Therapeutic Class Overview
Restless Legs Syndrome

Therapeutic Class
Overview/Summary: The agents Food and Drug Administration (FDA)-approved for the treatment of restless legs syndrome (RLS) include the nonergot derivative dopamine agonists pramipexole (Mirapex®), ropinirole (Requip®) and rotigotine (Neupro®), as well as an extended-release (ER) formulation of the anticonvulsant gabapentin enacarbil (Horizant®).[1-4] The mechanism by which the dopamine agonists exert their effects in RLS is unknown, although RLS may to be related to dopaminergic dysfunction and these agents may be beneficial due to their stimulation of dopamine receptors.[2-4] Gabapentin enacarbil is a prodrug of the anticonvulsant gabapentin (Neurontin®). The mechanism by which gabapentin is effective in RLS has not been established. Gabapentin is structurally related to the inhibitory neurotransmitter gamma-aminobutyric acid (GABA) but has no effect on GABA binding, uptake or degradation. Gabapentin enacarbil is rapidly hydrolyzed to gabapentin in the gastrointestinal tract. The ER formulation achieves more predictable serum concentrations and is not interchangeable with immediate-release gabapentin. Gabapentin enacarbil ER is the only gabapentin-containing product that is FDA-approved for the treatment of RLS.[6] Moreover, gabapentin enacarbil ER does not demonstrate saturable absorption which results in a higher bioavailability and less variability in serum levels compared to gabapentin.[1]

For the management of RLS, gabapentin enacarbil ER, pramipexole and ropinirole are dosed once daily in the evening, prior to the onset of symptoms and rotigotine is applied once daily. Dose adjustments are recommended with gabapentin enacarbil ER and pramipexole in patients with renal impairment. Ropinirole undergoes hepatic metabolism by the cytochrome P450 1A2 enzyme, and drug interactions may occur with inducers or inhibitors of this enzyme. Pramipexole and ropinirole have similar side effect profiles, although hallucinations have been reported more frequently with pramipexole and somnolence and hypotension with ropinirole. Rotigotine use is commonly associated with application site reactions and nausea. The dopamine agonist all carry a warning regarding falling asleep during activities of daily living and patients should be advised to avoid potentially dangerous activities including driving. Similarly, gabapentin enacarbil ER carries a warning to patients regarding somnolence and its effect on driving.[1-4] Both pramipexole and ropinirole are available generically.[5] Gabapentin enacarbil ER is only available as a branded tablet; however, gabapentin is available generically in various strengths and formulations.[5] Rotigotine is only available as a brand name patch.[5]

Table 1. Current Medications Available in the Class[1-6]

Generic (Trade Name)	Food and Drug Administration Approved Indications	Dosage Form/Strength	Generic Availability
Gabapentin enacarbil ER (Horizant®)	Treatment of moderate-to-severe primary restless legs syndrome	Extended-release tablet: 300 mg 600 mg	-
Pramipexole (Mirapex® Mirapex ER®†)	Treatment of moderate-to-severe primary restless legs syndrome, treatment of the signs and symptoms of idiopathic Parkinson's disease*	Extended-release tablet:† 0.375 mg 0.75 mg 1.5 mg 2.25 mg 3.0 mg 3.75 mg 4.5 mg Tablet: 0.125 mg 0.25 mg 0.5 mg 0.75 mg	✔ (immediate-release)

		1 mg 1.5 mg	
Ropinirole (Requip®, Requip® XL†)	Treatment of moderate-to-severe primary restless legs syndrome, treatment of the signs and symptoms of idiopathic Parkinson's disease*	Extended-release tablet:† 2 mg 4 mg 6 mg 8 mg 12 mg Tablet: 0.25 mg 0.5 mg 1 mg 2 mg 3 mg 4 mg 5 mg	✔
Rotigotine (Neupro®)	Treatment of moderate-to-severe primary restless legs syndrome, treatment of the signs and symptoms of idiopathic Parkinson's disease*	Transdermal Patch: 1 mg/24 hours 2 mg/24 hours 3 mg/24 hours 4 mg/24 hours‡ 6 mg/24 hours‡ 8 mg/24 hours‡	-

ER, XL=extended-release
*Despite being FDA-approved for the treatment of idiopathic Parkinson's disease, the focus of this review will be on the role of the dopamine agonists in restless legs syndrome.
†Dosage form not approved for use in restless legs syndrome.
‡ Strength not recommended in restless legs syndrome

Evidence-based Medicine

- The clinical studies evaluating gabapentin enacarbil extended-release (ER) are similar in design. All studies were placebo-controlled and enrolled adult patients with primary restless legs syndrome (RLS) who were symptomatic and had a baseline International Restless Legs Syndrome (IRLS) score of ≥15. Varying doses of gabapentin enacarbil ER were evaluated (600 to 1,800 mg/day); however, the Food and Drug Administration-approved dosing is 600 mg once-daily.[1,7-13]
- Overall, treatment with gabapentin enacarbil ER significantly decreased IRLS total scores compared to placebo, and significantly greater proportions of patients receiving gabapentin enacarbil ER were rated as clinician- and patient-reported Clinical Global Impression-Improvement responders. Moreover, data demonstrate that gabapentin enacarbil ER significantly improved other sleep rating scale scores compared to placebo. Within all studies, the most commonly reported adverse events associated with gabapentin enacarbil ER were somnolence and dizziness.[7-13]
- The results of a meta-analysis evaluating pramipexole and ropinirole in patients with moderate to severe primary RLS indicate that both pramipexole and ropinirole treatment improved scores on the IRLS scale compared to placebo (pramipexole, -7.16; 95% CI, -9.77 to -4.54 ropinirole, -3.50; 95% CI, -4.75 to -2.25). Each agent was also associated with a greater response on CGI-I scale compared to placebo (pramipexole, RR, 1.60; 95% CI, 1.34 to 1.92, ropinirole, RR, 1.32; 95% CI, 1.21 to 1.43). Ropinirole showed a significant increase in study withdrawals secondary to adverse events, while pramipexole did not.[14]
- A recent comparative effectiveness review published by the Agency for Healthcare Research and Quality failed to identify any head-to-head trials comparing the FDA-approved agents in RLS, but

concluded that dopamine agonists and gabapentin reduce symptoms and improve patient-reported sleep outcomes and disease-specific quality of life compared to placebo in patients with RLS.[15]

- The efficacy of rotigotine for Restless Legs Syndrome (RLS) was based on two randomized, double-blind controlled trials that compared rotigotine ranging from 0.5 to 3 mg/24 hours with placebo in patients with moderate to severe primary RLS.[16,17] The two primary outcome measures were changes in the International RLS Rating Scale (IRLS Scale) and a Clinical Global Impression-I (CGI-I) assessment. Rotigotine significantly improved both the IRLS and the CGI-I scores in both studies compared to placebo. Several additional trials published confirm the efficacy and safety of rotigotine.[18-21]
- A five-year study involving the safety of rotigotine was completed and found that 30% of the patients discontinued rotigotine due to adverse effects, with the most frequent treatment-emergent adverse event being application site reaction, which occurred in 37% of all patients in the first year. More than half of the patients who discontinued treatment because of adverse events (47/89 [53%]) did so during the first year of maintenance. 56 of the total 89 (63%) patients to discontinue rotigotine due to adverse effects did so due to application site reactions.[19]

Key Points within the Medication Class

- According to Current Clinical Guidelines:
    - Dopamine agonists are the drugs of choice in most patients with daily restless legs syndrome (RLS). Pramipexole and ropinirole are associated with fewer side effects; therefore they are preferred over pergolide.[22]
    - Ergot-dopamine agonists require special monitoring due to increased incidence of cardiac valvular fibrosis and other fibrotic side effects. Because of their negative side-effect profile, these agents are not recommended as initial therapy for the treatment of RLS. If used, cardiopulmonary monitoring for fibrosis is necessary.[23]
    - Gabapentin is considered an alternative to dopamine agonists, especially in patients with neuropathic pain. Other anticonvulsants that are likely effective in RLS include carbamazepine and valproic acid.[23]
    - Low-potency opioids such as propoxyphene or codeine and opioid agonists like tramadol are recommended as alternative treatment to dopamine agonists.[22-25]
- Other Key Facts:
    - Both pramipexole and ropinirole are available generically, while gabapentin enacarbil extended release (ER) and rotigotine are only available as a branded product.[5]
    - Generic formulations of gabapentin (Neurontin®) are available in various strengths.[5]
    - Gabapentin enacarbil is the only gabapentin product that is indicated for restless legs syndrome; the other gabapentin formulations are indicated for the treatment of postherpetic neuralgia and as adjunctive therapy in the treatment of partial seizures.[5,6]
    - In comparison to other recommended agents such as opioids and benzodiazepines, gabapentin enacarbil ER may be associated with a more favorable safety profile, and associated with less risk of dependence.[1]

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Therapeutic Class Review
Restless Legs Syndrome

Overview/Summary

Restless legs syndrome (RLS) is a neurological disorder characterized by the irresistible urge to move one's legs with or without unpleasant sensations. The exact pathophysiology of RLS has not been elucidated, but it may be closely linked to abnormalities in the dopaminergic system and iron metabolism.[1] The agents Food and Drug Administration (FDA)-approved for the treatment of RLS include the nonergot derivative dopamine agonists pramipexole (Mirapex®), ropinirole (Requip®) and rotigotine (Neupro®), as well as an extended-release (ER) formulation of the anticonvulsant gabapentin enacarbil (Horizant®).[2-5] Both pramipexole and ropinirole are also FDA-approved for the treatment of idiopathic Parkinson's disease; however, the focus of this review will be on their role in the management of RLS. The mechanism by which these agents exert their effects in RLS is unknown, although, these conditions may to be related to dopaminergic dysfunction and these agents may be beneficial due to their stimulation of dopamine receptors.[2-6]

Gabapentin enacarbil is a prodrug of the anticonvulsant gabapentin (Neurontin®), and the therapeutic effect of gabapentin enacarbil in RLS is attributable to gabapentin. The precise mechanism by which gabapentin is efficacious in RLS is not established. Gabapentin is structurally related to the inhibitory neurotransmitter gamma-aminobutyric acid (GABA) but has no effect on GABA binding, uptake or degradation.[2] Gabapentin enacarbil is rapidly hydrolyzed to gabapentin in the gastrointestinal tract. The ER formulation achieves more predictable serum concentrations and is not interchangeable with immediate-release gabapentin. Gabapentin enacarbil ER is the only gabapentin-containing product that is FDA-approved for the treatment of RLS.[5] Other formulations of gabapentin are FDA-approved for the treatment of postherpetic neuralgia and as adjunctive therapy in the treatment of partial seizures.[6,7] Moreover, gabapentin enacarbil ER does not demonstrate saturable absorption which results in a higher bioavailability and less variability in serum levels compared to gabapentin.[2,8]

Gabapentin enacarbil ER, pramipexole and ropinirole are dosed once daily in the evening, prior to the onset of symptoms. Rotigotine patches are applied once daily. Dose adjustments are recommended with gabapentin enacarbil ER and pramipexole in patients with renal impairment. Both agents, along with rotigotine, carry a warning regarding falling asleep during activities of daily living and patients should be advised to avoid potentially dangerous activities including driving. Similarly, gabapentin enacarbil ER carries a warning to patients regarding somnolence and its effect on driving.[2-7] Rotigotine use is associated with several common adverse effects including application site reactions and nausea.[5] Both pramipexole and ropinirole are available generically. Ropinirole is also available generically in an ER tablet, although this product is not approved for RLS. Gabapentin enacarbil ER is only available as a branded tablet; however, gabapentin is available generically in various strengths and formulations. Rotigotine is only available as a brand name patch.

Gabapentin enacarbil ER and the dopamine agonists have not been directly compared in clinical studies, but they have all demonstrated efficacy in the treatment RLS and their other FDA-approved indications compared to placebo. A recent comparative effectiveness review published by the Agency for Healthcare Research and Quality failed to identify any head-to-head trials comparing FDA-approved agents in RLS, but concluded that dopamine agonists and gabapentin reduce symptoms and improve patient-reported sleep outcomes and disease-specific quality of life compared to placebo in patients with RLS.[9] Consensus treatment guidelines for RLS have not been updated to reflect the role of gabapentin enacarbil ER. Clinical guidelines recommend dopamine agonists as the drugs of choice in daily RLS, with pramipexole and ropinirole being preferred over ergot-derived dopamine agonists due to their favorable side effect profile.[10-13] Gabapentin may be considered an alternative to dopamine agonists, especially in patients with neuropathic pain. Other alternative products that may be efficacious for the treatment of RLS include the anticonvulsants, opioids and benzodiazepines.[11,13]

Medications

Table 1. Medications Included Within Class Review[2-5]

Generic Name (Trade Name)	Medication Class	Generic Availability
Gabapentin enacarbil ER (Horizant®)	Anticonvulsant	-
Pramipexole (Mirapex®, Mirapex ER®*)	Dopamine agonists	✔ (immediate-release)
Ropinirole (Requip®, Requip® XL*)	Dopamine agonists	✔
Rotigotine (Neupro®)	Dopamine agonist	-

ER, XL=extended-release.
* Dosage form not approved for use in restless legs syndrome.

Indications

Table 2. Food and Drug Administration Approved Indications[2-5]

Indication	Gabapentin enacarbil ER	Pramipexole	Ropinirole	Rotigotine
Treatment of the signs and symptoms of idiopathic Parkinson's disease*		✔	✔	✔
Treatment of moderate-to-severe primary restless legs syndrome	✔	✔ (immediate release)	✔ (immediate release)	✔

ER=extended-release
*Despite being FDA-approved for the treatment of idiopathic Parkinson's disease, the focus of this review will be on the role of the dopamine agonists in restless legs syndrome.

Pramipexole may potentially be used off-label for the treatment of fibromyalgia and depression.[6]

Pharmacokinetics

Table 3. Pharmacokinetics[2-7]

Generic Name	Bioavailability (%)	Absorption (%)	Renal Excretion (%)	Active Metabolites	Serum Half-Life (hours)
Gabapentin enacarbil ER	75	Not reported	95	None	5.1 to 6.0
Pramipexole*	>90	Not reported	90	None	8.5 to 12
Ropinirole*	45 to 55	Not reported	88	None	6
Rotigotine	1 to 46†	Not reported	71	None	5 to 7

ER=extended-release
* Immediate-release
† Dependent on location of patch

Clinical Trials

The clinical studies demonstrating the safety and efficacy of gabapentin enacarbil ER, pramipexole and ropinirole in the treatment of restless legs syndrome (RLS) are outlined in Table 4.[14-52]

The clinical studies evaluating gabapentin enacarbil ER are similar in design. All trials were placebo-controlled and enrolled adult patients with primary RLS who were experiencing RLS symptoms and had a baseline International Restless Legs Syndrome (IRLS) score ≥15. Varying doses of gabapentin enacarbil ER were evaluated (600 to 1,800 mg/day); however, the Food and Drug Administration-approved dosing is 600 mg once-daily. Overall, treatment with gabapentin enacarbil ER significantly decreased IRLS total scores compared to placebo, and significantly greater proportions of patients receiving gabapentin enacarbil ER were rated as clinician- and patient-reported Clinical Global Impression-Improvement responders. Moreover, data demonstrate that gabapentin enacarbil ER significantly improved other sleep rating scale scores compared to placebo. Within all trials, including a long-term, one year safety trial, the most commonly reported adverse events associated with gabapentin enacarbil ER were somnolence and dizziness.[14-20]

For the treatment of RLS the dopamine agonists have each consistently demonstrated greater efficacy over placebo for reducing symptoms of RLS.[21-52] Only a single, two-day, head-to-head trial comparing pramipexole and ropinirole exists in which the periodic movements in sleep (PLMS) index was significantly reduced with ropinirole compared to pramipexole (*P*=0.0004).[35] Pramipexole and ropinirole have each shown benefit in the management of RLS, as demonstrated by improvements in IRLS scores, periodic limb movements during sleep (PLMS), patient and physician assessment scales, as well as sleep and quality of life.[21-45] The results of a meta-analysis evaluating pramipexole, ropinirole, rotigotine and sumanirole in patients with moderate to severe primary RLS as compared to placebo indicated that both pramipexole and ropinirole treatment improved scores on the IRLS scale and the Clinical Global Impression-Improvement scale. However, ropinirole showed a significant increase in study withdrawals secondary to adverse events, while pramipexole did not.[36] Trials including pramipexole or ropinirole for the treatment of RLS beyond one year weeks are lacking. The results of a small (N=16), open-label study comparing ropinirole and gabapentin showed that there was no difference between the treatments with regard to the number of PLMS or PLMS index, however each group experienced significant improvements from their respective baseline values.[45]

