

Pharmacologic Therapy for Primary Restless Legs Syndrome

A Systematic Review and Meta-analysis

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Importance: Restless legs syndrome (RLS) is a neurological disorder characterized by unpleasant sensations in the legs and a distressing, irresistible urge to move them. We conducted a systematic review to evaluate efficacy, safety, and comparative effectiveness of pharmacologic treatments for primary RLS.

Evidence Acquisition: We included randomized controlled trials (RCTs), published in English, reporting efficacy outcomes and harms of pharmacologic treatments for primary RLS of at least 4 weeks' duration. MEDLINE and other databases were searched through June 2012. Reviewers extracted outcomes and adverse events and rated the strength of evidence.

Results: We identified 29 eligible RCTs. We found high-strength evidence that the proportion of patients who had a clinically important response (International Restless Legs Syndrome [IRLS] responders), defined as a 50% or greater reduction from baseline in mean IRLS symptom scale scores, was greater with dopamine agonist therapy compared with placebo (61% vs 41%) (risk ratio, 1.60 [95% CI, 1.38-1.86]; 7 trials). Dopamine agonists also im-

proved patient-reported sleep scale scores and quality-of-life measures. High-strength evidence demonstrated that calcium channel alpha-2-delta ligands increased the proportion of IRLS responders compared with placebo (61% vs 37%) (risk ratio, 1.66 [95% CI, 1.33-2.09]; 3 trials). Adverse events associated with dopamine agonists included nausea, vomiting, and somnolence. Alpha-2-delta ligands adverse events included somnolence and unsteadiness or dizziness.

Conclusions and Relevance: On the basis of short-term RCTs that enrolled highly selected populations with long-term high-moderate to very severe symptoms, dopamine agonists and calcium channel alpha-2-delta ligands reduced RLS symptoms and improved sleep outcomes and disease-specific quality of life. Adverse effects and treatment withdrawals due to adverse effects were common.

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RESTLESS LEGS SYNDROME (RLS) is characterized by unpleasant sensations in the legs and a distressing, irresistible urge to move them. The etiology of primary RLS is unknown. The disorder also occurs secondary to other conditions such as iron deficiency, end-stage renal disease, and pregnancy.¹ A family history of RLS is common,¹ but genome-wide association studies have produced inconsistent findings.² Restless leg syndrome can result in reduced quality of life (QoL) and have a negative impact on sleep, leading to daytime fatigue. Effective treatment options are not well established, and scant evidence exists to guide treatment selection.

Diagnostic criteria for RLS were established by the International Restless Legs Syndrome (IRLS) Study Group in 1995³ and revised in 2003.¹ The criteria include the following: (1) an urge to move the legs, usually accompanied by uncomfortable or unpleasant sensations in the legs; (2) unpleasant sensations or urge to move that begin or worsen during periods of rest or inactivity such as lying or sitting; (3) unpleasant sensations or urge to move that are partly or totally relieved by movement such as walking, bending, and stretching, at least as long as the activity continues; and (4) unpleasant sensations or urge to move that are worse in the evening or at night than during the day or only occur in the evening or night.

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Restless leg syndrome varies in symptom severity and frequency. Mild RLS may cause minor annoyance, but severe RLS can negatively affect work, social activities, function, and emotional well-being. Sleep disruption induced by RLS may lead to poor daytime functioning, anxiety, and depression. Sleep deprivation and daytime fatigue are common reasons patients with RLS seek treatment.⁴ Prevalence estimates for bothersome RLS in the United States range from 1.5% to 7.4% in adults.^{1,5} The variation reflects different approaches to diagnosing RLS and defining its presence and severity and the fact that many RLS questionnaires do not account for individuals who have other conditions with similar symptoms.

Pharmacologic treatment is generally reserved for patients whose symptoms are frequent (several times per week) and cause moderate to very severe discomfort and bother. Three dopamine agonists (pramipexole, ropinirole, and rotigotine) and 1 calcium channel alpha-2-delta ligand (gabapentin enacarbil) are currently approved by the Food and Drug Administration (FDA) for treatment of moderate to severe RLS.

We conducted a systematic review to evaluate the effectiveness and harms of pharmacologic treatments for patients with primary RLS. This report is based on research conducted by the Minnesota Evidence-based Practice Center under contract to the Agency for Healthcare Research and Quality (AHRQ) and is available on the AHRQ web site.⁶

METHODS

STUDY SELECTION

We included randomized controlled trials (RCTs) that enrolled individuals with primary RLS as defined by the IRLS Study Group.^{1,3} Eligible trials were published in English, evaluated pharmacologic interventions for RLS vs placebo or active intervention, lasted at least 4 weeks, and reported validated RLS symptom or QoL scale scores, clinician and patient global impact scale scores, or measures of sleep quality. We limited interventions to drugs approved for use for any condition in the United States.

INFORMATION SOURCES

We searched the bibliographic databases MEDLINE, EMBASE, and Natural Standards through June 2012 for RCTs evaluating treatment efficacy and reported adverse effects (eAppendix 1; <http://www.jamainternalmed.com>). To identify completed trials and to reduce publication bias, we searched Cochrane Central, the International Controlled Trials Registry Platform (ICTRP), Clinicaltrials.gov, FDA websites, and the National Institutes of Health (NIH) RePORTer. We included eligible unidentified trials referred by peer reviewers.

