0)	73/404 (18.1)	10/100 (10.0)			47/404 (11.6)	8/100 (8.0)	47/404 (11.6)	6/100 (6.0)
Oertel, 2010[35]			10/46 (21.7)	1/21 (4.8)			8/46 (17.4)	3/21 (14.3)	5/46 (10.9)	2/21 (9.5)
Oertel, 2008[9]	19/285 (6.7)	5/55 (9.1)	41/285 (14.4)	5/55 (9.1)	11/285 (3.9)	1/55 (1.8)	22/285 (7.7)	4/55 (7.3)		
Trenkwalder, 2008[10]	37/341 (10.9)	11/117 (9.4)	55/341 (16.1)	4/117 (3.4)			43/341 (12.6)	8/117 (6.8)		

*Crossover trial versus levodopa/benserazide, numbers unclear; **Single-blind phase, all subjects received ropinirole.

Appendix G. Table 3 Specific adverse effects for the dopamine agonist trials Part C

Study	Application site reactions n/N (%)		Dizziness n/N (%)		Augmentation n/N (%)		Augmentation leading to study withdrawal n/N (%)		Withdrawal due to insufficient effect n/N (%)	
	Treatment	Placebo	Treatment	Placebo	Treatment	Placebo	Treatment	Placebo	Treatment	Placebo
Pramipexole										
Bassetti, 2011[1]			13%*	17%*	5 events*	15 events*				
Ferini-Stamb, 2008[7]									5/182 (2.7)	33/187 (17.6)
Högl, 2011[3]					18/152** (11.8)	14/149** (9.4)				
Montagna, 2011[4]									7/203 (3.4)	20/201 (10.0)
Oertel, 2007[11]			8/230 (3.5)	4/115 (3.5)						
Winkelman, 2006[15]			25/258 (9.7)	6/86 (7.0)			1/259† (0.4)	1/86† (1.2)		
Ropinirole										
Adler, 2004[12]			5/22 (22.7)	0/22 (0)					1/22 (4.5)	0/22 (0)
Benes, 2011[2]			17/197 (8.6)	2/67 (3.0)						
Bogan, 2006[13]			18/187 (9.6)	11/193 (5.7)	3/187 (1.6)	1/193 (0.5)			2/187 (1.1)	5/193 (2.6)
Kushida, 2008[8]										
Montplaisir, 2006[14]			36/202†† (17.8)						12/45 (26.7)	20/47 (42.6)
Trenkwalder, 2004[16]									4/147 (2.7)	11/139 (7.9)
Walters, 2004[17]			20/131 (15.3)	6/136 (4.4)					2/131 (1.5)	6/136 (4.4)
Rotigotine										
Hening, 2010[5]	109/404 (27.0)	5/100 (5.0)	21/404 (5.2)	6/100 (6.0)					19/405 (4.7)	8/100 (8.0)
Oertel, 2010[35]	8/46 (17.4)	1/21 (4.8)							1/46 (2.2)	0/21 (0)
Oertel, 2008[9]	50/285 (17.5)	1/55 (1.8)	12/285 (4.2)	4/55 (7.3)					3/286 (1.0)	2/55 (3.6)
Trenkwalder, 2008[10]	145/341 (42.5)	2/117 (1.7)	18/341 (5.3)	3/117 (2.6)	ASRS§	0.30 (0.44)‡			22/341 (6.5)	37/117 (31.6)

*Crossover trial versus levodopa/benserazide, numbers unclear. ** Classified as augmentation cases. Among the 18 pramipexole cases, 14 augmentation and 4 insufficient data for definitive conformation. Among 14 placebo cases, 9 confirmed augmentation; 5 insufficient data for definitive conformation. † Defined as "worsened RLS." †† Single-blind phase, all subjects received ropinirole. §ASRS=Augmentation Severity Rating Scale. 1mg=0·31 (0·46), 2mg=0·24 (0·41), 3mg=0·25 (0·42)‡. ‡Mean (SD).