The efficacy of rotigotine for Restless Legs Syndrome (RLS) was based on two randomized, double-blind controlled trials that compared rotigotine ranging from 0.5 to 3 mg/24 hours with placebo in patients with moderate to severe primary RLS.[47,48] The two primary outcome measures were changes in the International RLS Rating Scale (IRLS Scale) and a Clinical Global Impression-I (CGI-I) assessment. Rotigotine significantly improved both the IRLS and the CGI-I scores in both studies compared to placebo. Several additional trials published confirm the efficacy and safety of rotigotine.[49-52] A five-year study involving the safety of rotigotine was completed and found that 30% of the patients discontinued rotigotine due to adverse effects, with the most frequent treatment-emergent adverse event being application site reaction, which occurred in 37% of all patients in the first year. More than half of the patients who discontinued treatment because of adverse events (47/89 [53%]) did so during the first year of maintenance. Fifty-six of the total 89 (63%) patients to discontinue rotigotine due to adverse effects did so due to application site reactions.[50]

Table 4. Clinical Trial

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
Restless Legs Syndrome				
Lee et al[14] Gabapentin enacarbil ER 600 or 1,200 mg QPM vs placebo	DB, MC, PC, RCT Adult patients with primary RLS with a baseline IRLS score >15 and experiencing RLS symptoms on ≥15 nights during the month before screening and on four or more nights during the week-long screening period	N=325 12 weeks	Primary: Gabapentin enacarbil ER 1,200 mg/day change in baseline IRLS and proportion CGI-I responders Secondary: Change in baseline IRLS, proportion of patients rated as responders on CGI-I at weeks one and 12; 24-hour RLS symptom diary; change in baseline PghSD, MOS Sleep Scale, and PSQ; safety	Primary: Gabapentin enacarbil ER 1,200 mg/day significantly decreased IRLS compared to placebo (-13.0±9.12 vs -9.8±7.69; adjusted treatment difference, -3.5; 95% CI, -5.6 to -1.3; P=0.0015). A significantly greater proportion of patients receiving gabapentin enacarbil ER 1,200 mg/day were rated as clinician-reported CGI-I responders compared to patients receiving placebo (77.5 vs 44.8%; OR, 4.3; 95% CI, 2.34 to 7.86; P<0.0001). Secondary: Gabapentin enacarbil ER 600 mg/day significantly decreased IRLS compared to placebo (-13.8.0±8.09 vs -9.8±7.69; adjusted treatment difference, -4.3; 95% CI, -6.4 to -2.3; P<0.0001). A significantly greater proportion of patients receiving gabapentin enacarbil ER 600 mg/day were rated as clinician-reported CGI-I responders compared to patients receiving placebo (72.8 vs 44.8%; OR, 3.3; 95% CI, 1.84 to 5.99; P<0.0001). Significant decreases in IRLS were observed by week one with gabapentin enacarbil ER 1,200 (P=0.0017) and 600 mg/day (P<0.0001) compared to placebo. Similar results were observed for the proportion of patients rated as clinician-reported CGI-responders at week one. Similar results were observed for the proportions of patients rated as patient-reported CGI-I responders at weeks one (600 mg/day, 50.0%; P<0.0001, 1,200 mg/day, 49.5%; P=0.0001) and 12 (600 mg/day, 78.9%; 1,200 mg/day, 47.8%; P<0.0001 for both) for both doses of gabapentin enacarbil ER compared to placebo (22.7 and 47.9%). With regard to the 24-hour RLS symptom diary, there was an increase in the estimated median time to onset of RLS symptoms with all treatments. At the end of the 24-hour period 35.3, 37.0, and 23.0% of patients receiving gabapentin enacarbil ER 600 mg/day, gabapentin enacarbil ER 1,200

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
				mg/day, and placebo were free from symptoms (P values not reported). With regard to PghSD, both doses of gabapentin enacarbil ER significantly decreased wake after sleep onset times compared to placebo (600 mg/day; P=0.0081, 1,200 mg/day; P=0.0007). There were no differences between the two treatments doses with changes in total sleep time (P=0.6778 and P=0.1161). Gabapentin enacarbil ER 1,200 mg/day significantly improved all MOS sleep scale domains compared to placebo, with greatest improvements in sleep disturbance (P<0.0001), sleep quantity (P=0.0001), sleep adequacy (P<0.0001), and daytime somnolence (P=0.0309). Gabapentin enacarbil ER 600 mg/day significantly improved sleep disturbance (P<0.0001), sleep quantity (P=0.0209) and sleep adequacy (P=0.003) compared to placebo. All items on the PSQ significantly improved with both doses of gabapentin enacarbil ER compared to placebo (P<0.05 for all). The most commonly reported treatment-emergent adverse events with gabapentin enacarbil ER were dizziness and somnolence. The median duration of dizziness was four, five and three days with gabapentin enacarbil ER 1,200 mg/day, gabapentin enacarbil ER 600 mg/day, and placebo. The median duration of somnolence was 16, 35, and 30 days with the three treatments. Three patients experienced a serious adverse event; one with placebo and two with gabapentin enacarbil ER 600 mg/day. No clinically relevant changes in vital signs, electrocardiograms, or laboratory parameters were observed.
Bogan et al[15] Gabapentin enacarbil ER 1,200 mg QPM vs placebo	DB, MC, PC, PG, RCT Patients ≥18 years of age with severe primary RLS, with a baseline	N=194 12 weeks	Primary: Relapse rates Secondary: Time to relapse; change in baseline IRLS, two domains of	Primary: Relapse rates (worsening of RLS symptoms) were significantly lower with gabapentin enacarbil ER compared to placebo (9 vs 23%; OR, 0.35; 95% CI, 0.2 to 0.8; P=0.02). Secondary: Time to relapse was significantly longer with gabapentin enacarbil ER compared to placebo (P=0.03).

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
All patients were deemed responders (improvements on IRLS and CGI-I at week 24 and stable while taking gabapentin enacarbil ER 1,200 mg/day for one month) at the end of a 24 week SB phase in which all patients received gabapentin enacarbil ER 1,200 mg/day.	IRLS score >15 and experiencing RLS symptoms on ≥15 nights during the month before screening and on four or more nights during the week long screening period and creatinine clearance ≥60 mL/minute		MOS Sleep Scale, PSQ, and RLS QOL questionnaire; proportion of patients rated as responders on CGI-C and CGI-I; onset and severity of RLS symptoms and safety	Placebo significantly decreased IRLS compared to gabapentin enacarbil ER (-3.9±6.49 vs -1.9±7.01, adjusted treatment difference, -2.1; P=0.03). Placebo significantly improved two MOS Sleep Scale domains compared to gabapentin enacarbil ER (sleep disturbance, 10.2±19.02 vs 2.3±18.32; adjusted treatment difference, -7.0; P=0.007, sleep adequacy, -11.6±24.01 vs -4.3±22.28; adjusted treatment difference, 7.7; P=0.02). Differences were not observed between the two treatments in the changes of daytime somnolence (P=0.18) and sleep quantity (P=0.72). With regard to the PSQ, a significantly greater proportion of patients receiving gabapentin enacarbil ER reported fewer nights with RLS symptoms (P=0.05), fewer night-time awakenings (P=0.04), and fewer hours awake per night due to RLS symptoms (P=0.02) compared to patients receiving placebo. No differences were observed between treatments with regard to reported higher overall quality of sleep (P=0.15) or ability to function during the daytime in the past week (P=0.54). No difference was observed between the two treatments in RLS QOL overall life-impact score (-2.2±7.86 vs -4.2±11.53; adjusted treatment difference, 1.9; P=0.19). There were no differences in the proportions of clinician-reported CGI-C (75 vs 67%; OR, 1.47; 95% CI, 0.8 to 2.8; P=0.24) and patient-reported CGI-I (88 vs 79%; OR, 1.8; 95% CI, 0.8 to 3.9; P=0.15) responders between gabapentin enacarbil ER and placebo. The estimated time to onset of RLS symptoms was 14.5 hours (95% CI, 13.5 to 17.5) for placebo. This measure could not be estimated for gabapentin enacarbil ER (vs placebo; P=0.04). Somnolence and dizziness were the most commonly reported treatment-emergent adverse events. The median duration throughout the entire trial was 42.0 and 29.5 days of somnolence and 13.0 and 26.0 for dizziness with

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
				gabapentin enacarbil ER and placebo. There were no clinically relevant changes in laboratory values, vital signs, or electrocardiograms with either treatment.
Kushida et al[16] PIVOT RLS-1 Gabapentin enacarbil ER 1,200 mg QPM vs placebo	DB, MC, PC, RCT Patients ≥18 years of age with moderate to severe primary RLS, and a baseline IRLS score >15 and experiencing RLS symptoms on ≥15 nights during the month before screening and on four or more nights during the week-long screening period	N=222 12 weeks	Primary: Change in IRLS from baseline, proportion of patients rated as responders on CGI-I Secondary: Change in baseline CGI-I, RLS QOL, MOS Sleep Scale, PghSD, RLS pain scale, and PSQ and safety	Primary: Gabapentin enacarbil ER significantly decreased IRLS compared to placebo (-13.2±9.21 vs -8.8±8.63; adjusted treatment difference, -4.0; 95% CI, -6.2 to -1.9; P=0.0003). A significantly greater proportion of patients were rated as clinician-reported CGI-I responders with gabapentin enacarbil ER compared to placebo (76.1 vs 38.9%; OR, 5.1; 95% CI, 2.8 to 9.2; P<0.0001). Secondary: More patients rated themselves as responders based on CGI-I with gabapentin enacarbil ER compared to placebo (73.6 vs 42.6%; P<0.0001). Gabapentin enacarbil ER significantly increased RLS QOL scores compared to placebo (21.4±17.00 vs 14.1±17.32; P<0.0001). All MOS Sleep Scale domains significantly improved with gabapentin enacarbil ER compared to placebo (daytime somnolence; P=0.0018, sleep quantity; P=0.0084, sleep adequacy; P<0.0001, and sleep disturbance; P<0.0001). With regard to the PghSD, there was no difference between gabapentin enacarbil ER and placebo in the increases in total sleep time (P=0.1870); however, gabapentin enacarbil ER significantly decreased average daily wake time after sleep onset compared to placebo (P=0.0033). In patients with baseline RLS pain scale scores ≥4, gabapentin enacarbil ER significantly decreased scores compared to placebo (-3.7 to -1.9; P<0.0001). All PSQ sleep outcomes improved significantly with gabapentin enacarbil ER compared to placebo (sleep quantity; P<0.0001, next-day functioning; P=0.0002, number of nights with RLS symptoms; P<0.0001, number of

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
				nighttime awakenings from RLS symptoms; P=0.0429, and number of hours awake due to RLS symptoms; P=0.0189). Treatment-emergent adverse events were reported by 82 and 74% of patients receiving gabapentin enacarbil ER and placebo, respectively. The most commonly reported adverse events with gabapentin enacarbil ER were somnolence and dizziness. The median duration of somnolence was 14.5 and 17.0 days with gabapentin enacarbil ER and placebo. The median duration of dizziness was 5.5 and 9.0 days.
Kushida et al[17] Gabapentin enacarbil ER 1,800 mg QPM vs placebo	DB, MC, PC, XO Treatment-naïve patients 18 to 69 years of age with a diagnosis of RLS and a baseline IRLS score >15 and experiencing RLS symptoms on ≥15 nights during the month before screening and on four or more nights during the week-long screening period	N=38 35 days (active treatment, 14 days in each group; wash out period, 7 days)	Primary: Change in baseline IRLS Secondary: Change in baseline IRLS at day seven and CGI-I at days eight and 15, and PSQ; 24-hour patient diary; poly-somnography; suggested immobilization test and safety	Primary: Gabapentin enacarbil ER significantly decreased IRLS compared to placebo (-12.1±6.5 vs -1.9±6.3; P<0.0001). Secondary: Gabapentin enacarbil ER significantly decreased IRLS compared to placebo after seven days (-11.7±7.5 vs -3.7±6.0; P<0.0001). The proportion of patients rated as "much improved" or "very much improved" was significantly greater with gabapentin enacarbil ER compared to placebo for both clinician- (76.5 vs 14.7%; P<0.0001) and patient-reported (85.3 vs 14.7%; P<0.0001) CGI-I. Gabapentin enacarbil ER significantly improved all PSQ questions, except ability to function, compared to placebo. Gabapentin enacarbil ER significantly decreased the amount of time in which RLS symptoms were present over 24-hour assessment compared to placebo (day seven, -184.4±240.7 vs -43.2±287.6 minutes; P=0.0001; day 14, -205.6±226.1 vs -97.9±252.9 minutes; P=0.005). On day 14, evening and night-time symptom severities were rated as absent or mild by 82 to 97% and 66 to 88% of gabapentin enacarbil ER- and placebo-treated patients. Gabapentin enacarbil ER significantly improved wake time after persistent sleep onset, wake time during sleep, and number of awakenings at day 14 compared to placebo. PLM parameters were numerically improved with

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
				gabapentin enacarbil ER compared to placebo; however, these differences were not significant. Gabapentin enacarbil ER significantly shortened Stage I sleep and extended Stage III/IV sleep compared to placebo. REM and Stage II sleep times were similar between the two treatments. With regard to the SIT test, on day 14, VAS scores steadily increased to a maximum value at 60 minutes of 21.8±29.8 and 40.3±29.8 with gabapentin enacarbil ER and placebo (P=0.0012). Treatment-emergent adverse events were reported by 77.8 and 38.9% of patients receiving gabapentin enacarbil ER and placebo, respectively. The most commonly reported were somnolence and dizziness. The majority of adverse events were mild or moderate in intensity.
Winkelman et al[18] Gabapentin enacarbil ER 1,200 mg QPM vs placebo	DB, MC, PC, XO,RCT Patients ≥18 years of age with a diagnosis of primary RLS a baseline IRLS score >15 and symptoms for at least four of seven evenings/nights and 15 days in the previous month	N=136 9 weeks (active treatment, 4 weeks in each group; washout period,1 week)	Primary: Change from baseline in WTDS at four and 10 weeks Secondary: PLMAI/hour of sleep, number of awakenings, PLMAWI, total sleep time, sleep efficiency, wake time after sleep onset, sleep onset latency, latency to persistent sleep time, IRLS scores, SPSD scores, PGI and CGI-I	Primary: The reduction in WTDS favored gabapentin enacarbil ER over placebo at four and 10 weeks (treatment difference, -26.0 minutes; 95% CI, -35.64 to -16.36; P<0.0001). Secondary: Treatment with gabapentin enacarbil ER was associated with reduced PLMAI over both crossover periods compared to placebo (treatment difference, -3.07; 95% CI, -5.04 to -1.10; P=0.002). A lower number of awakenings were reported in patients receiving gabapentin enacarbil ER compared to placebo (treatment difference, -2.49; 95% CI, -3.33 to -1.65; P<0.001). Significantly lower PLMAWI was observed with gabapentin enacarbil ER compared to placebo (treatment difference, -0.14; 95% CI, -0.21 to -0.06; P<0.001). Scores for total sleep time, sleep efficiency, wake time after sleep onset, sleep onset latency, latency to persistent sleep time were improved with gabapentin enacarbil ER treatment compared to placebo (P value not reported).

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
				Compared to patients receiving placebo, gabapentin enacarbil ER significantly reduced IRLS scores over the treatment period (-14.99 vs -8.42; P<0.0001). Significantly higher SPSD scores were reported in the gabapentin enacarbil ER group relative to placebo (P<0.0001). Compared to the placebo period, treatment with gabapentin enacarbil ER was associated with higher CGI-I scores (74.0 vs 36.2%; P value not reported) and PGI for "better night sleep" (75.4 vs 40.7%; P<0.001).
Ellenbogen et al[19] Gabapentin enacarbil ER 600 to 1,800 mg QPM	ES, MC, OL Adult patients with primary RLS who had completed one of four different double-blind, randomized controlled trials	N=573 1 year	Primary: Safety Secondary: Change from baseline in IRLS, proportion of patients rated as responders on CGI-I	Primary: Overall, 80.1% of patients reported at least one treatment emergent adverse event. Most were rated mild or moderate in intensity. The most commonly reported adverse events were somnolence and dizziness. Overall, 11.2% of patients withdrew from the study due to an adverse event. Somnolence and dizziness were the most common treatment-emergent adverse event leading to withdrawal. Twenty patients reported treatment-emergent and non-treatment-emergent serious adverse events; none of which were considered to be treatment-related, except of mental status change reported in one patient. One patient died due to a fall 25 days after receiving the final dose of gabapentin enacarbil ER 1,200 mg. Changes in clinical chemistry and hematology values were within the normal reference range at each assessment. No notable changes in vital signs were observed, and no patient withdrew because of adverse events relating to vital signs. Four patients had clinically significant treatment-emergent adverse events related to electrocardiogram abnormalities that were judged related to study drug in two patients and not related to study in two. ESS scores decreased with gabapentin enacarbil ER, and two patients indicated possible sleep attacks as assessed by the SOS questionnaire.