DATA EXTRACTION AND QUALITY ASSESSMENT

Data from included studies were abstracted into evidence tables by 1 reviewer (R.M.) and validated by a second reviewer (T.J.W.). Our primary outcome was IRLS responders defined as patients with a 50% or greater reduction in IRLS scale score from baseline. We also assessed the 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 impression (CGI) or patient-assessed global impression scales; RLS QoL; patient-reported sleep quality; number of individuals experiencing adverse effects; dropouts; dropouts due to adverse effects; treatment discontinuation because of adverse effects; specific adverse effects; and augmentation.

We used criteria developed by the Cochrane Collaboration⁷ in rating individual RCTs as good, fair, or poor quality based on the adequacy of allocation concealment, blinding, reporting of reasons for attrition, and how analyses accounted for incomplete data (eAppendices 2-4). Using methods developed by AHRQ and the Effective Health Care Program,⁸ we evaluated overall strength of evidence for outcomes for each treatment comparison based on the criteria of risk of bias, consistency, directness, and precision. We resolved discrepancies in quality and strength of evidence ratings by discussion and consensus.

DATA SYNTHESIS AND ANALYSIS

For trials that included similar populations, interventions, and outcomes and that presented sufficient data, we calculated pooled random-effects esti-

mates of overall risk ratios (RRs), weighted mean differences (WMDs), or standardized mean differences (SMDs) and the corresponding 95% confidence intervals. Data were pooled and analyzed in Review Manager statistical software (RevMan version 5.1; The Nordic Cochrane Centre, The Cochrane Collaboration). 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% and effect sizes that did not fall on the same side of “no effect” suggested substantial heterogeneity. Number needed to treat (NNT) and number needed to harm (NNH) were calculated for dichotomous outcomes. For the fixed-dose trials, we analyzed only doses recommended for current clinical practice if possible. We examined funnel plots and performed Egger intercept tests⁹ to detect publication bias.

RESULTS

Our literature search for RCTs of pharmacologic treatments of primary RLS yielded 29 references meeting our inclusion criteria, shown in **Figure 1**.

DOPAMINE AGONIST THERAPY

Efficacy of dopamine agonists was evaluated in 18 randomized, double-blind, placebo-controlled studies¹⁰⁻²⁷ and 2 comparative effectiveness studies.^{28,29} Two placebo-controlled studies^{26,27} and 1 comparative effectiveness trial²⁹ assessed cabergoline (an ergot-derived dopamine agonist). Cabergoline is not FDA approved for RLS treatment and is rarely used in the United States owing in part to FDA warnings about cardiac valvular complications. For this reason, we did not include 2 cabergoline placebo-controlled studies^{26,27} with the other dopaminergic trials. We describe findings of the single comparative effectiveness trial of cabergoline vs levodopa because it is one of two comparative effectiveness studies identified²⁹; the other was a crossover trial comparing pramipexole to dual-release levodopa-benserazide.²⁸ Sixteen placebo-controlled dopamine agonists (n=4861) were included, 5 evalu-

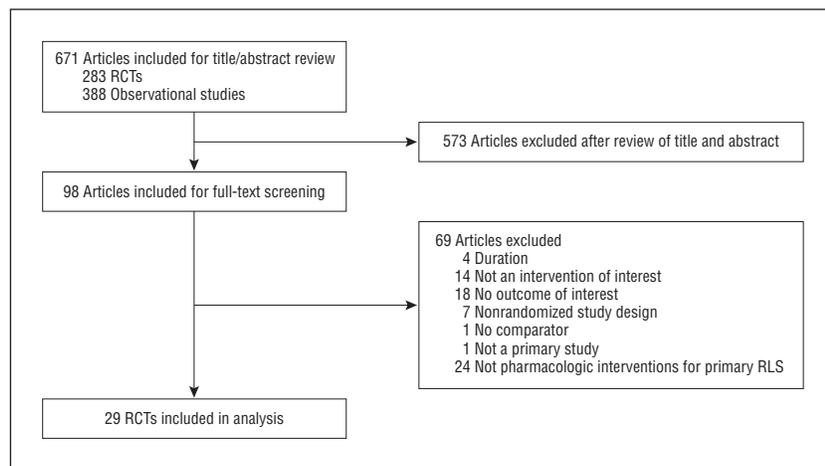


Figure 1. Study flow diagram. RCTs indicates randomized controlled trials; RLS, restless leg syndrome.

ated pramipexole¹⁰⁻¹⁴; 7, ropinirole¹⁵⁻²¹; and 4, rotigotine²²⁻²⁵ (**Table 1** and eTable 1). Only 2 trials lasted 24 weeks or more,^{22,24} and none exceeded 28 weeks. The overall mean age of participants was 55 years, and 65% were women. Nearly all (96%) participants in the 7 trials that reported race were white.^{10,12-14,17,22,24}

Most studies required at least “high-moderate” to “severe” symptom severity (most trials required an IRLS scale score of ≥ 15 [IRLS scale range, 0-40] at baseline and some required a score >20) with frequent symptom occurrence and duration of at least 1 month. Mean symptom severity was “severe” at baseline, with an overall mean IRLS scale score of 25.1. Duration of RLS varied with a mean of 17 years for ropinirole to 2 years for rotigotine trials. Trials enrolled patients who were newly diagnosed as well as those who had and had not received prior RLS treatments.

