Therapeutic Class Overview
Dopamine Agonists

Therapeutic Class

- **Overview/Summary:** The three nonergot-derived dopamine agonists include pramipexole (Mirapex®), ropinirole (Requip®) and rotigotine (Neupro®). Furthermore, extended-release formulations are available for both pramipexole (Mirapex® ER) and ropinirole (Requip® XL).[1-5] All of the nonergot-derived dopamine agonists are Food and Drug Administration (FDA)-approved for the management of idiopathic Parkinson's disease, while rotigotine and the immediate-release pramipexole and ropinirole products are also indicated for moderate-to-severe primary restless legs syndrome (RLS). The exact mechanism by which these agents exert their therapeutic effect has not been fully established; however, both conditions appear to be related to dopaminergic dysfunction and the benefit of the dopamine agonists may be due to their stimulation of dopamine receptors.[1-5] The rotigotine transdermal patch was approved by the FDA in April 2012. Rotigotine transdermal patch was originally approved as a treatment for Parkinson's disease in 2007; however, it was withdrawn from the market in 2008 due to a manufacturing issue causing formation of rotigotine crystals within the patches.[6]

  The immediate-release formulations of pramipexole and ropinirole are administered three times daily for Parkinson's disease and once daily in the evening for the treatment of RLS. Rotigotine transdermal patches should be applied once daily for either condition. Dosing modifications are recommended with pramipexole in patients with renal impairment. Ropinirole undergoes hepatic metabolism by cytochrome P450 1A2, and there is potential for drug-drug interactions with inducers and inhibitors of this enzyme. The three agents have similar adverse event profiles; however, pramipexole is more often associated with hallucinations and ropinirole with somnolence and hypertension. Hallucinations and somnolence with rotigotine transdermal patch have been reported with similar incidences as pramipexole and ropinirole and appear to be dose-related. All of the nonergot-derived dopamine agonists have a warning regarding falling asleep during activities of daily living and patients should be advised to avoid potentially dangerous activities including driving.[1-5] Currently, pramipexole immediate-release and ropinirole immediate- and extended-release are available generically.[7]

Table 1. Current Medications Available in Therapeutic Class[1-5]

Generic (Trade Name)	Food and Drug Administration-Approved Indications	Dosage Form/Strength	Generic Availability
Pramipexole (Mirapex®*, Mirapex® ER)	Treatment of the signs and symptoms of idiopathic Parkinson's disease, treatment of moderate-to-severe primary restless legs syndrome (IR)	Extended-release tablet: 0.375 mg 0.75 mg 1.5 mg 2.25 mg 3 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 (Requip®*, Requip® XL*)	Treatment of the signs and symptoms of idiopathic Parkinson's disease, treatment of moderate-to-	Extended-release tablet: 2 mg 4 mg	✔

Generic (Trade Name)	Food and Drug Administration-Approved Indications	Dosage Form/Strength	Generic Availability
	severe primary restless legs syndrome (IR)	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 the signs and symptoms of idiopathic Parkinson's disease, treatment of moderate-to-severe primary restless legs syndrome	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	-

IR=immediate-release, ER, XL=extended release
*Generic available in at least one dosage form or strength.

Evidence-based Medicine

- Trials comparing the immediate- and extended-release formulations of pramipexole have demonstrated statistically significant improvements in Unified Parkinson Disease Rating Scale (UPDRS) Part II+III combined scores, and responder rates with both formulations compared to placebo; however; significant differences between the formulations have not been established.[8-10]
- The rotigotine transdermal patch has been associated with statistically significant improvements from baseline in UPDRS subscale scores and responder rates (≥20% reduction in UPDRS Part II+III scores from baseline) when compared to placebo.[11-15]
- In a study by Poewe et al, patients with Parkinson's disease were randomized to receive the rotigotine transdermal patch or pramipexole immediate-release for 16 weeks. The mean change in "off" time, was significantly improved with rotigotine transdermal patch (-1.58 hours; *P*<0.0001) and pramipexole (-1.94 hours; *P*<0.0001) compared to placebo; however, responder rates to therapy were similar between the active treatments (*P*=0.108).[16]
- Patients treated with either the rotigotine transdermal patch or ropinirole achieved a significantly greater responder rate in UPDRS Part II+III score compared to patients treated with placebo over 24 weeks (52 and 68 vs 30%; *P*<0.0001 for both).[17]
- For the treatment of restless legs syndrome (RLS) pramipexole, ropinirole and rotigotine transdermal patch have each demonstrated improvements in International Restless Legs Scale (IRLS) scores, periodic limb movements during sleep, patient and physician assessment scales, as well as sleep and quality of life compared to placebo.[18-48] Head-to-head studies comparing these agents in RLS are not available.
- The results of two meta-analyses evaluating pramipexole, ropinirole and rotigotine transdermal patch in patients with RLS indicate that all three agents improved scores on the IRLS scale and the Clinical Global Impression-Improvement scale compared to placebo.[47,48] Ropinirole was associated with a significant increase in study withdrawals secondary to adverse events, while pramipexole and rotigotine transdermal patch were not.[47,48]
- In a six-week dose-finding study, patients treated with the rotigotine transdermal patch experienced statistically significant reductions from baseline in IRLS scores with doses of 1 to 4 mg daily (*P*<0.05 for all). Improvements in IRLS scores were maintained in two open-label, extension studies lasting one and five years, respectively.[44-46]