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
				Patients achieved a delay in the estimated median time to onset of the first RLS symptom. Secondary: IRLS scores were reduced further and the proportion of patients rated as responders on CGI-I increased with further gabapentin enacarbil ER treatment.
Inoue et al[20] Gabapentin enacarbil ER 1,200 mg QPM At week 12, the dose could be increased to 1,500 mg QPM in patients with an inadequate clinical response or decreased to 900 mg for patients with poor tolerance.	MC, OL Patients 20 to 80 years of age with a diagnosis of RLS and a baseline IRLS score of >15 with symptoms present for ≥15 days per month and four or more days per week	N=182 52 weeks	Primary: IRLS scores at week zero, one, two, four and every four weeks until week 52 and IRLS responder rate Secondary: CGI-I PSQI responder rates and subscores, SF-36 subscores and safety assessments	Primary: Gabapentin enacarbil ER treatment was associated with lower IRLS scores from baseline by the first week of treatment (14.5±0.6 vs 24.4±0.4; P<0.001). IRLS score continued to significantly decrease throughout the treatment period at all evaluation points through to week 52 (P<0.001 for all time periods). By week 52, gabapentin enacarbil ER was associated with lower IRLS scores compared to baseline (6.3±0.6 vs 24.4±0.4; P<0.001). The IRLS responder rate at week 52 was 80.3% (P value not reported). Secondary: Responder rates were 87.1% with regard to both CGI-I and PSQI scores for symptom improvement. Gabapentin enacarbil ER significantly improved PSQI and SF-36 subscores after 52 weeks compared to baseline values (P<0.001 and P=0.003, respectively). Adverse events considered to be treatment-related occurred in 90.7% of patients, the most common being dizziness (46.2%), somnolence (41.2%) and nasopharyngitis (30.2%). No changes in laboratory parameters were reported.
Ma et al[21] Pramipexole 0.125 QPM titrated to efficacy and tolerability over first four weeks	DB, MC, PC, PG, RCT Patients 18 to 75 years of age with moderate to severe	N=387 6 weeks	Primary: Change in IRLS scores at week six and proportion of CGI-I at week six	Primary: The mean change in IRLS scores from baseline to week six were significantly greater for patients randomized to receive pramipexole compared to placebo (-15.87±8.8 vs -11.35±8.5; P<0.0001). At week six, the proportion of patients with a CGI-I assessment of ‘‘much improved’’ and ‘‘very much improved’’ was 81.9% in the pramipexole group

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
vs placebo	symptoms of RLS, IRLS score of >15 with symptoms persistent for two or more days per week for the three months prior to study entry		Secondary: IRLS responder rate, PGI responder rate, ESS, RLS-6 rating scales and VAS	and 54.3% in the placebo group (P<0.0001). Secondary: Compared to placebo, the IRLS responder rate was significantly higher in patients randomized to receive pramipexole (73.8 vs 48.9%; P<0.0001). Similarly, more patients treated with pramipexole compared to placebo were considered to be PGI responders at week six (68.6 vs 43.5%; P<0.0001). There was no difference between the pramipexole and placebo groups with regard to ESS scores for falling asleep in various activities of daily living (-2.78±0.29 vs -3.22±0.40; P=0.3294). Greater improvements were reported in the pramipexole treatment group compared to placebo with regard to "satisfaction of sleep at night" (P<0.001), time of falling asleep" (P<0.0001) and "intensity of tiredness and sleepiness at day" (P=0.0048), the three components of RLS-6. There were reductions in VAS scores among both treatment groups at week six; however, greater improvements were reported with pramipexole compared to placebo (-4.0 ± 3.2 vs -2.8 ± 2.9, respectively; P<0.0001).
Högl et al[22] Pramipexole 0.125 to 0.750 mg QHS vs placebo The dose could be titrated weekly to a maximum of 0.750 mg QHS.	DB, MC, PC, RCT Patients with a diagnosis of RLS and a baseline IRLS score >15 who were experiencing symptoms at least twice per week in three months prior to	N=331 26 weeks	Primary: Change from baseline in IRLS score Secondary: IRLS responder rates, PGI and CGI-I responder rates, RLS-QOL and RLS-6 scores	Primary: Patients randomized to receive pramipexole reported a significantly greater reduction from baseline in IRLS score compared to placebo. Treatment differences between groups occurred as early as week one of treatment (-7.2 vs -4.6; P<0.001) and continued to weeks four (-12.0 vs -8.8; P<0.001), six (-13.6 vs -9.9; P<0.001), 12 (-13.2 vs -10.3; P<0.01), 18 (-13.2 vs -10.3; P<0.01) and 26 (-13.7 vs -11.1; P<0.01). Secondary: Overall, the IRLS responder rate was 58.6% for patients treated with pramipexole compared to 42.8% for placebo (P=0.0044). More patients randomized to pramipexole compared to placebo were determined to be CGI-I responders (68.5 vs 50.3%; P=0.0010), and PGI responders (62.3 vs 44.0% (P=0.0011).

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
	study entry and ferritin >30 ng/mL			Pramipexole treatment was associated with a significantly greater improvement in RLS-6 scores compared to placebo with regard to sleep satisfaction (P=0.0489), symptom severity while falling asleep (P=0.0315) and symptom severity during the night (P=0.0735). No differences in daytime symptom scores were reported (P>0.05)
Montagna et al[23] Pramipexole 0.125 to 0.750 mg QHS vs placebo The dose could be titrated weekly over the first four weeks to a maximum of 0.750 mg.	DB, PC, RCT Patients 18 to 80 years of age with a diagnosis of RLS and a baseline IRLS score >15, who were experiencing symptoms at least twice per week in three months in addition to a score of two or more on item 10 of IRLS (mood disturbance)	N=404 12 weeks	Primary: Change from baseline in IRLS and BDI-II score and responder rate to item 10 of IRLS Secondary: Responder rates on CGI-I, PGI, IRLS and BDI-II, change from baseline in HADS-A, RLS-6 and RLS QOL scores	Primary: After 12 weeks of treatment, patients receiving pramipexole experienced greater mean reductions in IRLS scores compared to the placebo group (-14.2 vs -8.1; P<0.0001). Similarly, a greater reduction from baseline in BDI-II total score occurred in the pramipexole group (-7.3 vs -5.8; P=0.0199). A higher responder rate to item 10 of the IRLS was reported in the pramipexole group compared to patients randomized to placebo (75.9 vs 57.3%; P<0.0001). Secondary: A significantly higher IRLS responder was reported at week 12 for patients receiving treatment with pramipexole compared to placebo (59.9 vs 32.7%; P<0.0001); however, no difference in BDI-II responders was reported (57.4 vs 52.7%; P=0.3821). Both CGI-I and PGI responder rates were significantly higher at the earliest time point measured (from day one for PGI, from day nine for CGI-I) in the pramipexole group compared to placebo (P<0.05 for both). At week 12, CGI-I responder rates were 69.3% with pramipexole compared to 36.9% for placebo (P<0.0001). A similar responder rate was observed for PGI at week 12 (62.9 vs 38.0%, respectively; P<0.0001). The median reduction in depression score on the HADS-A scale was significantly greater in the pramipexole group compared to placebo (-3 vs -2; P<0.0110). The placebo-adjusted changes in RLS QOL scores from baseline favored treatment with pramipexole (7.5; 95% CI, 7.2 to 7.8; P<0.0001).

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
				On RLS-6 scales, the median score reductions at week 12 were significantly greater in the pramipexole group for all items except severity of daytime RLS symptoms during activity (P<0.05 for all).
Inoue et al[24] Pramipexole 0.125 to 0.750 mg QHS vs placebo The dose could be titrated weekly over the first four weeks to a maximum of 0.750 mg.	DB, MC, PC, PG, RCT Patients 20 to 80 years of age with a diagnosis of primary RLS with a baseline IRLS score >15 and more than five PLM per hour while in bed	N=41 6 weeks	Primary: Change from baseline in PLMI Secondary: Change in PLMSI, total number of PLM, and total number of PLM during sleep, PLMWI, PLMAI, total number of awakenings/ arousals, and total number of PLM during sleep with arousals, SIT parameter scores, IRLS scores, responder rates on IRLS, PGI and CGI-I, ESS and PSQI scores	Primary: The median changes in PLMI were -23.15 in the pramipexole group and -5.85 in the placebo group (P=0.0146). Secondary: Compared to placebo, pramipexole significantly reduced median values of PLMSI (-20.95 vs -5.75; P=0.0317), total number of PLM (-184.5 vs -46.5; P=0.0146) and total number of PLM during sleep (-137.0 vs -36.5; P=0.0186). There were no statistically significant differences between pramipexole and placebo for PLMWI (-20.35 vs -4.30; P=0.1047), PLMAI (-6.85 vs -2.95; P=0.0984), total number of awakenings/arousals (-35.5 vs -15.5; P=0.5296), and total number of PLM during sleep with arousals (-43.0 vs -22.0; P=0.0899). There were no differences between pramipexole and placebo with regard to SIT-PLM (P=0.5263), SIT-VAS average score (P=0.7812) or SIT-VAS maximum score (P=0.9534). Pramipexole was associated with a significant difference in SIT-PLM in a subset of patients with >15 movements/hour at baseline (-68.0 vs -16.5; P=0.0489). Patients randomized to receive pramipexole reported significantly lower IRLS scores compared to placebo at week one, two, four and six (P<0.001 for all time points). Compared to the placebo group, a significantly higher proportion of patients treated with pramipexole were considered IRLS treatment responders (70.0 vs 33.3%; P=0.0294). The proportion of PGI responders at week six was 95.0% of pramipexole-treated and 38.1% of placebo-treated patients (P<0.0001). The proportion of clinician-assessed responders (CGI-I) was significantly

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
				higher in the pramipexole group compared to placebo (80.0 vs 52.4%; P=0.0488). There were no significant differences in ESS scores between patients treated with pramipexole or placebo (P=0.2274). The mean change in PSQI score from baseline was significantly greater for patients treated with pramipexole compared to placebo at week six (P=0.0016).
Manconi et al[25] Pramipexole 0.25 mg at bedtime on day two vs placebo	DB, PC, PRO, RCT Patients 18 to 70 years of age with a diagnosis of RLS and IRLS score >20, experiencing symptoms at least twice per week in the six months prior to study entry and PLMS >10 during baseline PSG	N=32 2 days	Primary: Changes VAS scores for symptom severity Secondary: PLMS index of entire night, during REM and nREM sleep, total number of LM and total number of PLMS sequences	Primary: Following a single dose of pramipexole, the mean VAS score changed from 7.4±1.68 to 1.3±1.62 (P<0.00001). In the placebo group, no change in VAS score from baseline was reported (P=NS). Secondary: Mean PLMS index scoring for the entire night following treatment was significantly lower for patients treated with pramipexole compared to placebo (9.4 vs 48.8; P=0.0002). The PLMS index was lower during REM sleep for patients treated with pramipexole compared to placebo (17.4 vs 32.0; P value not reported). Compared to placebo the mean PLMS index scoring during nREM sleep was significantly lower with pramipexole (19.6 vs 64.2; P=0.00005). Compared to placebo fewer total PLMS sequences were reported in patients receiving treatment with pramipexole (7.1 vs 10.5; P value not reported).
Hornyak et al[26] Pramipexole 0.125 to 0.750 mg QHS vs placebo The dose could be titrated to a maximum of 0.750 mg.	Subanalysis of two DB, MC, PC, RCT (trials 615 and 604) Patients with idiopathic RLS symptoms on two or more days per week throughout the	N=369 and N=604 (for trials 615 and 604, respectively) 12 weeks	Primary: Change from baseline in VAS scores for RLS-related limb pain Secondary: Not reported	Primary: In trial 615, the median 12-week change from baseline VAS limb-pain score was -33.5 for pramipexole and -11.0 for placebo (P<0.0001). A VAS score decrease of ≥30% occurred in 72.5% pramipexole-treated patients compared to 51.4% placebo-treated patients (OR, 2.49; P<0.0001). In trial 604, the median 12-week reduction in VAS limb-pain score was -31.0 in the pramipexole treatment group and -11.0 for placebo (P<0.0001). A reduction of VAS score by ≥30% occurred in 68.7% of the pramipexole group, compared with 45.7% of the placebo group (P<0.0001).

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
	prior three months, and a baseline IRLS score >15			Secondary: Not reported
Oertel et al[27] Pramipexole 0.125 to 0.750 mg QHS vs placebo The dose could be titrated in weekly intervals to a maximum of 0.750 mg.	DB, MC, RCT Patients 18 to 80 years of age with a diagnosis of primary RLS and a baseline IRLS score of >15 with moderate to severe symptoms present for at least two days per week	N=345 6 weeks	Primary: Change from baseline in the IRLS score and CGI-I responder rate Secondary: Proportion of PGI and IRLS responders, VAS scores for symptom severity and safety	Primary: The reduction from baseline in IRLS score was significantly higher in the pramipexole treatment group compared to placebo (-12.3 vs -5.7; P<0.001). More patients receiving pramipexole were considered to be CGI-I responders than placebo (62.9 vs 32.5%; P<0.0001). Secondary: A greater proportion of patients were determined to be both IRLS and PGI responders in the pramipexole treatment group compared to placebo (52.5 vs 28.9% and 61.6 vs 31.6% respectively; P<0.0001 for both). Pramipexole demonstrated a benefit over placebo in severity of symptoms while getting to sleep (P<0.0001), during the course of the night (P<0.0001) and during the day (P<0.0001). The most frequently reported adverse events associated with pramipexole treatment compared to placebo included nausea (9.6 vs 5.2%), fatigue (9.1 vs 4.3%) and headache (7.0 vs 6.1%).
Partinen et al[28] Pramipexole 0.125 mg QHS pramipexole 0.25 mg QHS vs pramipexole 0.50 mg QHS vs	DB, PC, PG, RCT Patients 27 to 76 with moderate to severe idiopathic RLS with a baseline IRLS score >15 and at least five PLMS per hour	N=109 3 weeks	Primary: Change from baseline in PLMI index Secondary: IRLS, CGI and PGI responders, quality of sleep, daytime well being, PLMSI, PLMWI, PLMAI,	Primary: Compared to placebo, all doses of pramipexole demonstrated significant reductions from baseline in PLMI index (-52.70, -31.05, -26.55 and -30.00 vs -3.00 for pramipexole 0.125 mg, 0.25 mg, 0.50 mg, 0.75 mg and placebo, respectively; P<0.05 for all strengths compared to placebo). Secondary: The PGI responder rates were higher across the pramipexole groups than in the placebo group. By week three, the proportion of patients rating their condition as 'very much better' was 27.2% in the 0.50 mg group and 23.8% in the 0.75 mg group, compared to 4.8% in the placebo group. In the 0.50 mg and 0.75 mg groups, respectively, 50 and 33.3% of patients were classified