More than half (60%) of patients in rotigotine trials had received previous RLS treatment, vs 26% and 44% for pramipexole and ropinirole, respectively. Seven trials excluded patients with augmentation and/or 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. Four studies investigated multiple fixed doses of the drug.^{14,22-24}

IRLS Responders ($\geq 50\%$ Score Reduction)

The proportion of IRLS responders was significantly greater with dopamine agonist therapy compared with placebo (61% vs 41%) (RR, 1.60 [95% CI, 1.38 to 1.86]; NNT, 4.9) (**Figure 2**) (high-strength evidence).^{12-14,22-25} There was no evidence of a difference in treatment efficacy between the pramipexole and rotigotine (eTable 2).

Responders on CGI Scale and Mean Change From Baseline in the IRLS Scale Score

The proportion of responders (with a rating of “much improved” or “very much improved”) in the CGI scale was greater for dopamine agonist therapy (68%) than for placebo (46%) (RR, 1.45 [95% CI, 1.36 to 1.55]; NNT, 4.4; 15 trials).^{10-14,16-25} Visual inspection of funnel plots and Egger test did not demonstrate publication bias (Egger intercept 2-sided $P = .32$) (eAppendix 5).

Treatment with dopamine agonists resulted in a small reduction in symptom severity based on mean change from baseline between treatment and placebo in IRLS scale scores. Mean change in the IRLS score favored active treatment (WMD, -4.56 points [95% CI, -5.42 to -3.70]; 14 trials)^{10-14,16-18,20-25} (eFigure 1). The magnitude of reduction in IRLS scale scores was greater with rotigotine therapy²²⁻²⁵ than with pramipexole¹⁰⁻¹⁴ or ropinirole treatment^{16-18,20,21} (test for interaction, $P = .02$). We

found no clear evidence of a dose effect in the 4 fixed-dose studies of rotigotine or pramipexole.^{14,22-24} Overall, evidence was high strength. Visual inspection of funnel plots and Egger test did not demonstrate publication bias (Egger intercept 2-sided $P = .20$) (eAppendix 6).

Cabergoline improved IRLS scores more than levodopa in a single comparative effectiveness trial lasting 30 weeks ($n = 361$) among adults with severe symptoms (mean IRLS score, 25.7) (WMD, -7.0 points [95% CI, -9.1 to -4.9]) (moderate-strength evidence).²⁹ One small crossover comparative effectiveness trial ($n = 39$) compared pramipexole with dual-release levodopa-benserazide in newly diagnosed, previously untreated patients over two 4-week periods.²⁸ Overall reductions of IRLS scores from baseline trended toward significant improvement with pramipexole treatment, with a mean reduction of 7.2 points compared with 4.0 points for levodopa-benserazide ($P = .054$). The subset of patients with severe RLS (IRLS baseline score, 21-30) showed significant reductions in IRLS scores with pramipexole vs levodopa/benserazide ($P = .047$) (low-strength evidence).

QoL and Patient-Reported Sleep Outcomes

Overall high-strength evidence demonstrated that dopamine agonists improved QoL and self-reported sleep measures compared with placebo. Dopamine agonist improved RLS specific QoL as measured by SMDs in RLS QoL scale scores. The effect size was small to medium in magnitude (SMD, 0.37 [95% CI, 0.27 to 0.48]; 9 trials)^{10,12,14,17,21-25} (eFigure 2). Results were similar across types of dopamine agonist treatment. Dopamine agonists improved patient-reported sleep quality compared with placebo as measured by the Medical Outcomes Study sleep problem index (MOS) scale (SMD, 0.38 [95% CI, 0.29 to 0.46]; 8 trials)^{10,17,18,20-24} (eFigure 3). The magnitude of effect was small to moderate.

Table 1. Strength of Evidence for Individual Outcomes in Placebo-Controlled Studies of Dopamine Agonists

Outcome, Source/Treatments	Trials, No.	Patients, No.	Summary Statistics,	
			RR, WMD, or SMD (95% CI)	NNT or NNH
IRLS responders ($\geq 50\%$ score reduction) ^{11-13,21-24}				
All trials vs placebo	7	2218	RR 1.60 (1.38 to 1.86)	NNT 4.9
Pramipexole	3	1079	RR 1.46 (1.22 to 1.74)	NNT 5.9
Rotigotine	4	1139	RR 1.76 (1.47 to 2.10)	NNT 3.8
CGI scale responders: (much–very much improved) ^{9-13,15-24}				
All trials vs placebo	15	4446	RR 1.45 (1.36 to 1.55)	NNT 4.4
Pramipexole	5	1747	RR 1.61 (1.40 to 1.86)	NNT 3.8
Ropinirole	6	1608	RR 1.37 (1.25 to 1.50)	NNT 5.7
Rotigotine	4	1091	RR 1.37 (1.22 to 1.54)	NNT 5.0
IRLS total score: mean change from baseline ^{9-13,15-17,19-24}				
All trials vs placebo	14	3578	WMD -4.56 (-5.42 to -3.70)	NNT NA
Pramipexole	5	1578	WMD -4.76 (-6.24 to -3.28)	NNT NA
Ropinirole	5	1517	WMD -3.49 (-4.44 to -2.54)	NNT NA
Rotigotine	4	585	WMD -6.09 (-7.71 to -4.46)	NNT NA
RLS quality of life ^{9,11,13,16,20-24}				
All trials vs placebo	9	2140	SMD 0.37 (0.27 to 0.48)	NNT NA
Pramipexole	3	912	SMD 0.43 (0.25 to 0.61)	NNT NA
Ropinirole	2	643	SMD 0.30 (0.14 to 0.45)	NNT NA
Rotigotine	4	585	SMD 0.37 (0.13 to 0.60)	NNT NA
Self-rated sleep MOS-SPI-II ^{9,16,17,19-23}				
All trials vs placebo	8	2052	SMD 0.38 (0.29 to 0.46)	NNT NA
Pramipexole	1	356	SMD 0.36 (0.15 to 0.57)	NNT NA
Ropinirole	4	1237	SMD 0.37 (0.24 to 0.49)	NNT NA
Rotigotine	3	459	SMD 0.43 (0.24 to 0.61)	NNT NA
Study withdrawals due to an adverse event ⁹⁻²⁴				
All trials vs placebo	16	4860	RR 1.37 (1.03 to 1.82)	NNH 24.6
Pramipexole	5	1791	RR 0.97 (0.69 to 1.35)	NNH -763.7
Ropinirole	7	1698	RR 1.48 (0.99 to 2.20)	NNH 27.8
Rotigotine	4	1370	RR 2.50 (1.33 to 4.70)	NNH 11.2
Patients with ≥ 1 adverse event ⁹⁻²⁴				
All trials vs placebo	16	4854	RR 1.19 (1.12 to 1.28)	NNH 7.6
Pramipexole	5	1790	RR 1.16 (1.04 to 1.29)	NNH 8.0
Ropinirole	7	1695	RR 1.20 (1.10 to 1.32)	NNH 8.7
Rotigotine	4	1369	RR 1.25 (1.00 to 1.59)	NNH 7.1