Key Points within the Medication Class

- According to Current Clinical Guidelines:
  - Levodopa is the most effective symptomatic antiparkinsonian drug. Within a few years of treatment, motor complications frequently develop with levodopa treatment. As older patients are more sensitive to neuropsychiatric adverse reactions and are less prone to developing motor complications, the early use of levodopa is recommended in the older population.[49-51]
  - The oral dopamine agonists pramipexole and ropinirole immediate-or extended-release are effective as monotherapy in early Parkinson's disease, with a lower risk of motor complications than levodopa.[49-51]
  - Amantadine or anticholinergics have a smaller impact on symptoms than levodopa. Anticholinergics are poorly tolerated in the elderly and their use is generally restricted to young patients.[49-51]
  - For the treatment of motor fluctuations, nonergot dopamine agonists are considered first-line treatment. Catechol-o-methyltransferase (COMT) inhibitors or MAO-B inhibitors may be used, without preference for one agent over another for initial treatment.[49-51]
  - The treatment of dyskinesias includes reducing the dose of levodopa, at a risk of increasing "off" time, or discontinuing MAO-B inhibitor or COMT inhibitors.[49-51]
  - The nonergot-derived dopamine agonists pramipexole, ropinirole and rotigotine transdermal patch are effective for the treatment of restless legs syndrome (RLS) and should be considered for initial therapy.[52,53]
  - Alternative products used for the treatment of RLS include the anticonvulsants, opioids and benzodiazepines.[52,53]
- Other Key Facts:
  - Pramipexole immediate-release (Mirapex®), ropinirole immediate-release (Requip®) and extended-release (Requip® XL) are available generically.[7]
  - Pramipexole extended-release (Mirapex® ER) and rotigotine transdermal patches (Neupro®) are only available as branded products.[7]

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Therapeutic Class Review
Dopamine Agonists

Overview/Summary

The three nonergot-derived dopamine agonists include pramipexole (Mirapex®), ropinirole (Requip®) and rotigotine transdermal patch (Neupro®). Furthermore, extended-release formulations are available for both pramipexole (Mirapex® ER) and ropinirole (Requip® XL).[1-5] All of the nonergot-derived dopamine agonists are Food and Drug Administration (FDA)-approved for the management of idiopathic Parkinson's disease, while rotigotine transdermal patch and the immediate-release pramipexole and ropinirole products are also indicated for moderate-to-severe primary Restless Legs Syndrome (RLS). The exact mechanism by which these agents exert their therapeutic effect has not been fully established; however, both conditions appear to be related to dopaminergic dysfunction and the benefit of the dopamine agonists may be due to stimulation of dopamine receptors.[1-5] The rotigotine transdermal patch was approved by the FDA in April 2012. Rotigotine transdermal patch was originally approved as a treatment for Parkinson's disease in 2007; however, it was withdrawn from the market in 2008 due to a manufacturing issue causing formation of rotigotine crystals within the patches.[6]