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
pramipexole 0.75 mg QHS vs placebo	and weekly RLS symptoms that disrupted sleep within previous three months		PLM, total number of PLMS, PLMSA, total number of awakenings/ arousals during sleep, sleep latency, sleep efficiency, total sleep time, percentage of delta sleep, percentage of stage REM sleep	as 'much better,' compared with 33.3% in the placebo group (P=0.039 and P=0.041 for pramipexole 0.50 and 0.75 mg). More than 60% of patients across all pramipexole treatment groups were rated as being 'much improved' or 'very much improved' (CGI-I responders) following three weeks of therapy, compared to 42.9% of patients in the placebo group. There was no difference in responder rates for patients treated with pramipexole 0.125 mg compared to placebo (P>0.31); however, the proportion of responders treated with the higher pramipexole doses (0.25, 0.50 and 0.75 mg) was significant compared to placebo (P=0.022, P=0.001 and P=0.008, respectively). No differences were reported between any of the pramipexole treatment groups and placebo with regard to daytime sleepiness. Subjective scores for sleep quality improved in all pramipexole and placebo groups. Compared to placebo (-3.45), the median changes from baseline PLMSI were significantly greater with all four doses of pramipexole (0.125 mg: -20.90, 0.25 mg: -26.65, 0.50 mg: -22.45, 0.75 mg: -27.00; P<0.05 for all compared to placebo). The reduction in PLMWI were significantly greater with all doses of pramipexole compared to placebo (0.125 mg: -41.20, 0.25 mg -36.50 and 0.50 mg: -38.45 vs -11.00; P<0.05 for all compared to placebo) No significant difference in PLMAI, total number of PLM during sleep with arousal or total number of awakenings/arousals occurred between pramipexole and placebo with the exception of the 0.25 mg dose (P<0.05). Significant improvements in sleep latency scores were reported with pramipexole 0.125 mg, 0.50 mg and 0.75 mg compared to placebo (P<0.05 for all), but not for the 0.25 mg group. No significant differences in sleep efficiency, total sleep time or time spent in stage REM sleep were reported between any of the pramipexole groups and

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
				placebo. The percentage of time spent in delta sleep significantly improved in the pramipexole 0.25 and 0.75 mg groups (P<0.05) compared to placebo. The adjusted mean change from baseline in IRLS score was -6.08 for placebo compared to -11.87, -15.18, -17.01 and -15.86 for patients receiving pramipexole 0.125 mg, 0.25 mg, 0.50 mg and 0.75 mg, respectively (P<0.05 for all strengths compared to placebo.
Inoue et al[29] Pramipexole 0.25 mg to 0.75 mg QHS The dose could be titrated every two weeks to a maximum of 0.75 mg QHS or decreased to 0.125 mg QHS according to the needs of the patient.	ES, OL Patients 20 to 80 years of age with a diagnosis of primary RLS and baseline IRLS score >15 who had completed a prior six-week double-blind trial	N=141 46 weeks	Primary: Change in IRLS scores and responder rates, CGI-I and PGI responder rates, PSQI and Japanese ESS scores Secondary: Not reported	Primary: During the open-label treatment period, the mean IRLS score decreased from baseline (10.1) to 8.2 at week 12, and 4.9 at week 52. The mean IRLS score at each visit after week 28 was significantly lower compared to baseline, with the exception of week 32 (P<0.01 for all). The proportion of IRLS responders at each visit from week 24 to 52, was significantly higher compared to baseline, except for week 32 (P<0.05 for all time periods). The proportions of CGI-I and PGI responders were 81.2% and 79.0% respectively, at week 12 and 94.1% and 92.4%, respectively, at week 52 (P<0.05 for all). The mean PSQI change during the open-label period was -3.1 (95% CI, -3.8 to -2.5). By week 52, the mean Japanese ESS score decreased by -4.0 (95% CI, -4.9 to -3.1). Of the patients enrolled in the extension phase, 87.9% experienced an adverse event, mostly of mild or moderate intensity. No deaths or episodes of sudden onset of sleep were reported. The most common adverse events were nasopharyngitis, somnolence, headache, nausea and vomiting. Only small changes in laboratory parameters, systolic and diastolic blood pressure, and pulse rate were observed. No new findings on ECG were reported.

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
				Secondary: Not reported
Winkelman et al[30] Pramipexole 0.125 mg QHS The dose could be titrated by 0.125 to 0.25 mg every week until symptoms were eliminated.	RETRO Patients with a confirmed diagnosis of RLS by IRLS group criteria who were maintained on pramipexole for at least six months	N=59 Median duration of 21.2 months	Primary: Rates of augmentation and pramipexole tolerance Secondary: Not reported	Primary: Augmentation developed in 32% (19/59) of patients treated with pramipexole. The mean time to onset of augmentation was 8.8±6.5 months. Patients treated with pramipexole were significantly more likely to develop augmentation if the patient experienced augmentation to prior levodopa therapy (P<0.05). Pramipexole tolerance occurred in 46% (27/59), of patients. In these patients, mean total daily dose increased from 0.43 mg to 0.82 mg over the period of treatment. The duration of treatment was longer in the group with tolerance compared to patients who did not develop tolerance (P=0.04) although there was no significant correlation between duration of pramipexole treatment and change in pramipexole dose. Ten percent of patients had persistent symptoms after sleep onset, with this being more common in patients who developed augmentation compared to those without augmentation (P=0.08), and in those with tolerance compared to those without tolerance (P=0.08).
Inoue et al[31] Pramipexole 0.25 mg QHS vs pramipexole 0.50 mg QHS vs pramipexole 0.75 mg QHS	DB, MC, PC, RCT Patients 20 to 80 years of age with primary RLS and a baseline IRLS score >15	N=154 6 weeks	Primary: Change from baseline in IRLS Secondary: IRLS, PGI and CGI-I responder rates at week six, Japanese ESS, PSQI and laboratory parameters	Primary: Pramipexole was associated with reductions in IRLS score from baseline across all treatment groups (0.25 mg: -12.3; 95% CI, -14.5 to -10, 0.50 mg: -12.5; 95% CI, -14.6 to -10.4, 0.75 mg: -13.9; 95% CI, -13.9 to -9.6). Secondary: At week six, IRLS responder rates were 60.4, 58.5 and 49.1% for patients receiving 0.25 mg, 0.50 mg and 0.75 mg of pramipexole, respectively. Responder rates at week six were significantly higher compared to responder rates at week two for the 0.25 and 0.50 mg doses only (P=0.0218, P=0.0016 and P=0.0833, respectively). The PGI responder rates at week six were 72.9, 79.3 and 67.9% for patients receiving pramipexole doses of 0.25 mg, 0.50 mg and 0.75 mg, respectively.

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
				A higher responder rate was reported across all groups at week six compared to week two (P<0.05 for all). The CGI-I responder rates following week six of treatment were 77.1, 75.5 and 69.8% for the 0.25 mg, 0.50 mg and 0.75 mg pramipexole treatment groups, respectively. All responder rates were significantly higher compared to their respective percentages at week two (P<0.05 for all). Reductions from baseline in PSQI occurred in all treatment groups by week six (0.25 mg: -3.2; 95% CI, -4.0 to -2.5, 0.50 mg: -3.2; 95% CI, -3.9 to -2.5, 0.75 mg: -2.5; 95% CI, -3.3 to -1.8). Patients in all three groups pramipexole groups experienced an improvement in Japanese ESS score compared to their respective baseline values (0.25 mg: -2.6; 95% CI, -3.7 to -1.4, 0.50 mg: -3.0; 95% CI, -4.1 to -1.9, 0.75 mg: -2.3; 95% CI, -3.4 to -1.2). No differences in laboratory parameters occurred with any of the pramipexole treatment groups.
Winkelman et al[32] Pramipexole 0.25 mg QHS vs pramipexole 0.50 mg QHS vs pramipexole 0.75 mg QHS vs placebo	DB, PC, RCT Patients 18 to 80 years of age with moderate to severe RLS and baseline IRLS score of ≥15 and symptoms least two days per week	N=344 12 weeks	Primary: Change from baseline in IRLS scores and CGI-I responder rate Secondary: IRLS and PGI responder rates, VAS scores, ESS, RLSQOL	Primary: Each dose of pramipexole demonstrated a significantly greater reduction in IRLS score from baseline compared to placebo (-12.8 for 0.25 mg, -13.8 for 0.50 mg, -14.0 for 0.75 mg vs -9.3 for placebo; P<0.01 for all). Seventy-two percent of patients treated with pramipexole were designated responders compared to 51.2% of those receiving placebo (P=0.0005). Individual results were also significant and were reported as 74.7% for the 0.25 mg dose (P<0.0005), 67.9% for the 0.50 mg dose (P<0.0484) and 72.9% for the 0.75 mg dose (P<0.0038). Secondary: The IRLS responder rate was significantly greater with all doses of pramipexole (61.4 to 62.1%) compared to placebo (42.4%; P<0.05 for all groups compared to placebo).

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
				The PGI responder rate was 61.4% with pramipexole patients and 44.7% of placebo-treated patients (P=0.0056). However, when assessed individually, only the difference between the 0.25 mg group and placebo group reached statistical significance (P value not reported). Changes from baseline in RLS symptom severity while getting to sleep (-43.1 vs -29.0; P=0.0001), during the night (-41.3 vs -24.3; P<0.0001), during the day (-16.0 vs -9.2; P=0.0081), as well as satisfaction with sleep (-38.4 vs -25.8; P=0.0016) all significantly favored pramipexole treatment over placebo, yet the difference in daytime somnolence between active therapy and placebo did not reach statistical significance (P=0.3028). Greater improvements in RLS QOL scores were evident with pramipexole compared to placebo at all doses (P=0.0041 for 0.25 mg, P=0.0002 for 0.50 mg and P=0.0029 for 0.75 mg).
Manconi et al[33] Pramipexole 0.25 mg at bedtime on day two vs bromocriptine 2.5 mg at bedtime on day two vs placebo	AC, PC, PG, PRO, RCT, SB Treatment naïve patients 18 to 70 years of age diagnosed with RLS for at least six months with symptoms more than twice-weekly and an IRLS score of ≥20	N=45 2 days	Primary: PLMS index during entire night, REM and nREM sleep, total LM index, total number of PLMS sequences and periodicity index	Primary: The PLMS index during the entire night was significantly reduced with pramipexole compared to both bromocriptine and placebo (-33.8 vs -20.5 and 8.9, respectively; P=0.0009). Pramipexole treatment was also associated with greater reductions in PLMS during nREM sleep compared to bromocriptine and placebo (-34.7 vs -25.4 and 9.6, respectively; P=0.002). There were no differences in PLMS index between the treatment groups during REM sleep (P=NS). Pramipexole was associated with a significantly lower total LM index for the total duration of sleep compared to both bromocriptine and placebo treatment groups (-31.4 vs -20.2 and 8.7; P=0.0025). The total number of PLMS sequences for the total sleep duration did not differ significantly between the treatment groups (P=NS).
Bassetti et al[34] Pramipexole 0.125 to 0.750 mg QHS,	DB, MC, RCT, XO Patients 25 to 85 years of age	N=39 10 weeks (active treatment, 4	Primary: Change from baseline in PLMI Secondary:	Primary: Combining both crossover periods, pramipexole was noninferior to levodopa/benserazide with regard to the mean change from baseline in PLMI scores (-11.5 vs -7.7; P=0.00015).

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
vs levodopa/benserazide ER 125 to 375 mg QHS The dose of pramipexole could be increased every three to five days to a maximum of 0.750 mg QHS.	with RLS and presented with symptoms of more than five PLM/h during bedtime on three consecutive nights	weeks in each group; washout period, 2 weeks)	Change in IRLS score, VAS scores during the day, at sleep onset and at night, SF-36 scores for QOL, daytime sleepiness, and mood, ESS and HADS scores	Secondary: There was a trend towards lower IRLS scores with pramipexole compared to levodopa/benserazide after both crossover periods, however, differences between the groups did not reach statistical significance (-7.2 vs -4.0; P=0.054). Patients treated with pramipexole reported significantly lower VAS scores for symptoms during the day (-8.5 vs 1.8; P=0.05); however, there were no differences in scores at sleep onset (-9.3 vs -8.6; P=0.67) or during the night (-14.1 vs -18.5; P=0.65). After both crossover periods, QOL scores for daytime sleepiness were similar between the pramipexole and levodopa/benserazide treatment groups (43.5 vs 45.0; P value not reported). Similar results were reported for the mental component of the SF-36 (43.1 vs 42.5, respectively; P value not reported). The ESS scores were similar among the two treatment groups. Reported HADS scores were similar between patients in both treatment groups with regard to anxiety (8.0 vs 8.3 for pramipexole and levodopa/benserazide, respectively; P value not reported) and depression (11.6 vs 11.2, respectively; P value not reported).
Manconi et al[35] Pramipexole 0.25 mg at bedtime on day two vs ropinirole 0.50 mg at bedtime on day two vs placebo	AC, DB, PC, PG, PRO, RCT Treatment naïve patients diagnosed with RLS for at least six months with symptoms more than twice weekly and a baseline IRLS score of ≥20	N=45 2 days	Primary: PLMS index during entire night, REM and nREM sleep, total LM index and total number of PLMS sequences Secondary: Not reported	Primary: The PLMS index was significantly lower with ropinirole treatment compared to pramipexole and placebo during nREM sleep (-47.1 vs -37.2 and 9.4; P=0.0004), and the entire nights total sleep (-40.2 vs -33.8 and 8.9; P=0.0005) but not during REM sleep (P=NS). Patients treated with ropinirole had a significantly lower LM index compared to pramipexole and placebo during the entire nights total sleep (-40.7 vs -31.4 and 8.7; P=0.001). There was no difference in the number of PLMS sequences among patients randomized to receive pramipexole, ropinirole or placebo (P=NS).

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
Baker et al[36] Pramipexole 0.125 to 0.750 mg/day vs ropinirole 0.25 to 6.00 mg/day vs rotigotine 0.5 to 4.5 mg/day vs sumanirole 0.5 to 4 mg/day	MA (14 RCT) Patients with a mean age of 51 to 76 years old with moderate-to-severe RLS	N=3,197 Up to 12 weeks	Primary: Percentage of responders to medications determined by the CGI-I scale and change in the IRLS score from baseline Secondary: Safety	Primary: The nonergot dopamine agonists demonstrated a significantly greater response as measured by the CGI-I scale compared to placebo (RR, 1.36; 95% CI, 1.24 to 1.49). Each individual agent, showed a greater response on CGI-I scale compared to placebo with the exception of sumanirole (pramipexole, RR, 1.60; 95% CI, 1.34 to 1.92, ropinirole, RR, 1.32; 95% CI, 1.21 to 1.43, rotigotine, RR, 1.41; 95% CI, 1.12 to 1.79). Results of the second outcome significantly favored nonergot dopamine agonist treatment with a weighted mean difference in the IRLS score of -4.83 (95% CI, -6.42 to -3.43) for the class, -7.16 (95% CI, -9.77 to -4.54) for pramipexole and -3.50 (95% CI, -4.75 to -2.25) for ropinirole. Results were not reported for rotigotine or sumanirole. Secondary: An increased risk of withdrawal was observed as a class relative to placebo (RR, 1.35; 95% CI, 1.00 to 1.81), however only ropinirole was associated with a significant difference in withdrawal upon subgroup analysis (RR, 1.49; 95% CI, 1.06 to 2.10) compared to pramipexole (RR, 1.15; 95% CI, 0.49 to 2.69), rotigotine (RR, 0.46; 95% CI, 0.08 to 2.58) and sumanirole (RR, 1.11; 95% CI, 0.06 to 19.45).
Benes et al[37] Ropinirole 0.50 to 4.0 mg QPM vs placebo	DB, MC, PC, PG, RCT Patients 18 to 80 years of age with moderate to severe idiopathic RLS, baseline IRLS score >15, RLS diagnostic index score of ≥11	N=266 12 weeks	Primary: Change from baseline in MADRS Secondary: BDI-II, HAMD, IRLS scores, CGI-I and CGI-S responder rates, MOS, safety and tolerability	Primary: After 12 weeks of treatment, patients treated with ropinirole had significantly greater reductions in MADRS scores compared to placebo (-10.1 vs -6.5; P<0.001). Secondary: In both the ropinirole and in the placebo groups, the total HAMD score decreased from baseline by -8.2 ± 5.5 and -5.4 ± 6.4 points, respectively. The adjusted difference between the two treatment groups was -2.7 points in favor of ropinirole (95% CI: -4.4 to -1.1; P<0.001). The total BDI-II score decreased by 8.6 ± 7.0 and 6.5 ± 7.8 points in the

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
	and MADRS score of ≥12 at baseline in addition to experiencing RLS symptoms ≥15 nights in the four weeks preceding enrollment			ropinirole and placebo groups, respectively (mean difference, -2.6, 95% CI, -4.6 to -0.7; P=0.009). At week 12, the adjusted mean changes from baseline in IRLS were -14.7 points (95% CI, -16.1 to -13.4) in the ropinirole group and -9.9 points (95% CI, -12.2 to -7.6) in the placebo group (mean difference, -4.8; 95% CI, -7.5 to -2.1; P<0.001) The CGI-I response rate was 64.3% in the ropinirole group and 46.7% in the placebo group (P=0.02). Similarly, 34.5% of the patients in the ropinirole group and 13.3% of the patients in the placebo group were deemed CGI-S responders (P<0.005). In all MOS sleep subscales, patients randomized to receive ropinirole improved more than the placebo group. Significant treatment differences were found for the subscales ‘‘sleep disturbance,’’ ‘‘sleep adequacy,’’ and ‘‘sleep quantity’’ (P<0.001 for all). Treatment-emergent adverse events were reported in 62.4% of patients treated with ropinirole compared to 38.55% of patients receiving placebo. More patients treated with ropinirole experienced an adverse event that lead to a dose reduction (25.9 vs 17.9%; P value not reported). The most commonly reported adverse events that occurred more frequently with ropinirole compared to placebo were nausea, headache, fatigue, dizziness, vomiting, abdominal pain and hyperhidrosis.
Kushida et al[38] Ropinirole 0.50 to 6.0 mg divided in two daily doses vs placebo	DB, MC, PC, RCT Patients 18 to 79 years of age with RLS and a baseline IRLS score of ≥20 and >15 on the	N=362 12 weeks	Primary: Change from baseline in IRLS, CGI-I and PGI responder rates Secondary: Not reported	Primary: Ropinirole was associated with a statistically significant reduction in IRLS total score compared to placebo (mean treatment difference, -4.11; 95% CI, -6.08 to -2.14; P<0.001). A significantly greater proportion of patients randomized to ropinirole treatment were classified as CGI-I responders at all assessment points compared to placebo (OR, 2.43; 95% CI, 1.57 to 3.76; P<0.001).