Outcome, Source/Treatments	Risk of Bias ^a	Directness ^a	Precision ^a	Consistency ^a	Evidence Rating ^b
IRLS responders ($\geq 50\%$ score reduction) ^{11-13,21-24}					
All trials vs placebo	Low	Direct	Precise	Consistent	High
Pramipexole	Low	Direct	Precise	Consistent	High
Rotigotine	Low	Direct	Precise	Consistent	High
CGI scale responders: (much–very much improved) ^{9-13,15-24}					
All trials vs placebo	Low	Direct	Precise	Consistent	High
Pramipexole	Low	Direct	Precise	Consistent	High
Ropinirole	Low	Direct	Precise	Consistent	High
Rotigotine	Low	Direct	Precise	Consistent	High
IRLS total score: mean change from baseline ^{9-13,15-17,19-24}					
All trials vs placebo	Low	Direct	Precise	Consistent	High
Pramipexole	Low	Direct	Precise	Consistent	High
Ropinirole	Low	Direct	Precise	Consistent	High
Rotigotine	Low	Direct	Precise	Consistent	High
RLS quality of life ^{9,11,13,16,20-24}					
All trials vs placebo	Low	Direct	Precise	Consistent	High
Pramipexole	Low	Direct	Precise	Consistent	High
Ropinirole	Low	Direct	Precise	Consistent	High
Rotigotine	Low	Direct	Precise	Consistent	High
Self-rated sleep MOS-SPI-II ^{9,16,17,19-23}					
All trials vs placebo	Low	Direct	Precise	Consistent	High
Pramipexole	Low	Direct	Precise	Unknown	Moderate
Ropinirole	Low	Direct	Precise	Consistent	High
Rotigotine	Low	Direct	Precise	Consistent	High
Study withdrawals due to an adverse event ⁹⁻²⁴					
All trials vs placebo	Low	Direct	Precise	Consistent	High

(continued)

Table 1. Strength of Evidence for Individual Outcomes in Placebo-Controlled Studies of Dopamine Agonists (continued)

Outcome, Source/Treatments	Risk of Bias ^a	Directness ^a	Precision ^a	Consistency ^a	Evidence Rating ^b
Pramipexole	Low	Direct	Imprecise	Consistent	Moderate
Ropinirole	Low	Direct	Imprecise	Consistent	Moderate
Rotigotine	Low	Direct	Precise	Consistent	High
Patients with ≥1 adverse event ⁹⁻²⁴					
All trials vs placebo	Low	Direct	Precise	Consistent	High
Pramipexole	Low	Direct	Precise	Inconsistent	Moderate
Ropinirole	Low	Direct	Precise	Consistent	High
Rotigotine	Low	Direct	Precise	Consistent	High

Abbreviations: CGI, clinician-assessed global impression; IRLS, International Restless Legs Syndrome; MD, mean difference; MOS-SPI-II, Medical Outcomes Scale–Sleep Problems Index II; NA, not applicable; NNH, number needed to harm; NNT, number needed to treat; RLS, restless leg syndrome; RR, relative risk; SMD, standardized mean difference; WMD, weighted mean difference (a negative SMD and WMD indicates that the active treatment is more effective than placebo).

^aThe strength of the evidence was evaluated based on 4 required domains: (1) risk of bias, whether the studies for a given outcome or comparison have good internal validity, reflects the aggregate quality of the trials evaluated; (2) consistency is the degree of similarity in the effect sizes, ie, same direction of effect, of the included studies; (3) directness indicates a single, direct link between the intervention of interest and the outcome; and (4) precision is the degree of certainty surrounding an effect estimate of a given outcome.

^bStrength of evidence was rated using the following grades: (1) high confidence indicated that further research is very unlikely to change the confidence in the estimate of effect, meaning that the evidence reflects the true effect; (2) moderate confidence denoted that further research may change our confidence in the estimate of effect and may change the estimate; (3) low confidence indicated that further research is very likely to have an important impact on the confidence in the estimate of effect and is likely to change the estimate, meaning that there is low confidence that the evidence reflects the true effect; and (4) insufficient, indicating that the evidence was unavailable or did not permit a conclusion.