Appendix G. Table 4 Withdrawals and adverse effects for the alpha-2-delta ligands trials Part A

Study	Any study withdrawals n/N (%)		Withdrawals due to adverse effects n/N (%)		Patients with ≥ 1 adverse event n/N (%)		Patients with ≥ 1 severe adverse effects n/N (%)		Patients with ≥ 1 serious adverse effects n/N (%)	
	Treatment	**Placebo**	**Treatment**	**Placebo**	**Treatment**	**Placebo**	**Treatment**	**Placebo**	**Treatment**	**Placebo**
Gabapentin enacarbil										
Lee, 2011[18]	26/228 (11.4)	20/97 (20.6)	15/228 (6.6)	6/97 (6.2)					2/226 (0.9)	1/96 (1.0)
Winkelman 2011[19]*	22 of 136 patients (16.2%) did complete trial (both phases, GEn=8, placebo=11, and 3 during the washout period)		8 of 136 patients (5.9%) (both phases)		86/127 (67.7)	70/132 (53.0)				
Bogan, 2010[21]**	12/96 (12.5)	14/98 (14.3)	0/96 (0)	3/98 (3.1)	49/96 (51.0)	45/98 (45.9)	2/96 (2.1)	5/98 (5.1)	1/96 (1.0)	2/98 (2.0)
Kushida, 2009[23]	14/114 (12.3)	16/108 (14.8)	10/114 (8.8)	3/108 (2.8)	93/113 (82.3)	80/108 (74.1)				
Gabapentin										
Garcia-Borreguero, 2002[24]*	All patients** 3/24 (12.5), 1 during GABA phase and 2 during placebo phase		All patients** 1/24 (4.2) during placebo phase							
Pregabalin										
Allen, 2010[20]	14/114 (12.3)	2/23 (8.7)	10/114 (8.8)	1/23 (4.3)	73/114 (64.0)	13/23 (56.5)	11 patients total†		1/114 (<1)	0/23
Garcia-Borreguero, 2010[22]	6/30 (20.0)	9/28 (32.1)	4/30 (13.3)	0/28	25/30 (83.3)	9/28 (32.1)				

* Crossover trial; ** Double-blind phase. All subjects had active treatment in a 24-week single-blind phase and were then randomized to either gabapentin enacarbil or placebo; † Not broken down by treatment arm;

Appendix G. Table 5 Adverse effects for the alpha-2-delta ligands trials Part B

Study	Somnolence n/N (%)		Dizziness n/N (%)		Dry mouth n/N (%)		Headache n/N (%)		Fatigue n/N (%)	
	Treatment	Placebo	Treatment	Placebo	Treatment	Placebo	Treatment	Placebo	Treatment	Placebo
Gabapentin enacarbil										
Lee, 2011[18]	45/226 (19.9)	2/96 (2.1)	39/226 (17.3)	5/96 (5.2)	14/226 (6.2)	2/96 (2.1)	32/226 (14.1)	8/96 (8.3)	9/226 (4.0)	5/96 (5.2)
Winkelman 2011[19]*	16/127 (12.6)	2/132 (1.5)	26/127 (20.5)	3/132 (2.3)	6/127 (4.7)	5/132 (3.8)	11/127 (8.7)	9/132 (6.8)		
Bogan, 2010[21]**	3/96 (3.1) 97/326 (29.8) during single-blind phase	1/98 (1.0)	2/96 (2.1) 72/326 (22.1) during single-blind phase	1/98 (1.0)			4/96 (4.2) 41/326 (12.6) during single-blind phase	2/98 (2.0)		
Kushida, †2009[23]	Moderate 19/113 (16.8) Severe 0/113	Moderate 0/108 Severe 0/108	Moderate 11/113 (9.7) Severe 0/113	Moderate 1/108 (0.9) Severe 1/108 (0.9)			Moderate 8/113 (7.1) Severe 0/113	Moderate 4/108 (3.7) Severe 0/108	Moderate 5/113 (4.4) Severe 1/113 (0.9)	Moderate 0/108 Severe 0/108
Gabapentin										
Garcia-Borreguero,* 2002[24]	2/23 (8.7)	0/24			1/23 (4.3)	0/24	0/23	1/24 (4.2)	*Malaise* 6/23 (26.1)	*Malaise* 2/24 (8.3)
Pregabalin										
Allen, 2010[20]	18/114 (15.8)	1/23 (4.3)	16/114 (14.0)	1/23 (4.3)	6/114 (5.3)	0/23	15/114 (13.2)	3/23 (13.0)	9/114 (7.9)	0/23
Garcia-Borreguero, 2010[22]	13/30 (43.3)	4/28 (14.3)	*Unsteadiness* 15/30 (50.0)	*Unsteadiness* 3/28 (10.7)	3/30 (10.0)	0/28	4/30 (13.3)	1/28 (3.6)		

* Crossover trial; ** Double-blind phase. All subjects had active treatment in a 24-week single-blind phase and were then randomized to either gabapentin enacarbil or placebo; † Mild effects not reported here