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
	insomnia severity index with ≥15 nights of RLS symptoms within the previous month and symptom onset occurred after 5 PM			Higher PGI responder rates were achieved with ropinirole compared to placebo at all assessment points beginning on day one (OR, 1.99; 95% CI, 1.16 to 3.42; P=0.013) and through day seven (P<0.05 for days two through seven) and at week 12 (OR, 3.24; 95% CI, 2.05 to 5.12; P<0.001).
Montplaisir et al[39] Ropinirole 0.50 to 4.0 mg QHS vs placebo All patients received ropinirole for the first 24 weeks. If a response was achieved (six point reduction in IRLS score), patients were then randomized to continue ropinirole or placebo for additional 12 weeks.	DB, MC, PC, RCT Patients 18 to 80 years of age with a diagnosis of RLS and a baseline IRLS score of ≥15 and a history of ≥15 nights of RLS symptoms in previous month	N=202 36 weeks	Primary: Proportion of patients relapsing during double-blind treatment phase Secondary: Time to relapse, proportion of patients withdrawing due to lack of efficacy, CGI-I responders, change in IRLS, MOS, RLS QOL scores	Primary: During the double-blind treatment phase, relapse rates were higher in the placebo group (57.8%) compared to the ropinirole group (32.6%). Those in the ropinirole group were significantly less likely to relapse during treatment (OR, 0.33; 95% CI, 0.13 to 0.81; P= 0.0156). Secondary: The median time to relapse was not calculated for the ropinirole group, as less than 50% of patients relapsed. In the placebo group, the median time to relapse was 28 days. The time for 25% of patients to relapse was 56 days for patients taking ropinirole and 25 days for the placebo group. Patients treated with ropinirole were less likely to relapse compared to patients receiving placebo (OR, 0.40; 95% CI, 0.21 to 0.77; P=0.0006). Withdrawal rates due to lack of efficacy were higher in the placebo group (51.3%) compared to ropinirole (29.3%; OR, 0.40; 95% CI, 0.1 to 0.9; P=0.0372). Twelve weeks after randomization (week 36), more patients in the ropinirole group (68.9%) compared to the placebo group (46.7%) were CGI-I responders compared to placebo group (OR, 2.6; 95% CI, 1.1 to 6.3; P=0.0298). The treatment difference in IRLS score favored ropinirole treatment over placebo (-4.6 points; 95% CI, -8.6 to -0.6; P=0.0246).

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
				The treatment difference favored ropinirole for sleep disturbance (treatment difference, -21.9; 95% CI, -31.8 to -10.0; P=0.0003), somnolence (treatment difference, -9.1; 95% CI, -16.4 to -1.9; P=0.0136) sleep quantity (treatment difference, 60 minutes; 95% CI, 6 to 120; P=0.0346). Scores for sleep adequacy were not significantly different between the treatment groups. During the double blind phase, RLS QOL scores decreased significantly further with placebo compared to ropinirole (-17.0 vs -5.2; P=0.004).
Allen et al[40] Ropinirole 0.50 to 4.0 mg QHS vs placebo	DB, MC, PC, PG, RCT Patients 18 to 79 years of age who met IRLS Study Group criteria for RLS and had five PLMS per hour on PSG screening	N=65 12 weeks	Primary: Change In PLMS/hour Secondary: Change in PLMA/hour, PLMW/hour, sleep latency, sleep efficiency, percentage of TST spent in stage II sleep, percentage of TST spent in stage III or IV sleep, MOS rating scales, IRLS total score	Primary: The adjusted treatment difference in PLMS/hour significantly favored ropinirole treatment over placebo (-27.2; 95% CI, -39.1 to -15.4; P<0.0001). For patients randomized to receive ropinirole, the PLMS per hour was reduced to the normal level of five or fewer for 53.6% of patients and was 15 or fewer for 71.4% of patients at week 12. In the placebo group, PLMS per hour were reduced to five or fewer for 14.8% of patients and to 15 or fewer for 40.7% of patients at week 12. Secondary: After 12 weeks of treatment the PLMA per hour decreased from 7.0 to 2.5 in the ropinirole group compared to an increase from 4.2 to 6.0 in the placebo group, (-4.3; 95% CI, -7.6 to -1.1; P=0.0096). There was a significance difference in PLMW/hour from baseline favoring ropinirole treatment over placebo (-39.5; 95% CI, -56.9 to -22.1; P<0.0001). The average sleep latency in the ropinirole group was significantly decreased compared to placebo group (treatment difference, -9.8 minutes; 95% CI, -17.2 to -2.4; P=0.0106). There were significant differences between the treatment groups with regard to changes in the minutes and percentage of time spent in stage II sleep, which increased in the ropinirole group but decreased in the placebo group (P=0.0001). Conversely, an increase in minutes of stage III/IV sleep was

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
				demonstrated in the placebo group compared to a smaller increase from baseline in the ropinirole group (P=0.0038). At week 12, ropinirole treatment was associated with significant improvements in the "sleep adequacy" component of the MOS sleep scale compared to treatment with placebo (P=0.0316). The differences between the treatments for the other components of the MOS sleep scale were not significant. There was a trend toward greater improvements in IRLS score with ropinirole; however, the difference between groups was not significant (-1.2; P=0.5645).
Adler et al[41] Ropinirole 0.50 to 6.0 mg divided in two daily doses vs placebo	DB, PC, XO Patient ≥18 years of age with a diagnosis of RLS and a baseline IRLS score of ≥10	N=22 9 weeks (active treatment, 4 weeks in each group; washout period,1 week)	Primary: Change in mean RLS scores Secondary: Global change score, ESS, RLS symptom diary and adverse events	Primary: The mean RLS scores were lower at the end of the ropinirole treatment period compared with at the end of the placebo treatment period (13±12 vs 25±7; P<0.001). Secondary: Global change scores for improvement in symptoms were higher in the ropinirole treatment group compared to placebo (P<0.001). There was no difference between the treatment groups with regard to ESS scores (P=0.31). Diary scores for symptoms were significantly lower for patients treated with ropinirole (0.12) compared to the placebo treatment group (0.23; P=0.008). Adverse events with onset during ropinirole treatment were significantly more frequent than adverse events with onset during placebo treatment, notably dizziness and nausea (P<0.05). Two patients discontinued study drug during ropinirole treatment (one due to lack of efficacy, one with dizziness, nausea, and vomiting) and one during placebo treatment (syncope).
Trenkwalder et al[42] Ropinirole 0.25 to 4.0 mg QHS vs	DB, PC, MC, RCT Patients 18 to 79 years of age with RLS and a	N=284 12 weeks	Primary: Change from baseline in IRLS score to week 12 Secondary:	Primary: The mean reduction in total IRLS score at week 12 was significantly greater in the ropinirole treatment group compared to placebo (-11.04 vs -8.03; adjusted difference, -3.01; 95% CI, -5.03 to -0.99; P=0.0036). Secondary:

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
placebo	baseline IRLS score of >15 and experiencing symptoms at least 15 nights/month in the previous month or prior to treatment		CGI-I responder rate, change from baseline in the total IRLS score to week one, impact of treatment on sleep, RLS QOL and safety	A significantly greater proportion of patients met CGI-I criteria in the ropinirole group compared to placebo (53.4 vs 40.9%; OR, 1.7; 95% CI, 1.02 to 2.69; P=0.0416). Improvements in the mean total IRLS score were significantly greater with ropinirole compared to placebo after one week (-8.19 vs -5.14; adjusted difference, -3.05; 95% CI, -4.72 to -1.38; P=0.0004). There were significant improvements in sleep adequacy (P=0.0015), quantity (P=0.0331), daytime somnolence (P=0.0064) and sleep disturbance (P=0.0245) observed with ropinirole treatment relative to placebo. Similarly, significant improvements in QOL scores occurred with ropinirole treatment compared to placebo (17.1 vs 12.6; P=0.0314). Nausea and headache occurred more frequently with ropinirole treatment (37.7 and 19.9%) compared to placebo (6.5 and 16.7%, respectively).
Walters et al[43] Ropinirole 0.125 to 4 mg daily vs placebo	DB, MC, RCT Patients 18 to 79 with primary RLS with a baseline IRLS score of ≥15 and experiencing symptoms ≥15 nights/month in the previous month or prior to treatment	N=267 12 weeks	Primary: Change in IRLS score at week 12 Secondary: CGI-I responder rate at week one and 12, time to response on the CGI-I scale, change in IRLS score at week one, time to IRLS response, change from baseline in domains of the MOS sleep scale, the RLS QOL	Primary: At week 12, in the mean reduction total IRLS score, was significantly greater in the ropinirole treatment group compared to placebo (-11.2 vs -8.7; P=0.0197). Secondary: A significantly greater proportion of patients met CGI-I criteria in the ropinirole group compared to placebo at week 12 (59.5 vs 39.6%; P=0.001). Similar results were found in regard to CGI-I responder rates at week one, with 36.6% of patients taking ropinirole and 16.4% of placebo-treated patients considered to be responders (P=0.0003). The median time to a response was shorter with ropinirole compared to (14 vs 22 days; P=0.0004). After the first week of treatment, patients treated with ropinirole had significantly greater reductions in IRLS compared to placebo (-8.4 vs -4.8; P<0.0001), although the median time to a response was not different between the groups (P=0.0588).

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
			questionnaire, the MOS SF-36 Health Survey and the WPAI questionnaire	Ropinirole treatment significantly improved symptoms of daytime somnolence (P=0.0043), sleep disturbance (P<0.0001), sleep adequacy (P<0.0001) and sleep quantity (P=0.0097) compared to placebo. Compared to placebo, ropinirole treatment improved the overall life-impact score on the RLS QOL questionnaire (17.40 vs 12.90; P=0.0263), mental-health domain (P=0.0041), social functioning (P=0.0331) and vitality (P=0.0049) on the SF-36 Health Survey. Differences in the WPAI questionnaire scores did not achieve statistical significance. Nausea and fatigue were the most common adverse events, with a higher incidence in the ropinirole group compared to placebo (39.7 and 15.3% vs 8.1 and 6.6%). Headache was also common but more often in the placebo group (25.7 vs 22.1%).
Garcia-Borreguero et al[44] Ropinirole 0.50 to 4.0 mg QHS	ES, MC, OL, Subjects completing the following parent studies: Study 188, Study 190 (TREAT RLS 1), Study 194 (TREAT RLS 2), and Study 218) and subjects who met the definition of relapse during the double-blind phase of Study 188 To be eligible for	N=310 52 weeks	Primary: Adverse events, sitting stable blood pressure and heart rate, weight, and laboratory assessments Secondary: Changes in IRLS score, CGI-I responder rate, MOS sleep scores, WPAI, RLS QOL, SF-36	Primary: During open-label treatment, 91.35% of patients receiving ropinirole reported at least one treatment-related adverse event. The majority of patients reported adverse events that were mild or moderate in intensity. The most commonly reported adverse event was nausea (37.2%) with 64.3% of patients reporting only a single episode. Of the 115 patients reporting nausea, 85.2% reported nausea that was mild or moderate in intensity. The majority of the most common adverse events were first reported in the initial 12 weeks of the study. Adverse events deemed related or possibly related to the study drug were reported in 172 patients. Among the 115 subjects with nausea overall, 85.2% of cases were deemed related or possibly related to the study drug. Mean values for blood pressure, heart rate, and body weight were within normal limits at all time points and remained generally unchanged over time. Six patients had a sitting diastolic blood pressure value of clinical note. Two had a low (<50 mm Hg) and significant decrease (≥20 mm Hg). A total of 12 patients (3.9%) had a sitting systolic blood pressure value of clinical note at

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
	the parent studies, subjects were between 18 and 79 years of age, with idiopathic RLS and ≥15 nights of RLS symptoms during the previous month and a have total score ≥15 based on the IRLS rating scale			any post-baseline assessment, one of whom had a low (<90 mm Hg) and significant decrease (≥30 mm Hg). Secondary: The IRLS total score was improved by an average of 12 and 10 points from baseline to week 52 for the observed case analysis and last observation carried forward, respectively. The CGI-I responder rates at week 52 were reported as 82.8% and 71.9% for the observed case analysis and last observation carried forward analysis, respectively. At week 48, all domains of the MOS sleep scale and WPAI were improved compared to their respective baseline values. The scores on the RLS QOL questionnaire improved by a mean of 15.6 points at week 48 in the observed case analysis and 12.8 at week 48 in the last observation carried forward analysis.
Happe et al[45] Gabapentin 300 to 1200 mg QHS vs ropinirole 0.25 to 1.50 mg QHS Gabapentin doses greater than 300 mg daily were administered twice daily.	AC, OL, RCT Patients with a diagnosis of RLS	N=16 4 weeks	Primary: Number of PLMS, PLMS index, PMLS arousal index, IRLS scores, ESS Secondary: QOL and PSQI	Primary: Patients treated with either gabapentin or ropinirole experienced significant reductions in the number of PLMS from baseline (P=0.017 and P=0.028, respectively) Compared to baseline values, both gabapentin and ropinirole treatment were associated with significant reductions in the PLMS index (P=0.012 and P=0.018, respectively). There was no difference between gabapentin and ropinirole in PLMS index after four weeks (22.6±24.9 vs 13.2±13.5; respectively; P=0.752). There was no different in the PLMS arousal index for patients treated with either gabapentin or ropinirole for four weeks (2.4±2.1 vs 9.3±17.4; respectively; P=0.831). The difference in IRLS scores between gabapentin and ropinirole was not significant following four weeks of treatment (6.8±3.9 vs 8.1±4.9; respectively;

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
				P=0.489). Patients randomized to gabapentin treatment experienced similar reduction in ESS compared to ropinirole following four weeks of treatment (6.0±3.8 vs 7.3±2.9; respectively; P=0.459). Secondary: Total scores of the PSQI improved significantly in the gabapentin group (P<0.05), whereas there were no significant changes in these scores in the ropinirole group. Quality of life improved in both groups but was not statistically significant.
Giorgi et al[46] Phase 1: Ropinirole 0.25 to 4 mg PO QD vs placebo	Phase 1: DB, MC, PC, PG, RCT, Patients 18 to 79 years of age diagnosed with idiopathic RLS with an IRLS score ≥ 24	N=404 Phase 1: 26 weeks	Primary: Change in IRLS total score from baseline at week 12 Secondary: Change in IRLS total score from baseline at week 26, the percentage of patients with a score of much improved or very much improved on the CGI-1 at weeks 12 and 26, the time to a CGI-1 score of much improved or very much improved during double-blind	Primary: Mean change from baseline in the IRLS total score at week 12 indicated significantly greater improvement with ropinirole than with placebo (adjusted mean treatment difference, –2.1; 95% CI, –4.0 to –0.1; P=0.039) Secondary: Mean change from baseline in the IRLS total score at week 26 indicated significantly greater improvement with ropinirole than with placebo (adjusted mean treatment difference, –2.5; 95% CI, –4.6 to –0.3; P=0.023). For CGI-1, significantly more patients in the ropinirole group than in the placebo group scored as being much improved or very much improved at week 12 (68% versus 52%; adjusted OR, 1.94; 95% CI, 1.23 to 3.06; P=0.004) and at week 26 (84% versus 64%; adjusted OR, 2.69; 95% CI, 1.39 to 5.20; P=0.003). For CGI-Severity, at week 26, the odds of having a rating of normal or borderline ill did not significantly differ between ropinirole (46%) and placebo (45%) (adjusted OR, 1.01; 95% CI, 0.59 to 1.73; P=0.977). Mean Medical Outcomes Survey Sleep Scale score changes from baseline indicated significantly greater improvement with ropinirole than with placebo for sleep disturbance at week 12 (adjusted mean treatment difference, –9.0; 95% CI, -13.6 to-4.4; P<0.001) and at week 26 (adjusted mean treatment