The immediate-release formulations of pramipexole and ropinirole are administered three times daily for Parkinson's disease and once daily in the evening for the treatment of RLS. Rotigotine transdermal patches should be applied once daily for either condition. Dosing modifications are recommended with pramipexole in patients with renal impairment. Ropinirole undergoes hepatic metabolism by cytochrome P450 1A2, and there is potential for drug-drug interactions with inducers and inhibitors of this enzyme. The three agents have similar adverse event profiles; however, pramipexole is more often associated with hallucinations and ropinirole with somnolence and hypertension. Hallucinations and somnolence with rotigotine transdermal patch have been reported with similar incidences as pramipexole and ropinirole and appear to be dose-related. All of the nonergot-derived dopamine agonists have a warning regarding falling asleep during activities of daily living and patients should be advised to avoid potentially dangerous activities including driving.[1-5] Currently, pramipexole immediate-release and ropinirole immediate- and extended-release are available generically.[7]

The nonergot-derived dopamine agonists have not been directly compared, but they have demonstrated efficacy in the treatment of both Parkinson's disease and RLS in placebo-controlled trials and with active comparators such as levodopa and bromocriptine.[8] Levodopa has long been the mainstay of therapy for the treatment of Parkinson's disease although chronic use is associated with the development of dyskinesias, and its effects are dependent on metabolic conversion to cross into the central nervous system.[8] Moreover, the nonergot-derived dopamine agonists have a longer duration of action compared to levodopa and require less frequent administration. A number of clinical practice guidelines support the use of dopamine agonists for the treatment of early stage Parkinson's disease particularly in younger patients who are more likely to develop the motor complications associated with levodopa. Unfortunately, the dopamine agonists are associated with a higher incidence of adverse events such as hallucinations, somnolence and edema and are somewhat less effective in managing motor symptoms and deficiencies in activities of daily living compared to levodopa.[9-11]

Consensus treatment guidelines generally recommend the nonergot-derived dopamine agonists as first-line therapy for the management of RLS, with pramipexole, ropinirole and rotigotine transdermal patch being preferred over ergot-derived dopamine agonists secondary to their more favorable safety profile.[12-14] Alternative products used for the treatment of RLS include the anticonvulsants, opioids and benzodiazepines.[14]

Medications

Table 1. Medications Included Within Class Review

Generic Name (Trade Name)	Medication Class	Generic Availability
Pramipexole (Mirapex®*, Mirapex® ER)	Dopamine agonists	✔
Ropinirole (Requip®*, Requip® XL*)	Dopamine agonists	✔
Rotigotine (Neupro®)	Dopamine agonists	-

ER, XL=extended release.
*Generic available in at least one dosage form or strength.

Indications

Table 2. Food and Drug Administration-Approved Indications[1-5,15]

Indication	Pramipexole	Ropinirole	Rotigotine
Treatment of the signs and symptoms of idiopathic Parkinson's disease	✔	✔	✔
Treatment of moderate-to-severe primary restless legs syndrome	✔ (IR)	✔ (IR)	✔

IR=immediate-release

Pramipexole may potentially be used off-label for the treatment of fibromyalgia.[15] Studies evaluating the use of pramipexole and ropinirole in the management of treatment-resistant depression are ongoing.

Pharmacokinetics

Table 3. Pharmacokinetics[1-5,15]

Generic Name	Bioavailability (%)	Absorption (%)	Renal Excretion (%)	Active Metabolites	Serum Half-Life (hours)
Pramipexole	>90 (IR)	Not reported	90	None	8 to 12*
Ropinirole	55 (IR and XL)	Not reported	88	None	6
Rotigotine	<46	Not reported	71	None	3

IR=immediate-release, XL=extended-release
*Elderly patients.

Clinical Trials

Clinical trials demonstrating the safety and efficacy of the nonergot-derived dopamine agonists are described in Table 4.

Numerous clinical trials have compared pramipexole, ropinirole and rotigotine transdermal patch to either placebo or more established medications, such as levodopa, for the management of Parkinson's disease. Studies directly comparing these agents in the treatment of Parkinson's disease are lacking. A decrease in the risk of developing dyskinesias and other motor complications has been observed with the dopamine agonists compared to levodopa; however, levodopa is generally associated with greater improvements in the Unified Parkinson Disease Rating Scale (UPDRS) motor and activities of daily living scores, than with pramipexole and ropinirole.[23,25,28] Using neuroimaging, trials have assessed the difference in the rate of progression of dopaminergic degeneration between pramipexole and levodopa (CALM-PD-CIT trial) and between ropinirole and levodopa (REAL-PET study).[23,28] Results from these trials showed that dopamine agonist therapy is associated with a slower rate of progression compared to levodopa therapy.