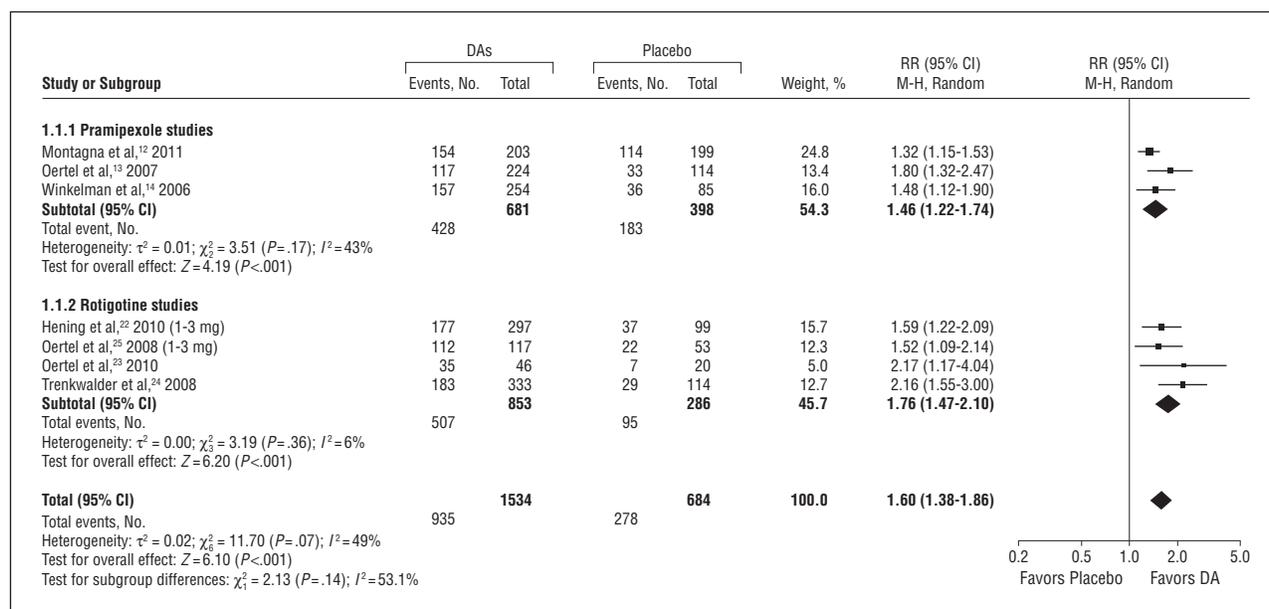


Figure 2. Dopamine agonists (DAs) vs placebo. Proportion of participants reporting greater than 50% reduction in mean International Restless Legs Syndrome score from baseline. M-H indicates Mantel-Haenszel; RR, risk ratio.

CALCIUM CHANNEL ALPHA-2-DELTA LIGANDS

Calcium channel alpha-2-delta ligands were evaluated in 7 randomized, double-blind, placebo-controlled studies (N = 1096)³⁰⁻³⁶ (Table 2 and eTable 3) including the prodrug gabapentin enacarbil,³⁰⁻³³ pregabalin,^{34,35} or gabapentin.³⁶ None of the trials lasted longer than 12 weeks. The mean age of participants

was 51 years, and nearly all (94%) were white. Women constituted 60% of participants. The overall mean baseline IRLS scale score was 24. The mean RLS disease duration was 12 years. One study 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 scale) to single-

blind gabapentin enacarbil treatment were then randomized to continuing gabapentin enacarbil treatment or placebo in a 12-week double-blind phase.³¹

IRLS Responders (≥50% Score Reduction)

Calcium channel alpha-2-delta ligand therapy was superior to placebo in increasing the proportion of

Table 2. Strength of Evidence for Individual Outcomes in Placebo-Controlled Studies of Calcium Channel Alpha-2-Delta Ligands

Outcome, Source/Treatments	No. of Trials	Patients, No.	Summary Statistics, RR, WMD, or SMD (95% CI)	NNT or NNH
IRLS responders ($\geq 50\%$ score reduction) ^{29,33,34}				
All trials vs placebo	3	503	RR 1.66 (1.33 to 2.09)	NNT 4.1
Gabapentin enacarbil	1	321	RR 1.54 (1.18 to 2.01)	NNH 4.7
Pregabalin	2	182	RR 2.03 (1.33 to 3.11)	NNT 3.4
CGI scale responders: (much–very much improved) ^{29,31,33}				
All trials vs placebo	3	662	RR 1.60 (1.21 to 2.10)	NNT 3.2
Gabapentin enacarbil	2 ^b	538	RR 1.80 (1.51 to 2.14)	NNT 3.0
Pregabalin	1	124	RR 1.14 (0.80 to 1.64)	NNT 11.1
IRLS total score: mean change from baseline ^{29,31,33}				
All trials vs placebo	3	475	WMD -4.26 (-5.75 to -2.77)	NNT NA
Gabapentin enacarbil	2 ^a	431	WMD -4.18 (-5.76 to -2.60)	NNT NA
Pregabalin	1	44	WMD -4.90 (-9.41 to -0.39)	NNT NA
Self-rated sleep MOS-SPI-II ^{29,31}				
Gabapentin enacarbil	2	431	SMD 0.53 (0.33 to 0.72)	NNT NA
Patients with ≥ 1 adverse event ^{29,31,33,34}				
All trials vs placebo	5	933	RR 1.17 (0.1.00 to 1.36)	NNH 8.6
Gabapentin enacarbil	3	738	RR 1.09 (0.1.00 to 1.19)	NNH 9.5
Pregabalin	2	195	RR 1.67 (0.74 to 3.80)	NNH 4.0