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
			treatment, the percentage of patients considered normal or borderline ill based on the CGI-Severity at week 26, and mean changes from baseline on the Medical Outcomes Survey Sleep Scale, the RLS Quality of Life Questionnaire, and the Medical Outcomes Survey Short Form-36 at weeks 12 and 26, adverse effects, and augmentation and early morning rebound	difference, -8.2; 95% CI, -13.3 to -3.0; P=0.002), sleep adequacy at week 12 (adjusted mean treatment difference, 7.8; 95% CI, 2.3 to 13.2; P=0.005) and week 26 (adjusted mean treatment difference, 11.1; 95% CI, 4.9 to 17.3; P<0.001), and daytime somnolence at week 12 (adjusted mean treatment difference, -3.9; 95% CI, -7.6 to -0.3; P=0.035). Differences between ropinirole and placebo were not statistically significant for sleep quantity at either time point or for daytime somnolence at week 26. Mean standard deviation change from baseline in the overall life-impact score for the RLS Quality of Life Questionnaire at week 12 reflected significantly greater improvement with ropinirole than with placebo (adjusted mean treatment difference, 4.0; 95% CI, 0.4 to 7.7; P=0.031). The difference between ropinirole and placebo was nonsignificant at week 26 (adjusted mean treatment difference, 2.0; 95% CI, –1.8 to 5.9; P=0.296). No statistically significant differences between ropinirole and placebo were observed for the changes from baseline in the domains of the SF-36 at week 12 or week 26 (P value not reported). Adverse effects led to premature withdrawal in 32 patients (16%) in the ropinirole group and 14 patients (7%) in the placebo group in the double-blind phase. During double-blind treatment, adverse effects leading to withdrawal of 41 patients in either treatment group were nausea (13 ropinirole, two placebo), vomiting (six ropinirole, zero placebo), diarrhea (three ropinirole, one placebo), fatigue (three ropinirole, zero placebo), nasal congestion (two ropinirole, zero placebo), and insomnia (two ropinirole, one placebo). The incidences of augmentation and early morning rebound were ≤4% for ropinirole.
Trenkwalder et al[47] Rotigotine 1 mg/24 hours vs rotigotine 2 mg/24 hours	DB, MC, PC, RCT Patients 18 to 75 years of age with moderate to severe	N=458 24 week maintenance phase	Primary: Absolute change from baseline in IRLS sum score and in the CGI item 1 score	Primary: Each rotigotine group compared to placebo was significant for improvement in IRLS and CG1 item 1 scores (all P values<0.0001). The treatment difference of each randomized group compared to placebo in IRLS scores for the 1, 2 and 3 mg groups were -5.1 (95% CI, -7.6 to -2.7), -7.5 (95% CI, -10.0 to -5.1) and -8.2 (95% CI, -10.6 to -5.7), respectively. The differences in CGI item 1 score were -0.76 (95% CI, -1.13 to -0.38), -1.07 (95% CI, -1.44 to -

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
vs rotigotine 3 mg/24 hours vs placebo	idiopathic RLS		Secondary: Treatment responses for IRLS, CGI items 1 and 2 (50% improvement in IRLS or CGI item 1 score), IRL remitters (score of < 10), complete remitters (IRLS score of 0), changes in the severity of symptoms at bedtime during the night and during the day, satisfaction with sleep, severity of tiredness, safety assessment	0.69) and -1.21 (95% CI, -1.58 to -0.83), respectively. Significant results were maintained in analyses adjusting for the actual dose received (patients were allowed to titrate back a dose once if necessary) and for pretreatment with another dopamine agonist. Secondary: The difference in the proportion of IRLS treatment responses observed compared to placebo was 26.4%, 32.4% and 30.0% in the 1, 2 and 3 mg rotigotine groups, respectively (all P values<0.0001). The differences in CGI item 1 score responses observed compared to placebo were 19.3% (P<0.005), 21.6% (P<0.005) and 30.0% (P<0.0001), respectively. The differences in CGI item 2 score responses observed compared to placebo were 13.0% (P=0.0623), 29.5% (P<0.0001) and 29.7% (P<0.0001), respectively. There were significantly more IRLS remitters in all rotigotine groups compared to placebo (all P values<0.005). An IRLS score of 0 was achieved in 24% of patients in all rotigotine groups combined compared to 12% in the placebo group. Patients with moderate to severe daytime symptoms at baseline were improved to mild or no symptoms in 49%, 56%, and 58% of patients in the respective rotigotine groups compared to 30% of placebo patients. Improvement in severity of symptoms at night, sleep satisfaction and severity of tiredness were seen in all rotigotine groups compared to placebo (P values not reported). Treatment-emergent adverse events were reported in 78% and 55% of patients in the rotigotine and placebo groups, respectively. Of these adverse events, 15% and 8% were deemed severe in each group, respectively. Skin reactions occurred in 43% of patients taking rotigotine vs 2% of those receiving placebo.
Hening et al[48]	DB, MC, PC,	N=505	Primary:	Primary:

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
Rotigotine 0.5 mg/24 hours vs rotigotine 1 mg/24 hours vs rotigotine 2 mg/24 hours vs rotigotine 3 mg/24 hours vs placebo	RCT Patients 18 to 75 years of age with moderate to severe idiopathic RLS	24 week maintenance phase	Absolute change from baseline in IRLS sum score and in the CGI item 1 score Secondary: Treatment responses for IRLS, CGI items 1 and 2 (50% improvement in IRLS or CGI item 1 score), IRLS remitter rates (score of < 10), change from baseline to end of maintenance in restless leg syndrome severity scale (RLS-6), CGI items 2 and 3, Medical Outcomes Study Sleep Scale, SDS, RLS QOL questionnaire, WPAI questionnaire, global subject rating of treatment efficacy, safety	Only the rotigotine 2 and 3 mg groups compared to placebo were significant for improvement in IRLS and CG1 item 1 scores (P values<0.001). The treatment difference for each randomized group compared to placebo in IRLS scores for the 0.5, 1, 2 and 3 mg groups were -2.2 (95% CI, -4.5 to 0.2), -2.3 (95% CI, -4.6 to 0.0), -4.5 (95% CI, -6.9 to -2.2) and -5.2 (95% CI, -7.5 to -2.9), respectively. The differences in CGI item 1 score were -0.35 (95% CI, -0.7 to 0.0), -0.32 (95% CI, -0.7 to 0.1), -0.65 (95% CI, -1.0 to -0.3) and -0.9 (95% CI, -1.3 to -0.5), respectively. Secondary: Overall, 56.6% and 49.8% of patients in the rotigotine groups achieved an IRLS and CGI item 1 treatment response, respectively. There were 40.8%, 49.5%, 53.7% and 62.1% IRLS remitters in the respective rotigotine groups with significantly more IRLS remitters in the 1, 2 and 3 mg groups compared to placebo (P values<0.05). An IRLS score of 0 was achieved in 23.3% of patients in all rotigotine groups combined compared to 9.1% in the placebo group. RLS-6 scores improved in all groups with no significant differences between rotigotine and placebo. There were also no significant differences between RLS QOL, SDS or WPAI scores between groups (No P values reported). Treatment was rated as “good” or “very good” in 54% of placebo patients and in 65%, 49%, 60% and 72% of patients taking rotigotine 0.5, 1, 2 and 3 mg, respectively. Treatment-emergent adverse events were reported in 88% and 84% of patients in the rotigotine and placebo groups, respectively. Of these adverse events, 20% and 12% were deemed severe in each group, respectively. Skin reactions was the most common adverse event in patients taking rotigotine and occurred in 27% of patients taking rotigotine vs 5% of those receiving placebo. ESS scores improved in all groups with no significant differences between rotigotine and placebo.

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
			assessment	
Oertel et al[49] Rotigotine 1 mg/24 hours or 2 mg/24 hours or 3 mg/24 hours vs placebo	DB, MC, PC, PG, RCT Patients 18 to 75 years of age diagnosed with idiopathic RLS	N=66 4 week maintenance phase (up to 3 weeks titration phase)	Primary: Change in PLMI from baseline to the end of maintenance Secondary: Change in PLM during sleep index, PLM during wakefulness index, total time in sleep stages, and sleep onset latency, proportion of subjects with a PLMI<15/hour, the proportion of subjects with a PLMI <5/hour, the proportion of subjects with a PLMSAI≤2/hour, and the proportion of subjects with a PLMSI <5/hour at the end of maintenance	Primary: At baseline, the primary efficacy variable PLMI was higher in rotigotine than placebo patients. Rotigotine treatment significantly reduced PLM during time in bed compared to placebo; At end of maintenance, a baseline-adjusted least square mean treatment ratio of 4.25 (95% CI, 2.48 to 7.28, P<0.0001) in favor of rotigotine was calculated. Secondary: There was also a markedly higher proportion of subjects with a PLMI <15/hour in the rotigotine group (P<0.05). A reduction in PLMI to <5/hour was observed in 39% of all rotigotine subjects but not in the placebo group (P<0.05). PLMSAI also improved more under rotigotine than placebo; a mean baseline PLMSAI of 8.57 ± 6.49 was reduced under rotigotine to 2.47 ± 3.71 at end of maintenance. Under placebo, mean baseline values of 6.5 ± 5.86 decreased to 4.95 ± 5.74. The least square mean treatment difference at end of maintenance was -3.12 in favor of rotigotine (P=0.0072). The PLMSAI was reduced to a clinically normal level (≤2/hour) for a higher number of rotigotine than placebo subjects (P<0.05). Changes in sleep efficiency at end of maintenance were not significantly different between the groups (P=0.36). At end of maintenance, PLMS during TST (PLMSI) and during wakefulness (PLMWI) had been reduced to a larger extent in rotigotine than placebo subjects. A reduction in PLMSI to normal levels (<5/hour) was observed in 53.7% of rotigotine and 10% of placebo subjects (P<0.05). Total sleep time increased by a baseline-adjusted mean of 16 min under rotigotine, and sleep stage two improved by 25 min, whereas slow-wave sleep (stage 3/4) was reduced by 10 min. Overall, changes in total sleep time, time spent in each sleep stage, and sleep onset latency were not considered different between the groups.
Oertel et al[50] Rotigotine 0.5 mg/24 hours	MC, OL, PC, RCT	N=295 5 years	Primary: Incidence and severity of	Primary: There were 295 patients that entered the open-label extension study. Five patients (2%) discontinued during the open-label titration period and 70 (24%)

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
to 4 mg/24 hour vs placebo	Patients 18 to 75 years of age with moderate-to-severe idiopathic RLS		adverse events, overall trial retention rate, and reasons for premature discontinuation Secondary: IRLS total score, RLS-6 scales, CGI-1, and augmentation	discontinued during the first year of follow-up. In total, 169 patients (57%) discontinued treatment before the end of maintenance, 31 (11%) because of lack of efficacy and 89 (30%) because of adverse events. There were 126 patients (43%) that completed the maintenance period. Overall, 273 patients (93%) had one or more treatment emergent adverse events. The most common dopaminergic adverse events were nausea, fatigue, headache, and dizziness. We recorded one case of pulmonary fibrosis and one case of obsessive compulsive disorder. Five patients (2%) had a sleep attack or sudden onset of sleep. Most patients had adverse events that were mild or moderate in intensity; 97 (33%) had a severe adverse event. Incidence of adverse events was highest in the first year, affecting 220 of 290 patients (76%), and then decreased to the end of year three (134/220 [61%] in year two; 103/191 [54%] in year three) and remained stable thereafter (93/159 [58%] in year four; 91/147 [62%] in year five). There were 117 treatment-emergent serious adverse events reported by 79 patients. Serious adverse events reported in more than one patient were osteoarthritis (N=11), myocardial infarction (N=4), toe deformity (N=4), radius fracture (N=3), uterine leiomyoma (N=3), syncope (N=3), varicose vein (N=3), coronary artery disease (N=2), goiter (N=2), nausea (N=2), sleep apnea syndrome (N=2), and hip arthroplasty (N=2). One death, due to myocardial infarction, was reported during the trial and was not judged to be related to the study drug. The most frequently reported treatment-emergent adverse events were application site reactions, with incidence highest in the first year and decreasing every year thereafter. Application site reactions occurred in 37% (106/290) of patients in year one, 17% (38/220) of patients in year two, 14% (27/191) of patients in year three, and in less than 6% of patients during year four (8/159) and year five (8/147). More than half of the patients who discontinued treatment because of adverse events (47/89 [53%]) did so during the first year of maintenance. The adverse events most often reported as reasons for discontinuation were

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
				application site reactions in 56 patients (19%), insomnia in four patients (1%), and depression in three patients (1%). Almost one-third (28/89 [31%]) of patients who discontinued because of adverse events were on the 4 mg/24 hours dose at the time of dropout; 23 patients (26%) were on 3 mg/24 hours, 22 (25%) were on 2 mg/24 hours, nine (10%) were on 1 mg/24 hours, and seven (8%) were on 0.5 mg/24 hours. Secondary: Mean IRLS score of patients entering the open-label study was 27.8 ± 5.9 at baseline of the double-blind trial. In patients who completed the maintenance period, mean IRLS score was reduced from a baseline score of 27.7 ± 6.0 by a mean of 18.7 ± 9.5 points to a score of 9.0 ± 9.2 at the end of maintenance. 39% (48/123) of patients who completed the trial were classified as symptom free according to the IRLS. Mean CGI-1 scores decreased by 2.8 ± 1·1 points from baseline. Ninty-four patients who completed the trial (76%) were classified as responders according to CGI-1. At the end of maintenance, 106 of 124 patients (85%) were in a category of low severity illness (40 [32%] normal, 43 [35%] borderline ill, and 23 [19%] mildly ill) as assessed by CGI-1, compared with nine (3%) at baseline. Change in condition (CGI item 2) was characterized as much or very much improved in 119 of 124 patients (96%). Mean RLS-6 scores showed a decrease that was sustained throughout five years of follow-up. The greatest mean absolute changes from baseline to the end of maintenance were recorded in the nighttime RLS-6 categories of sleep satisfaction (–4.5 ± 3.1 points), severity of symptoms falling asleep (–4·3 ± 3.1 points), and severity of symptoms during the night (–5.1 ± 2.9 points). Scores for daytime symptoms decreased by a mean of 2.9 ± 2.8 points while resting and 1.3 ± 1·9 points while active, and a mean decrease of 2.6 ± 2.9 points was seen in the daytime tiredness and sleepiness category. Clinically significant augmentation was recorded in 39 patients (13%), of whom 15 (5%) were receiving a dose of rotigotine within the range of 1 to 3

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
				mg/24 hours and 24 (8%) were receiving 4 mg/24 hours rotigotine.
Inoue et al[51] Rotigotine 1 mg/24 hours to 3 mg /24 hours vs placebo	MC, OL Patients 20 to <80 years of age diagnosed with idiopathic RLS	N=185 44 weeks maintenance phase	Primary: Mean change in total IRLS scores from baseline, PSQI scores, Medical Outcome Study SF-36 scores, the safety of long-term rotigotine treatment was examined based on the incidence of major adverse events, the severity of skin irritation, and augmentation assessment Secondary: Not reported	Primary: The IRLS total score was 23.2 ± 5.1 points at the start of the double-blind study, decreasing to 7.8 ± 7.6 points at week 52 of the long-term extension study. The IRLS total score was 12.2 points lower at week two of the long-term extension study than at the start of the double-blind trial, and remained almost stable until week 52. The IRLS responder rate was 58.2% at week two in the titration phase and increased to >70% throughout the maintenance phase. There was no difference in ferritin levels between IRLS responders and IRLS non-responders. The PSQI total score was 8.0 ± 3.1 at the start of the double-blind trial and decreased to 5.0 ± 2.9 at week 52 of the long-term extension study. There was a change of -3.0 ± 3.2 (95% CI, -3.5 to -2.6). Among 141 subjects with a PSQI total score of ≥5.5 at baseline, 76 (41.8%) had a score of <5.5 at week 52. For the SF-36, the items bodily pain, general health perception, vitality, role-emotional and mental health showed improvements at week 52 compared with the baseline, with an increase of >3 points for these items. Overall, 175/185 patients (94.6%) experienced adverse events during the long-term extension study. Eight serious adverse events occurred in five patients (cataracts, hemorrhagic diverticulitis, application site discoloration, traffic accident, contusion, cervical crushing, lumbar nerve root injury, and hematoma). No deaths occurred during the study period. Treatment-emergent adverse effects occurring at a rate of ≥5% were nasopharyngitis (52.4%), application site reaction (52.4%), nausea (28.6%), somnolence (15.7%), headache (13.5%), vomiting (8.1%), diarrhea (6.5%), fall (5.9%), upper abdominal pain (5.4%), and arthralgia (5.4%). The following adverse events resulted in discontinuation in 29/185 subjects (15.7%): application site reactions in 19 subjects, nausea in two subjects, somnolence in two subjects, and the other events in six subjects.