Available trials comparing the immediate- and extended-release formulations of pramipexole have demonstrated statistically significant improvements in UPDRS Part II+III combined scores, and responder rates with both formulations compared to placebo; however; significant differences between the formulations have not been established.[16-18] The rotigotine transdermal patch has been associated with statistically significant improvements from baseline in UPDRS subscale scores and responder rates

(≥20% reduction in UPDRS Part II+III scores from baseline) when compared to placebo.[31-33,37,38] In a study by Poewe et al, patients with Parkinson's disease for at least three years were randomized to receive the rotigotine transdermal patch or pramipexole immediate-release for 16 weeks. The mean change in "off" time, the primary endpoint, was significantly improved with rotigotine transdermal patch (-1.58 hours; *P*<0.0001) and pramipexole (-1.94 hours; *P*<0.0001) compared to placebo. The responder rate (≥30% reduction in absolute time "off" from baseline) was not significantly different between the groups (*P*=0.108).[39] In another study, patients treated with either the rotigotine transdermal patch or ropinirole achieved a significantly greater responder rate in UPDRS Part II+III score compared to placebo over 24 weeks (52 and 68 vs 30%; *P*<0.0001 for both).[40]

The results of meta-analyses have generally demonstrated that the nonergot-derived dopamine agonists are beneficial as adjunct to levodopa in patients with Parkinson's disease to allow for the reduction in the dose of levodopa, therefore ameliorating the motor complications associated with its long-term use.[21,22,26,27]

For the treatment of restless legs syndrome (RLS) pramipexole, ropinirole and rotigotine transdermal patch have each consistently demonstrated improvements in International Restless Legs Scale (IRLS) scores, periodic limb movements during sleep (PLMS), patient and physician assessment scales, as well as sleep and quality of life compared to placebo.[43-73] Only a single, two-day, head-to-head trial comparing pramipexole and ropinirole was identified. This trial found that periodic leg movements in sleep index (PLMSI) was significantly reduced with ropinirole compared to pramipexole (*P*=0.0004).[56] No head-to-head studies evaluating the rotigotine transdermal patch for the treatment of RLS were identified.

The results of two meta-analyses evaluating pramipexole, ropinirole and rotigotine transdermal patch in patients with moderate-to-severe primary RLS as compared to placebo indicated that all three agents improved scores on the IRLS scale and the Clinical Global Impression-Improvement scale.[72,73] In both analyses, ropinirole was associated with a significant increase in study withdrawals secondary to adverse events, while pramipexole and rotigotine transdermal patch were not.[72,73] Trials including pramipexole or ropinirole for the treatment of RLS beyond one-year are lacking. In a six-week dose-finding study, patients treated with the rotigotine transdermal patch experienced statistically significant reductions from baseline in IRLS scores with doses of 1 to 4 mg daily (*P*<0.05 for all). Improvements in IRLS scores were maintained in two open label, extension studies of one and five years.[69-71] The results of a small (N=16), open-label study comparing ropinirole and gabapentin demonstrated that there was no difference between the treatments with regard to the number of PLMS or PLMSI; however, each group experienced significant improvements from their respective baseline values.[66]