Outcome, Source/Treatments	Risk of Bias ^a	Directness ^a	Precision ^a	Consistency ^a	Evidence Rating ^b
IRLS responders ($\geq 50\%$ score reduction) ^{29,33,34}					
All trials vs placebo	Low	Direct	Precise	Consistent	High
Gabapentin enacarbil	Low	Direct	Precise	Unknown	Moderate
Pregabalin	Low	Direct	Precise	Consistent	High
CGI scale responders: (much–very much improved) ^{29,31,33}					
All trials vs placebo	Low	Direct	Precise	Consistent	High
Gabapentin enacarbil	Low	Direct	Precise	Consistent	High
Pregabalin	Low	Direct	Imprecise	Unknown	Low
IRLS total score: mean change from baseline ^{29,31,33}					
All trials vs placebo	Low	Direct	Precise	Consistent	High
Gabapentin enacarbil	Low	Direct	Precise	Consistent	High
Pregabalin	Low	Direct	Precise	Unknown	Moderate
Self-rated sleep MOS-SPI-II ^{29,31}					
Gabapentin enacarbil	Low	Direct	Precise	Consistent	High
Patients with ≥ 1 adverse event ^{29,31,33,34}					
All trials vs placebo	Low	Direct	Imprecise	Consistent	Moderate
Gabapentin enacarbil	Low	Direct	Precise	Consistent	High
Pregabalin	Low	Direct	Imprecise	Consistent	Moderate

Abbreviations: CGI, clinician-assessed global impression; IRLS, International Restless Legs Syndrome; MD, mean difference; MOS-SPI-II, Medical Outcomes Scale–Sleep Problems Index II; NA, not applicable; NNH, number needed to harm; NNT, number needed to treat; RR, relative risk; SMD, standardized mean difference; WMD, weighted mean difference (a negative SMD and WMD indicates that the active treatment is more effective than placebo).

^aThe strength of the evidence was evaluated based on 4 required domains: (1) risk of bias, whether the studies for a given outcome or comparison have good internal validity, reflects the aggregate quality of the trials evaluated; (2) consistency is the degree of similarity in the effect sizes, ie, same direction of effect, of the included studies; (3) directness indicates a single, direct link between the intervention of interest and the outcome; and (4) precision is the degree of certainty surrounding an effect estimate of a given outcome.

^bStrength of evidence was rated using the following grades: (1) high confidence indicated that further research is very unlikely to change the confidence in the estimate of effect, meaning that the evidence reflects the true effect; (2) moderate confidence denoted that further research may change our confidence in the estimate of effect and may change the estimate; (3) low confidence indicated that further research is very likely to have an important impact on the confidence in the estimate of effect and is likely to change the estimate, meaning that there is low confidence that the evidence reflects the true effect; and (4) insufficient, indicating that the evidence was unavailable or did not permit a conclusion.

IRLS responders (61% vs 37%; RR, 1.66 [95% CI, 1.33 to 2.09]; NNT, 4.1) (**Figure 3**). The evidence was high strength (eTable 2).

Responders on the CGI Scale and Mean Change From Baseline in The IRLS Scale Score

A significantly greater proportion of patients allocated to calcium channel alpha-2-delta ligand therapy were

rated improved or very much improved on the CGI scale (74% vs 44%; RR, 1.60 [95% CI, 1.21 to 2.10]; NNT, 3.2; 3 trials).^{30,32,34} Improvement was significant for gabapentin enacarbil therapy^{30,32} but not for pregabalin treatment³⁴ (test for interaction, $P = .03$) (high-strength evidence). Pooled weighted mean change in IRLS score from baseline vs placebo was -4.26 points (95% CI, -5.75 to -2.77; 3 trials)^{30,32,34} (eFigure 4).

Mean change in IRLS score from baseline in the crossover trial by Winkelman et al³³ significantly favored gabapentin enacarbil (WMD, -6.6 points [95% CI, -8.6 to -4.6]). 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 a IRLS score ≥ 15 points and a rating of “much worse” or “very much worse”