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
				Augmentation in 10 patients met the MPI criteria, including clinically significant augmentation in five of these patients (2.7%). One of these five patients discontinued administration because of augmentation. Single clinically significant episodes of augmentation were confirmed in four patients (2.2%), who recovered with no particular treatment thereafter, and one patient (0.5%) had non-clinically significant augmentation.
Inoue et al[52] Rotigotine 2 mg/24 hours vs rotigotine 3 mg/24 hours vs placebo	DB, MC, PC, PG, RCT Patients 20 to <80 years of age with a diagnosis of RLS	N=284 13 weeks (8 week maintenance phase)	Primary: Change in the IRLS total score from baseline to the end of treatment week 13 Secondary: Improvements in CGI-I and Patient PGI scores, and the total score on the Japanese version of the PSQI manifested the severity of subjective sleep disturbance, mainly insomnia	Primary: There were decreases in IRLS total scores in both rotigotine groups as early as week one in the titration phase, and the scores continued to decline until the end of therapy. The mean ± SD changes in IRLS total score from baseline to the end of therapy were -14.3 ± 8.9, -14.6 ± 9.0, and -11.6 ± 8.2 in the rotigotine 2 mg/24 hours, 3 mg/24 hours, and placebo groups, respectively. The mean differences in the change in IRLS total score from baseline to the end of treatment between the rotigotine 2 mg/24 hours group and the placebo group and between the rotigotine 3 mg/24 hours group and the placebo group were -2.8 ± 1.3 (95% CI, -5.3 to -0.3; P-0.030) and -3.1 ± 1.3 (95% CI, -5.6 to -0.6; P=0.016), respectively. The proportions of IRLS responders were 60.2%, 66.0%, and 47.4% in the rotigotine 2 mg/24 hours, rotigotine 3 mg/24 hours, and placebo groups, respectively. Secondary: The mean changes in PSQI score from baseline to the end of therapy in the rotigotine 2 mg/24 hours and 3 mg/24 hours groups were -3.1 ± 3.2 and -3.2 ± 3.3, respectively, which were not significantly different from the change in the placebo group (-2.5 ± 2.4; P=0.188 and P=0.112 respectively). However, the proportions of patients with a PSQI total score of <5.5 at the end of therapy were 77.4% (72/93 patients), 74.4% (67/90 patients), and 56.4% (53/94 patients) in the rotigotine 2 mg/24 hours, 3 mg/24 hours, and placebo groups, respectively. The proportions of patients with a PSQI total score of <5.5 at the end of therapy were significantly greater in both rotigotine groups than in the placebo group. The proportions of patients with CGI-I or PGI-I rated as much improved or

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
				very much improved (CGI-responders and PGI-I responders, respectively) in the rotigotine 2 mg/24 hour group were not significantly different from those in the placebo group (P=0.163 and P=0.107 respectively). On the other hand, the proportions of CGI-I and PGI-I responders were significantly greater in the rotigotine 3 mg/24 hour group than in the placebo group (P=0.018 and P=0.005 respectively).

Drug regimen abbreviations: QHS= daily at bedtime, TID=three times daily
Study abbreviations: DB=double-blind, CI=confidence interval, MA=meta-analysis, MC=multicenter, OR=odds ratio, PC=placebo controlled, PG=parallel group, PRO=prospective, R=randomized, RCT=randomized controlled trial, RR=relative risk, SE=standard error, SR=systematic review
Miscellaneous abbreviations: ADL=Activities of Daily Living, BDI-II=Beck Depression Inventory, CGI=Clinical Global Impression, CGI-I=Clinical Global Impressions-Improvement, ESS=Epworth Sleepiness Scale, HADS=Hospital Anxiety and Depression Scale, HAMD=Hamilton Rating Scale for Depression, IRLS=International RLS Study Group Rating Scale, LM=Leg Movements, MADRS=Montgomery-Asberg Depression Rating Scale, MOS=Medical Outcomes Study, MPI=Max Plank Institute, PET=Positron Emission Tomography, PGI=Patient Global Impression, PLMAI=Periodic Limb Movements Associated with Arousal Per Hour of Sleep, PLMI=Periodic Limb Movements During Time in Bed Index, PLMSAI=Periodic Limb Movements During Sleep Arousal Index, PLMSI= Periodic Limb Movements During Sleep Index, PLMWI= Periodic Limb Movements During Wakefulness Index, PghSD=Pittsburgh Sleep Diary, PSQI= Pittsburgh Sleep Quality Index, QOL=Quality of Life, REM=Rapid Eye Movement, RLS=Restless Legs Syndrome, SDS=self-rating depression scale, SF=Short Form, SIT=Suggested Immobilization Test, SPSD=Subjective Post-Sleep Diary, UPDRS=Unified Parkinson Disease Rating Scale, VAS=Visual Analogue Scale, WPAI=Work Productivity and Activity Impairment, WTDS=Wake Time During Sleep

Special Populations

Table 5. Special Populations[2-7]

Generic Name	Population and Precaution				
	Elderly/ Children	**Renal Dysfunction**	**Hepatic Dysfunction**	**Pregnancy Category**	**Excreted in Breast Milk**
Gabapentin enacarbil ER	Dosage adjustment may be required in elderly based on renal function. Safety and efficacy not established in children.	Renal dose adjustment is required; for creatinine clearances of ≥60 mL/min, a dose of 600 mg/day is recommended. For creatinine clearances of 30 to 59 mL/min, a starting dose of 300 mg/day is recommended and increase to 600 mg as needed. For creatinine clearances of 15 to 29 mL/min, a dose of 300 mg/day is recommended. For creatinine clearances of ≤15 mL/min, a dose of 300 mg every other day is recommended. Not recommended for use in patients with creatinine clearance of <15 mL who are on hemodialysis.	Not studied in hepatic dysfunction.	C	Unknown*
Pramipexole	No dosage adjustment required in elderly. Safety and efficacy not established in children.	Dose adjustment required in patients with mild to severe renal impairment. Not adequately studied in patients with a creatinine clearance <15 mL/min and hemodialysis patients.	Not studied in hepatic dysfunction.	C	Unknown
Ropinirole	No dosage adjustment required in elderly.	No dosage adjustment required.	Not studied in hepatic dysfunction.	C	Unknown

Generic Name	Population and Precaution				
	Elderly/ Children	Renal Dysfunction	Hepatic Dysfunction	Pregnancy Category	Excreted in Breast Milk
	Safety and efficacy not established in children.				
Rotigotine	No dosage adjustment required in elderly.	No dosage adjustment required.	Not studied in hepatic dysfunction.	C	Unknown

ER=extended-release

*It is unknown whether gabapentin enacarbil is secreted in human milk; however, gabapentin is found in human milk following oral administration.

Adverse Drug Events

The most commonly reported adverse events associated with the dopamine agonists and gabapentin enacarbil extended-release are included in Table 6. Adverse events that were reported most frequently in patients with either Parkinson's disease or restless legs syndrome were nausea, dizziness and somnolence. Motor complications associated with these agents, such as dyskinesia, were reported in clinical trials involving patients with advanced Parkinson's disease generally on adjunctive levodopa therapy. Cognitive symptoms such as hallucinations occurred with increased frequency in patients over the age of 65.

Table 6. Adverse Drug Events (%)[2-7]

Adverse Event	Gabapentin enacarbil ER	Pramipexole	Ropinirole	Rotigotine
Cardiovascular				
Hypertension	-	-	5	-
Orthostatic symptoms	-	-	6	-
Peripheral edema	<1 to 3	2 to 5	2 to 7	-
Postural hypotension	-	53*	-	-
Syncope	-	-	3 to 12	-
Central Nervous System*				
Amnesia	-	4 to 6	5*	-
Balance disorder	✔	-	-	-
Confusion	-	4 to 10	5 to 9	-
Depression	<1 to 3	-	-	-
Dizziness	13 to 22	25 to 26	11 to 40	3 to 20
Dream abnormalities	-	1 to 11*	-	-
Dyskinesia	-	47*	34*	-
Dystonia	-	2 to 8	-	-
Extrapyramidal syndrome	-	28*	-	-
Fatigue	6 to 7	3 to 9	8 to 11	3 to 18
Feeling abnormal	<1 to 3	-	-	-
Feeling intoxicated	1 to 3	-	-	-
Gait abnormalities	-	7*	-	-
Hallucinations	-	9 to 17	5 to 10	-
Headache	12 to 15	16	17	-
Hypertonia	-	7*	-	-
Hypokinesia	-	-	5	-
Insomnia	-	9 to 27	-	-

Adverse Event	Gabapentin enacarbil ER	Pramipexole	Ropinirole	Rotigotine
Irritability	4	-	-	-
Paresthesia	-	-	3 to 5	-
Somnolence	20 to 27	6 to 22	12 to 40	≥5
Tremor	-	-	6*	-
Gastrointestinal				
Abdominal pain/discomfort	-	-	3 to 9	-
Constipation	-	4 to 14	6	-
Diarrhea	-	1 to7	5	-
Dry mouth	3 to 4	3 to 7	3 to 5	-
Dyspepsia	-	1 to 4	4 to 10	-
Flatulence	2 to 3	-	-	-
Nausea	6 to 7	11 to 28	11 to 60	13 to 48
Vomiting	-	-	7 to 12	3 to 20
Musculoskeletal				
Arthralgia	-	-	4 to 7	-
Asthenia	-	10 to 14	6	-
Muscle cramps	-	-	2	-
Other				
Abnormal/blurred vision	✔	-	6	-
Accidental injury	-	17*	-	-
Anxiety	-	-	6	-
Anorexia	-	-	-	2 to 8
Application site reaction	-	-	-	19 to 46
Appetite increase	2	-	-	-
Breast enlargement	✔ †	-	-	-
Cough	-	-	3	-
Disorientation	✔	-	-	-
Elevated creatine kinase	✔ †	-	-	-
Falls	-	-	10*	-
General edema	-	4 to 5	6	-
Hyperhidrosis	-	-	3	-
Influenza	-	1 to 7	3	-
Increased drug level	-	-	7	-
Libido decrease	<1 to 2	-	-	-
Nasopharyngitis	-	>2	9	-
Nasal congestion	-	3 to 6	2	-
Nervousness	-	-	5	-
Pain	-	3 to 7	3 to 8	-
Pharyngitis	-	-	6 to 9	-
Urinary frequency	-	6*	-	-
Sweat increase	-	-	3 to 7	-
Upper respiratory tract infection	-	-	6	2 to 5
Urinary tract infection	-	-	5 to 6	-
Viral infection	-	-	11	-
Vertigo	-	-	2	-
Weight increased	2 to 3	-	-	-

ER=extended-release
- Event not reported or incidence <5%. † Reported with immediate-release gabapentin formulations
*Reported in clinical trials in patients with advanced Parkinson's disease possibly receiving concomitant levodopa therapy.

Contraindications/Precautions[2-7]

Gabapentin enacarbil ER, pramipexole, ropinirole, and rotigotine are contraindicated in patients with a known hypersensitivity to the respective product.

The dopamine agonists carry several warnings including falling asleep during activities of daily living, symptomatic hypotension and hallucinations.

Patients treated with pramipexole, ropinirole, and rotigotine have reported falling asleep while engaged in activities of daily living, including the operation of motor vehicles, sometimes resulting in accidents. While many patients report somnolence while taking pramipexole and ropinirole, some perceived that they had no warning signs such as excessive drowsiness, and believed that they were alert immediately prior to the event. The onset of these events has been reported as late as one year following the initiation of treatment. Many clinical experts believe that falling asleep while engaged in activities of daily living always occurs in a setting of preexisting somnolence, although patients may not give such a history. For this reason, patients should be continually reassessed for drowsiness or sleepiness, since these events may occur well after the start of treatment.

Patients should be counseled regarding the potential to develop drowsiness and should be specifically asked about factors that may increase the risk with pramipexole such as concomitant sedating medications, the presence of sleep disorders, and concomitant medications that increase pramipexole plasma levels (i.e., cimetidine). If a patient develops significant daytime sleepiness or episodes of falling asleep during activities that require active participation (i.e., conversations or eating), pramipexole discontinuation should be considered. If a decision is made to continue pramipexole, patients should be advised not to drive and to avoid other potentially dangerous activities. While dose reduction reduces the degree of somnolence, there is insufficient evidence to establish that a dose reduction will eliminate episodes of falling asleep while engaged in activities of daily living.

Dopamine agonists may impair the systemic regulation of blood pressure, resulting in postural hypotension, specifically during dose escalation. Patients with Parkinson's disease appear to have an impaired capacity to respond to a postural challenge. Parkinson's patients being treated with dopaminergic agonists should be closely, monitored for signs and symptoms of postural hypotension, especially during dose escalation.

Syncope, sometimes associated with bradycardia, was observed in patients with Parkinson's disease and restless legs syndrome (RLS) being treated with ropinirole and rotigotine. Caution should be used when initiating ropinirole or rotigotine treatment in patients with severe cardiovascular disease.

Ropinirole and rotigotine may potentiate the dopaminergic adverse reactions of levodopa and may cause and/or exacerbate preexisting dyskinesia in patients treated with levodopa for Parkinson's disease. Decreasing the dose of levodopa may ameliorate this adverse reaction.

Do not treat patients with a major psychotic disorder with extended-release (ER) dopamine agonists because of the risk of exacerbating the psychosis. In addition, many treatments for psychosis may decrease the effectiveness of the dopamine agonist.

Abrupt withdrawal or dose reduction in Parkinson's treatment has been associated with symptoms similar to neuroleptic malignant syndrome, although this effect has not specifically been linked to pramipexole, ropinirole, or rotigotine use. Fibrotic complications, such as retroperitoneal fibrosis, pulmonary infiltrates, pleural effusion and pericarditis have been related to ergot-derived dopamine agonists; however the risk with pramipexole, ropinirole, or rotigotine use is also unknown. Rebound, or the change of RLS symptoms to early morning, and augmentation (an escalation in overall symptoms, symptoms occurring in the early evening/afternoon or symptoms effecting areas other than the legs) have been reported with dopaminergic medications but have not been demonstrated during clinical trials with pramipexole, ropinirole, or rotigotine. Compulsive behaviors have also been observed in individuals treated with dopaminergic agents for Parkinson's disease.

Some epidemiologic studies have shown that patients with Parkinson's disease have a higher risk of developing melanoma than the general population. Whether the observed increased risk was caused by Parkinson's disease or other factors, such as drugs used to treat Parkinson's disease, was unclear. Patients who are using ropinirole, pramipexole, or rotigotine for any indication should undergo periodic dermatologic screening.

Rotigotine patches contain sodium metabisulfite, a sulfite that may cause allergic-type reactions including anaphylactic symptoms and life threatening or less severe asthmatic episodes in certain susceptible people. Rotigotine patches have been associated with application site reactions. It is recommended that patients that experience an application site reaction discontinue use of rotigotine patches. The backing layer of rotigotine patches contains aluminum and to avoid skin burns, rotigotine patches should be removed prior to magnetic resonance imaging or cardioversion. Exposure to heat may increase absorption and external sources of heat should be avoided. Use of rotigotine was also associated with elevation of blood pressure and heart rate and weight gain/fluid retention.