Appendix G. Table 6a Specific adverse effects for the alpha-2-delta ligands trials Part C

Study	Vision effects n/N (%)		Nausea n/N (%)		Augmentation/other n/N (%)	
	Treatment	Placebo	Treatment	Placebo	Treatment	Placebo
Lee, 2011[18] (gabapentin enacarbil)			12/226 (5.3)	4/96 (4.2)	Sudden onset of sleep (daytime) 1 subject	
Winkelman 2011[19]* (gabapentin enacarbil)			6/127 (4.7)	5/132 (3.8)		
Allen, 2010[20] (pregabalin)						
Bogan, 2010[21]** (gabapentin enacarbil)			3/96 (3.1) 21/326 (6.4) during single-blind phase	2/98 (2.0)		
Garcia-Borreguero, 2010[22] (pregabalin)	*Blurred vision* 3/30 (10.0)	*Blurred vision* 0/28	1/30 (3.3)	0/28	0/30	0/28
Kushida, 2009[23] (gabapentin enacarbil)	*Dry eye* Moderate 1/113 (0.9)	*Dry eye* Moderate 0/108	Moderate 4/113 (3.5) Severe 0/113	Moderate 2/108 (1.9) Severe 0/108		
Garcia-Borreguero, 2002*[24](gabapentin)	*Dry eye* 0/23	*Dry eye* 1/24 (4.2)	0/23	1/24 (4.2)	All patients 0/24	

*Crossover study; ** Double-blind phase. All subjects had active treatment in a 24-week single-blind phase and were then randomized to either gabapentin enacarbil or placebo; **

Appendix G. Table 7. Withdrawals and adverse effects for the dopamine agonist versus levopdopa Part A

Study	Any study withdrawals n/N (%)		Withdrawals due to adverse effects n/N (%)		Patients with ≥ 1 adverse event n/N (%)		Patients with ≥ 1 severe adverse effects n/N (%)		Patients with ≥ 1serious adverse effects n/N (%)	
	Treatment	Control	Treatment	Control	Treatment	Control	Treatment	Control	Treatment	Control
Trenkwalder 2007[27]	74/178 (41.6)	83/183 (45.4)	47/178 (26.4)	47/183 (25.7)	148/178 (83.1)	142/183 (77.6)			12/178 (6.7)	9/183 (4.9)

Appendix G. Table 8. Adverse effects for the dopamine agonist trials Part B

Study	Fatigue n/N (%)		Nausea n/N (%)		Vomiting n/N (%)		Headache n/N (%)		Somnolence n/N (%)	
	Treatment	Control	Treatment	Control	Treatment	Control	Treatment	Control	Treatment	Control
Trenkwalder, 2007[27]	22/178 (12.4)	8/183 (4.4)	55/178 (30.9)	19/183 (10.4)			24/178 (13.5)	17/183 (9.3)	19/178 (10.7)	7/183 (3.8)

Appendix G. Table 9 Specific adverse effects for the dopamine agonist versus levodopa Part C

Study	Application site reactions n/N (%)		Dizziness n/N (%)		Augmentation n/N (%)		Augmentation leading to study withdrawal n/N (%)		Withdrawal due to insufficient effect n/N (%)	
	Treatment	Control	Treatment	Treatment	Treatment	Control	Treatment	Control	Treatment	Control
Trenkwalder, 2007[27]			11/178 (6.2)	5/183 (2.7)	11/178 (6.2)	32/183 (17.5)	7/178 (3.9)	18/183 (9.8)	14/178 (7.9)	26/183 (14.2)

Appendix G. Table 10. Withdrawals and adverse effects for the iron trials (secondary RLS)

Study	Any study withdrawals n/N (%)		Withdrawals due to adverse effects n/N (%)		Withdrawals due to lack of efficacy n/N (%)		Patients with ≥ 1 adverse event n/N (%)		Adverse effects n/N (%)	
	Treatment	Placebo	Treatment	Placebo	Treatment	Placebo	Treatment	Placebo	Treatment	Placebo
Grote, 2009[30]	9/29 (31.0)	21/31 (67.7)	3/29 (10.3)	1/31 (3.2)	5/29 (17.2)	19/31 (61.3)	11/29 (37.9)	11/31 (35.5)	headache 4 effects* injection site rxn 1/29 (2.4)	headache 5 effects* injection site rxn 1/31 (3.2)
Wang, 2009[31]	0/11	0/7	0/11	0/7	0/11	0/7	NR	NR	NR	NR

* Not reported for unique patients

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