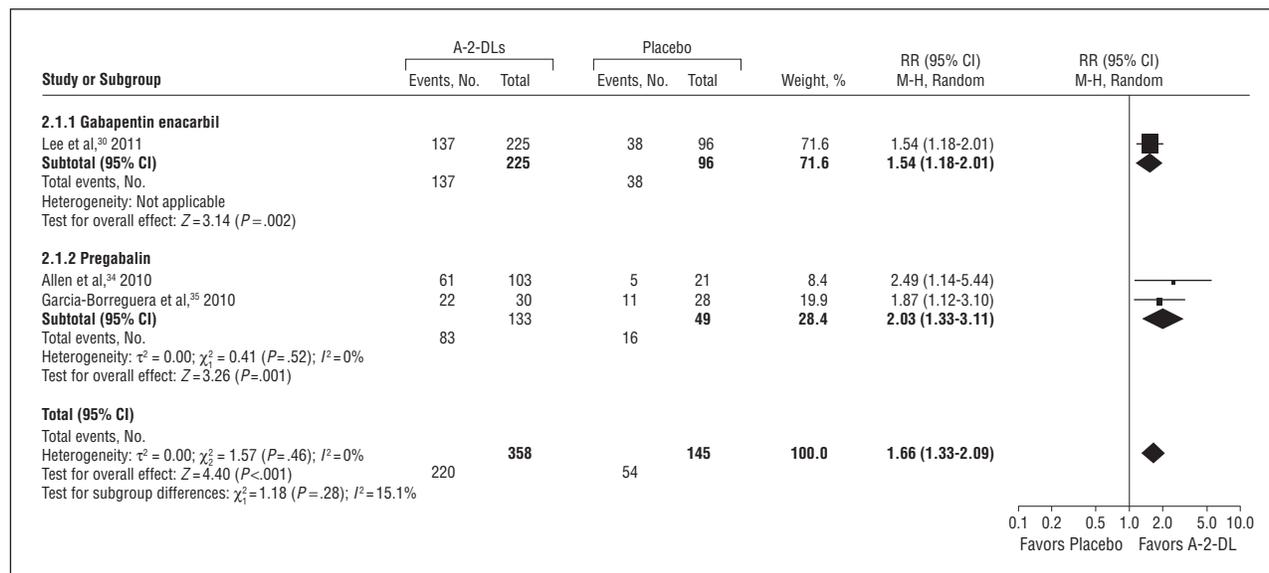


Figure 3. Calcium channel alpha-2-delta ligands (A-2-DLs) vs placebo. Proportion of participants reporting a greater than 50% reduction in mean International Restless Legs Syndrome score from baseline. M-H indicates Mantel-Haenszel; RR, risk ratio.

on the CGI scale) than patients allocated to placebo, 9% and 23%, respectively (RR, 0.41 [95% CI, 0.20 to 0.85]; NNT, -7.5).³¹ Two gabapentin enacarbil trials reported significantly improved sleep adequacy based on the MOS sleep adequacy domain (SMD, 0.53 [95% CI, 0.33 to 0.72]).^{30,32} The magnitude of effect was considered moderate and strength of evidence high.

MISCELLANEOUS PHARMACOLOGIC STUDIES

Two miscellaneous pharmacologic studies assessed adults with moderate to severe RLS.^{37,38} One small short-term RCT (n = 46) found that intravenous iron (ferric carboxymaltose) significantly improved IRLS symptom scale scores compared with placebo over 28 days of therapy³⁷ in adults without iron deficiency. Mean improvements for iron and placebo were reductions of 8.9 and 4.0 points, respectively, with a mean difference of -4.90 (95% CI, -9.27 to -0.53). The evidence strength was moderate. Ferric carboxymaltose also significantly improved CGI, RLS QoL, and sleep measures (MOS total score) vs placebo.

One small RCT evaluated the antidepressant bupropion.³⁸ The IRLS symptom scores after 6 weeks compared with baseline were 10.4 points lower with bupropion and 7.6 points

lower with placebo—not a statistically significant difference (P = .11). Evidence was low strength.

SHORT-TERM HARMS

Forest plots for study withdrawals and adverse events are shown in eFigures 5-17. Patients were less likely to withdraw from dopamine agonists than from placebo (20% vs 24%; RR, 0.79 [95% CI, 0.66 to 0.94]; NNH, -29.9; 16 trials) (moderate-strength evidence).¹⁰⁻²⁵ There was a 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]; NNH = 24.6; 16 trials) (high-strength evidence).¹⁰⁻²⁵ Risk of withdrawal due to adverse events differed between dopamine agonists (test for interaction, P = .02) with the highest increase associated with rotigotine (RR, 2.50 [95% CI, 1.33 to 4.70]; NNH, 11.2), primarily due to application site reactions. More patients reported at least 1 adverse effect with dopamine agonist compared with placebo (74% vs 61%; RR, 1.19 [95% CI, 1.12 to 1.28]; NNH, 7.6; 16 trials) (high-strength evidence).¹⁰⁻²⁵

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]; NNH, 6.7; 15 trials),¹¹⁻²⁵ vomiting (7% vs 2%; RR,

4.48 [95% CI, 2.68 to 7.48]; NNH, 19.7; 8 trials),^{15,16,20-22,25} and somnolence (12% vs 6%; RR, 2.04 [95% CI, 1.50 to 2.76]; NNH, 16.6; 8 trials)^{11,14,15,17,18,20,22,23} (overall high-strength evidence for these outcomes). Application site reactions were much more common with transdermal rotigotine than with placebo, 29% vs 3%, respectively (RR, 8.32 [95% CI, 3.45 to 20.05]; NNH, 3.9; 4 trials) (high-strength evidence).²²⁻²⁵

Patients allocated to calcium channel alpha-2-delta ligands were less likely to withdraw from treatment owing to any reason compared with patients allocated to placebo (12% vs 17%; RR, 0.71 [95% CI, 0.52 to 0.99]; NNH, -20.6; 5 trials)^{30-32,34,35} (high-strength evidence). Compared with placebo, alpha-2-delta ligands were 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]; NNH, 22.1; 4 trials)^{30,32,34,35} (moderate-strength evidence).