Gabapentin enacarbil ER may cause significant driving impairment as a result of somnolence and sedation. Patients being treated with gabapentin enacarbil ER should not drive until they have experience to assess whether gabapentin enacarbil ER impairs their ability to drive.

Gabapentin enacarbil ER is not interchangeable with other gabapentin products due to differences in pharmacokinetic profiles. Equivalent doses of gabapentin enacarbil ER and other gabapentin products results in different plasma concentrations between the products administered.

Gabapentin enacarbil ER is a prodrug of gabapentin, an anticonvulsant. Anticonvulsants may increase the risk of suicidal thoughts or behavior in patients taking these drugs regardless of indication. Patients treated with any anticonvulsant for any indication should be monitored for the emergence or worsening of depression, suicidal thoughts or behavior, and/or any unusual changes in mood or behavior.

Drug Reaction with Eosinophilia and Systemic Symptoms (DRESS), also known as multiorgan hypersensitivity, has been reported in patients treated with anticonvulsants, including gabapentin. These events may be fatal or life-threatening. DRESS typically, presents with fever, rash, and/or lymphadenopathy, with other organ system involvement, such as hepatitis, nephritis, hematological abnormalities, myocarditis, or myositis and may resemble an acute viral infection. Eosinophilia is often present.

If discontinuing gabapentin enacarbil ER, the dose should be reduced to 600 mg daily for one week prior to discontinuation to minimize the risk of withdrawal seizure. Patients receiving the recommended dose of 600 mg daily may discontinue the drug without using a taper.

In an oral carcinogenicity study, gabapentin enacarbil ER increased the incidence of pancreatic acinar cell adenoma and carcinoma in male and female rats. The clinical significance of this finding and how it translates to human subjects is unknown.

Drug Interactions[2-7]

There are no significant drug interactions listed for pramipexole. Ropinirole is metabolized by the enzyme cytochrome (CYP) P450 1A2, therefore there is the potential for an alteration in clearance of this agent with inhibitors (i.e., ciprofloxacin, fluvoxamine) and inducers (i.e., omeprazole, cigarette smoking) of this enzyme. Neither gabapentin enacarbil ER nor gabapentin are substrates, inhibitors or inducers of the major CYP P450 enzymes or P-glycoprotein. It is possible that the effectiveness of rotigotine could be diminished with the use of dopamine antagonists such as antipsychotics or metoclopramide.

Dosage and Administration

Table 7. Dosing and Administration[2-7]

Generic Name	Adult Dose	Pediatric Dose	Availability
Gabapentin enacarbil ER	Treatment of moderate-to-severe primary restless legs syndrome in adults: Extended-release tablet: 600 mg QD; doses above 1200 mg QD provided no additional benefit, but caused an increase in adverse events.	Safety and efficacy in pediatrics have not been established.	Extended-release tablet: 300 mg 600 mg
Pramipexole	Treatment of moderate-to-severe primary restless legs syndrome: Tablet: initial, 0.125 mg QD two to three hours before bedtime; maintenance, 0.125 mg to 0.5 mg QD two to three hours before bedtime; maximum, 0.5 mg QD two to three hours before bedtime	Safety and efficacy in pediatrics have not been established.	Extended-release tablet:† 0.375 mg 0.75 mg 1.5 mg 2.25 mg 3.0 mg 3.75 mg 4.5 mg Tablet: 0.125 mg 0.25 mg 0.5 mg 0.75 mg 1 mg 1.5 mg
Ropinirole	Treatment of moderate-to-severe primary restless legs syndrome: Immediate-release tablet: initial, 0.25 mg QD two to three hours before bedtime; maintenance, 1 mg to 4 mg QD two to three hours before bedtime; maximum, 4 mg QD	Safety and efficacy in pediatrics have not been established.	Extended-release tablet:† 2 mg 4 mg 6 mg 8 mg 12 mg Tablet: 0.25 mg 0.5 mg 1 mg 2 mg 3 mg 4 mg 5 mg
Rotigotine	Treatment of moderate-to-severe restless legs syndrome: Transdermal patch: initial, 1 mg transdermally every 24 hours; maintenance 1 to 3 mg every 24 hours; maximum, 3 mg every 24 hours	Safety and efficacy in pediatrics have not been established.	Transdermal Patch: 1 mg/24 hours 2 mg/24 hours 3 mg/24 hours 4 mg/24 hours‡ 6 mg/24 hours‡ 8 mg/24 hours‡

ER=extended-release, QD=once-daily

† Dosage form not approved for use in restless legs syndrome.
‡ Strength not recommended in restless legs syndrome

Clinical Guidelines

Table 8. Clinical Guidelines

Clinical Guideline	Recommendation(s)
American Academy of Sleep Medicine (AASM): **Practice Parameters for the Dopaminergic Treatment of Restless Legs Syndrome and Periodic Limb Movement Disorder (2004)**[10]	• The dopamine agonists pramipexole and ropinirole are effective in the treatment of restless legs syndrome (RLS) and periodic limb movement disorder (PLMD). • Levodopa with decarboxylase inhibitor and pergolide are effective in the treatment of RLS and PLMD. • Other dopamine agonists (talipexole, cabergoline, piribedil and alpha-dihydroergocryptine) may be effective in the treatment of RLS or PLMD, but the degree of efficacy of these agents has not been established. • The dopaminergic agents amantadine and selegiline may be effective in the treatment of RLS and PLMD, but the degree of efficacy of these agents has not been established. • No specific recommendations can be made regarding dopaminergic treatment of RLS or PLMD in the pediatric population or in pregnant women.
Medical Advisory Board of the Restless Legs Syndrome Foundation: **An Algorithm for the Management of Restless Legs Syndrome (2004)**[11]	Daily RLS • Dopamine agonists are the drugs of choice in most people with daily restless legs syndrome (RLS). Pramipexole and ropinirole are associated with fewer side effects; therefore they are preferred over pergolide. • Gabapentin is considered an alternative to dopamine agonists especially in patients with neuropathic pain. • Low-potency opioids such as propoxyphene or codeine and opioid agonists like tramadol are recommended as alternative treatment. • Nonpharmacological management, such as the discontinuation of medications that may exacerbate RLS (neuroleptic agents, metoclopramide, sedating antihistamines), is recommended in both daily and intermittent RLS. Bupropion may be considered in patients whose symptoms are worsened by antidepressants. • Avoiding caffeine, nicotine, and alcohol, the implementation of mental alerting activities and iron replacement in patients with iron deficiency should also be considered. Intermittent RLS • Dopamine agonists such as pramipexole or ropinirole administered intermittently may be effective but are not useful once symptoms have already begun. • The occasional use of immediate-release carbidopa/levodopa may be helpful for RLS symptoms that arise in the evening, at bedtime, during sleep or with certain activities, whereas the controlled-release formulation can be administered prior to bedtime for night-time awakenings. Levodopa has been associated with augmentation and rebound of symptoms. • Intermittent administration of low-potency opioids such as propoxyphene or codeine and opioid agonists like tramadol before sleep can successfully treat occasional RLS symptoms. • Benzodiazepines or benzodiazepine agonists may be effective when given prior to bedtime especially in patients with concurrent insomnia.

Clinical Guideline	Recommendation(s)
	Refractory RLS • Patients may respond differently to each dopamine agonist therefore switching agents is recommended if one is ineffective. • Changing to gabapentin is recommended in patients not adequately responding to initial therapy. • The addition of a second agent such as gabapentin, a benzodiazepine or an opioid is recommended in patients who are refractory to first-line therapy. • Switching to a high-potency opioid may be considered. This class of medication may be highly effective in the management of RLS symptoms.
European Federation of Neurological Societies Task Force (EFNS): **Guidelines on Management of Restless Legs Syndrome and Periodic Limb Movement disorder in Sleep (2006)**[12]	Primary RLS • Ropinirole is effective in improving restless legs syndrome (RLS) scale scores, quality of life, sleep latency and the Periodic Leg Movements in sleep Index/Arousals (PLMS-I/PLMS-A) at an average dose of 1.5 to 4.6 mg per day. • Pramipexole, bromocriptine, oxycodone, carbamazepine and valproate are probably effective in primary RLS. • Cabergoline raises RLS scores at doses of 0.5 to 2 mg once-daily and is possibly effective long-term. • Pergolide improves RLS severity and subjective quality of sleep at average doses of 0.40 to 0.55 mg daily. It is possibly effective long-term. • Gabapentin has demonstrated a decrease in RLS scores and improves sleep efficiency and PLMS-I at doses of 800 to 1,800 mg daily. • Levodopa/benserazide is effective in improving RLS symptoms, quality of sleep, sleep latency, PLMS-I and quality of life. Levodopa is possibly effective long-term. • Short-term use of rotigotine 4.5 mg transdermal patch improves RLS symptoms. • Clonazepam 1 mg at bedtime is probably effective in primary RLS however it is considered probably ineffective when dosed four times daily. • The short-term use of clonidine is probably effective in decreasing symptoms of RLS and sleep latency. • The use of oral iron supplementation and vibration are probably ineffective in the treatment of RLS. • There is insufficient evidence to make a recommendation for the use of iron dextran, magnesium oxide, amantadine, lamotrigine or topiramate. • No specific recommendations can be made in the treatment of RLS in the pediatric population or in pregnant women. Secondary RLS • Ropinirole and levodopa are probably effective in the treatment of RLS secondary to uremia, while iron dextran is probably effective short-term for this condition. • Gabapentin is recommended as probably effective in hemodialysis related RLS. • Short-term pergolide use at a dose of 0.25 mg daily is considered probably ineffective in the treatment of RLS secondary to hemodialysis. • There is insufficient evidence to support the use of benzodiazepines, opioids, clonidine, phenoxybenzamine, propranolol and talipexole in secondary RLS.

Clinical Guideline	Recommendation(s)
	PLMD • There is not enough evidence available to determine the effectiveness of non-ergot derivatives or anticonvulsants medications in periodic limb movement disorder (PLMD). • Bromocriptine is probably effective in PLMD secondary to narcolepsy. • Clonazepam 0.5 to 2.0 mg per day and levodopa are probably effective in reducing PLMS-I and PLMS-A. • Triazolam 0.125 to 0.500 mg/day is probably effective in improving sleep efficiency but not in the reduction of PLMS. • Modafinil and propoxyphene are probably ineffective while transdermal estradiol is considered ineffective for the treatment of PLMD. • No specific recommendations can be made in the treatment of PLMD in the pediatric population or in pregnant women.
The Movement Disorder Society: **Treatment of Restless Legs Syndrome: An Evidence-Based Review and Implications for Clinical Practice (2008)**[13]	Dopaminergic agents • Levodopa/benserazide or levodopa/carbidopa, at dosages of 100/25 to 200/50 mg is considered efficacious for the treatment of restless legs syndrome (RLS) although the number of patients included in Level I studies was not as large compared to other recommended treatments. Nonergot derived dopamine agonists • Ropinirole (0.25 to 4 mg) is efficacious for treating RLS in patients with moderate to severe clinical symptomatology. • Pramipexole (0.54 mg of base or 0.75 mg of salt) is efficacious for treating RLS symptoms in patients with moderate to severe clinical symptomatology. • The rotigotine transdermal patch is likely efficacious without special monitoring. Ergot derived dopamine agonists • Ergot-dopamine agonists require special monitoring due to increased incidence of cardiac valvular fibrosis and other fibrotic side effects. Because of their negative side-effect profile, these agents are not recommended as initial therapy for the treatment of RLS. If used, cardiopulmonary monitoring for fibrosis is necessary. • Bromocriptine (7.5 mg) is considered likely efficacious for the treatment of RLS, as one small study has shown that it has a significant effect on subjective RLS symptoms and PLMS, but it is currently rarely used for RLS treatment. • Pergolide (0.25 to 0.75 mg) has been shown to be efficacious in RLS for a therapeutic period up to one year proven by subjective sleep evaluation, the IRLS, and polysomnographic data. • Cabergoline (0.5 to 3 mg) has proven to be efficacious for the treatment of RLS. Opioids • Oxycodone is likely efficacious for the treatment of RLS in patients with significant daily symptoms, however, this recommendation is based on a single four week trial. • Methadone and tramadol are considered investigational for the treatment of RLS. Benzodiazepines

Clinical Guideline	Recommendation(s)
	• Clonazepam (0.5 to 1 mg) is considered investigational. It has a very long half-life and may cause daytime somnolence; it may cause unwanted blunting of consciousness, especially in the elderly, and can also decrease balance. Benzodiazepine receptor agonists • Zolpidem (10 mg) is considered investigational for RLS. The role of the sedative hypnotics, perhaps as adjuvant medications to benefit sleep in RLS, remains to be defined. Anticonvulsants • Gabapentin (200 mg to 2,000 mg) is efficacious for the treatment of RLS, and carbamazepine is likely efficacious. • Valproic acid is likely efficacious for the treatment of RLS, with special monitoring. There have been rare reports of hepatotoxicity, thrombocytopenia, and prolonged coagulation times, and regular blood monitoring is recommended. • Topiramate is considered to be investigational. N-Methyl-D-aspartic acid (NMDA) antagonists • Amantadine is investigational for the treatment of RLS. Up to one-third of patients may have central nervous system adverse effects. Clonidine • Clonidine is likely efficacious in RLS for those patients who are primarily bothered by symptoms at bedtime. Vitamins and minerals • Oral iron is not an efficacious treatment for RLS in iron-sufficient individuals. It is investigational for the treatment of RLS in iron-deficient RLS patients and should be used with appropriate evaluations to ensure the patients do not develop an iron overload indicating possible hemochromatosis. • Intravenous Iron dextran is likely efficacious for the treatment of RLS secondary to end-stage renal disease. Intravenous iron remains investigational for RLS patients with normal renal function with special monitoring. • Folic acid and magnesium are considered to be investigation in RLS.

Conclusions

The four agents approved by the Food and Drug Administration (FDA) for restless legs syndrome (RLS) are extended-release (ER) gabapentin enacarbil ER (Horizant®), pramipexole (Mirapex®), ropinirole (Requip®), and rotigotine (Neupro®) transdermal patches. Pramipexole, ropinirole, and rotigotine are nonergot derivative dopamine agonists that are also approved for the treatment of the signs and symptoms of idiopathic Parkinson's disease. Gabapentin enacarbil ER is a prodrug of the anticonvulsant gabapentin (Neurontin®) and the two products are not interchangeable due to their pharmacokinetics differences. Both pramipexole and ropinirole are available generically, while gabapentin enacarbil ER and rotigotine are not. All oral agents are dosed once daily in the evening prior to the onset of RLS symptoms with rotigotine being applied once daily at the same time each day.[2-7]

According current clinical guidelines, first-line treatment options for daily moderate-to-severe RLS include dopamine agonists. Despite the lack of FDA-approval, gabapentin is recognized as an off-label, second-line treatment option in RLS with daily symptoms, especially for patients who may have comorbid neuropathic pain. Opioids are also recommended as a second-line treatment option.[10-13]

To date, only a single, two-day, head-to-head study directly comparing the dopamine agonists against one another in RLS, and there are no head-to-head studies with gabapentin enacarbil ER. Gabapentin enacarbil ER, pramipexole, ropinirole, and rotigotine have consistently demonstrated their efficacy in improving both the objective and subjective symptoms associated with RLS compared to placebo, however, the duration of these studies are typically less than one year.[14-52] The major route of elimination of gabapentin enacarbil ER and pramipexole is renal excretion and dosing must be adjusted in patients with renal impairment, whereas ropinirole is extensively metabolized by the liver and may interact with drugs that undergo cytochrome P450 1A2 metabolism. The side effect profiles between pramipexole and ropinirole are comparable, although pramipexole has demonstrated a higher rate of hallucinations and ropinirole an increased risk of developing somnolence and hypotension.[2-7] Rotigotine is associated with application site reactions and nausea in many patients, especially in the first year of therapy.[5,50]

In comparison to other agents used for the treatment of RLS, such as opioids and benzodiazepines, gabapentin enacarbil ER may be associated with a more favorable safety profile, and associated with less risk of dependence. Moreover, symptom rebound and augmentation, a significant limitation to the treatment of RLS, have not been observed in clinical studies with gabapentin enacarbil ER, while augmentation has been reported with the dopamine agonists. The safety of gabapentin enacarbil ER is similar to gabapentin; with both agents most commonly associated with somnolence and dizziness.[2]

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