Short-term effects that were significantly greater with calcium channel alpha-2-delta ligands compared with placebo were somnolence (19% vs 3%; RR, 5.37 [95% CI, 2.38 to 12.12]; NNH, 6.0; 5 trials),^{30,32,34-36} unsteadiness or dizziness (17% vs 4%; RR, 4.11 [95% CI, 2.19 to 7.71]; NNH, 7.8; 4 trials),^{30,32,34,35} and dry mouth (6% vs 1%; RR, 3.31 [95% CI, 1.09 to 10.05]; NNH, 20.3; 4

trials).^{30,34-36} Evidence for these outcomes was high strength.

Three subjects each reported diarrhea (12.5%) and blood phosphorus decrease (12.5%) with intravenous iron therapy.³⁷ No subjects in the placebo arm reported these events. Two patients allocated to bupropion and 1 to placebo discontinued treatment owing to nausea.³⁸ No other adverse events were reported.

COMMENT

Results from small, placebo-controlled randomized trials of generally short duration in selected patients with “high-moderate” to “severe” RLS symptoms of long duration demonstrated that dopamine agonists and alpha-2-delta ligands were effective. They increased the percentage of individuals with primary RLS responding to treatment, reduced RLS symptoms, and improved disease-specific QoL and patient-reported sleep outcomes. Adverse effects and long-term treatment withdrawals due to adverse effects or lack of efficacy were common. Our findings provide independent evidence that adds to previous work evaluating RLS treatments.^{39,40} Our report includes evidence published through June 2012, focuses on pharmacologic therapies for patients with primary RLS, and emphasizes clinically relevant outcomes. Our findings provide information about the clinical benefits and harms of pharmacologic therapies especially relevant to primary care providers needing management guidance for patients they diagnose with RLS.

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.⁴¹ Evidence is lacking about the long-term effectiveness in, and applicability to, adults with less-severe or less-frequent RLS symptoms, nonwhite and older adults, those with multiple comorbidities, and children.

We found no peer-reviewed RCT data on the comparative benefits or harms of dopamine ago-

nists and alpha-2-delta ligands. Preliminary results from a 12-week placebo-controlled, 52-week active-comparator trial (n = 719) indicated that pregabalin was more effective than pramipexole in improving RLS symptoms.⁴²

Trial results may lack broad generalizability. Exclusion criteria were many. Subjects were typically recruited from RLS clinics rather than primary care or mental health settings; frequent sites for detection and management of individuals with suspected RLS. Enrollees had greater disease severity, frequency, and duration than reported by the estimated 1.5% 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 younger than 18 years, and nearly all enrollees were white. Studies rarely provided details to assess if secondary causes were adequately excluded such as iron deficiency or renal insufficiency. Treatment withdrawal for any reason was greater in patients assigned to placebo compared with active intervention, suggesting that short-term treatment benefits exceeded harms among enrollees. However, patient acceptability regarding the tradeoff of benefits to harms may differ in patients not enrolled in trials, individuals with less severe RLS, or those treated for a long duration.

Clinicians and patients should be aware of the large placebo response. Long-term observational studies reporting withdrawals due to loss of efficacy or adverse effects also suggest that pharmacologic treatment benefits are not sustained over time for many patients with RLS and that these treatments result in adverse effects leading to discontinuation.⁷ Withdrawal from mostly dopamine agonist and levodopa treatment was common, occurring in 13% to 57% of subjects owing to either lack of efficacy or adverse effects. Long-term augmentation ranged from 2.5% to 60% and varied markedly by type of dopamine agonist, follow-up time, study de-

sign, and method used to ascertain augmentation. Little data exist on long-term adherence and adverse effects for alpha-2-delta ligands.

For individuals unable to initiate or tolerate dopamine agonist or alpha-2-delta ligands, or for whom these drugs have failed, recommended pharmacologic treatments include off-label opioids (morphine, oxycodone, and methadone), sedative hypnotics, and tramadol. We found no eligible studies evaluating these agents, and none are FDA approved for RLS treatment. 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. Evidence on additional options is limited to 4 lower-quality trials. These trials provide low-strength evidence for a benefit with compression stockings,⁴³ near-infrared light,⁴⁴ and strength training and treadmill walking,⁴⁵ but not for the botanical extract valerian.⁴⁶

We urge caution in applying our findings to the more heterogeneous population of patients with RLS in primary care settings. The populations enrolled in these trials had RLS of high-moderate to severe intensity for many years; many participants had received previous unsuccessful drug treatment for RLS. In contrast, individuals presenting to primary care with new RLS-like symptoms may have milder symptoms or other conditions for which symptoms mimic RLS (eg, periodic leg movement disorders, nocturnal leg cramps, vascular or neurogenic claudication). They may also be younger or older or have more comorbidities than subjects included in available RCTs. Applicability concerns are more salient in light of direct-to-consumer marketing that has raised awareness of potential RLS symptoms.⁴⁷

In conclusion, among individuals with primary RLS and high-moderate to very severe RLS symptoms of long duration, dopamine agonists and alpha-2-delta ligands increased the percentage of those “responding to treatment,” reduced RLS symptom scores, and improved patient-reported sleep outcomes, disease-specific QoL, and

overall RLS impact compared with placebo. Adverse effects and treatment withdrawals due to adverse effects for dopamine agonists and alpha-2-delta ligands were common. We found no high-quality data on comparative effectiveness and harms of commonly used treatments nor effectiveness data on other interventions often used but lacking FDA approval for RLS treatment. In addition, long-term efficacy and adherence as well as applicability to adults with less-frequent or less-severe RLS symptoms, adult with more recent onset, children, or those with secondary RLS is not well known.

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