Table 4. Clinical Trials

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
Parkinson's Disease				
Poewe et al[16] Pramipexole ER 0.375 mg QD increased as needed to 4.5 mg QD vs pramipexole IR 0.125 mg TID increased as needed to 1.5 mg TID vs placebo The dose was titrated weekly over seven weeks, to a response level judged satisfactory by the investigator and at which patients rated themselves as at least "a little better" on the PGI-I scale.	AC, DB, MC, PC, RCT Patients ≥30 years of age with Parkinson's disease for <5 years and a level disability requiring initiation or augmentation of dopaminergic therapy	N=599 26 weeks	Primary: Change from baseline in UPDRS Part II+III combined score Secondary: PGI-I and CGI-I responder rates ("much" or "very much better/ improved"), UPDRS Part II+III responder rate (≥20% improvement from baseline score), UPDRS Part I, II and III scores separately, proportion of patients requiring levodopa rescue, scores on PDQ-39 and EQ-5D	Primary: The adjusted mean decreases in combine scores on UPDRS Part II+III were -8.2 for pramipexole ER and -8.7 for pramipexole IR compared to -1.2 for placebo (*P*<0.0001). The treatment difference between the pramipexole groups was -0.5 points (95% CI, -2.3 to 1.3). In the PPS, the adjusted mean decreases were -9.4 and -8.5, respectively, a difference of -0.9. The lower bound of the 95% CI did not exceed the predefined margin of -3.0, demonstrating noninferiority of pramipexole ER compared to IR. Secondary: A significantly greater proportion of patients receiving pramipexole ER were PGI-I responders compared to the placebo group (34.4 vs 16.5%; *P*=0.0008). More patients receiving pramipexole IR achieved a PGI-I response compared to patients receiving placebo (32.4 vs 16.5%; *P*=0.0020). The CGI-I response rate was higher for pramipexole ER (41.4%; *P*=0.0003) and pramipexole IR (45.1%; *P*<0.0001) groups compared to the placebo group (20.6%). A higher proportion of patients randomized to pramipexole ER or pramipexole IR achieved a UPDRS II+III response compared to patients in the placebo group (66.7 and 63.8 vs 35.0%, respectively; *P*<0.0001 for both). The UPDRS Part II scores were significantly lower for patients receiving either formulation of pramipexole compared to patients receiving placebo (*P*<0.0001 for both). Similarly, there were significant improvements in UPDRS Part III scores with both pramipexole formulations compared to placebo over 26 weeks (*P*<0.0001 for both). At week 26, 7.0% of patients receiving pramipexole ER and 4.3% of those receiving pramipexole IR received adjunct therapy with levodopa compared to patients receiving placebo (21.4%; *P*<0.0001 for both).

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
				There was a statistically significant improvement in PDQ-39 score for patients receiving pramipexole IR compared to patients receiving placebo (-6.5 vs -1.5; *P*=0.0043); however, there was no statistically significant difference with patients receiving the pramipexole ER formulation (-3.8; *P*=0.1802). No statistically significant improvement in EQ-5D VAS score was reported with either formulation of pramipexole compared to placebo (*P*>0.05 for both).
Schapira et al[17] Pramipexole ER 0.375 mg QD increased as needed to 4.5 mg QD vs pramipexole IR 0.125 mg TID increased as needed to 1.5 mg TID vs placebo The dose was titrated weekly over seven weeks, as tolerated, to a response level judged satisfactory by the investigator and at which patients rated themselves as at least "a little better" on the PGI-I scale.	AC, DB, MC, PC, RCT Patients ≥30 years of age with Parkinson's disease for ≥2 years who were receiving levodopa at an optimized dosage who continued to experience motor fluctuations (≥2 cumulative hours of daily "off" time during waking on two consecutive days)	N=517 Up to 26 weeks	Primary: Change from baseline in UPDRS Part II+III combined score Secondary: Change in diary-determined daily "off"-time, diary-determined daily "on" time (without dyskinesia, with untroublesome dyskinesia, and with troublesome dyskinesia), CGI-I and PGI-I responder rates ("much" or "very much improved/ better"), responder rate for a PGI-I assessment of early morning "off" symptoms, UPDRS Part II+III responder rate (≥20% improvement);	Primary: In the full analysis set at 18 weeks (LOCF), the mean decrease from baseline in UPDRS Part II+III score was -11.0 in the pramipexole ER group and -12.8 for the pramipexole IR group compared to -6.1 for the placebo group (*P*=0.0001 and *P*<0.0001, respectively). In the PPS (LOCF), the mean decreases were -12.8 and -13.6 in patients receiving pramipexole ER and IR, respectively, compared to the placebo group (-6.8; *P*<0.0001 for both). Secondary: "Off" time was decreased by -2.1 hours/day for patients receiving pramipexole ER and -2.5 hours/day for those randomized to receive pramipexole IR compared to -1.4 hours/day for patients receiving placebo (*P*=0.0199 and *P*<0.0001). The percentage of daily "off" time was reduced from baseline by 13.3 and 15.9% with pramipexole ER and IR, respectively, compared to 8.8% with placebo (*P*=0.122 and *P*<0.0001, respectively). The CGI-I responder rates were significantly higher with pramipexole ER (48.8%; *P*=0.0037) and IR (52.1%; *P*=0.0002) compared to placebo (32.7%). A greater percentage of patients were considered to be PGI-I responders in the pramipexole IR group compared to the placebo group (44.2 vs 27.0%; *P*=0.0005); however, there was no statistically significant difference for the pramipexole ER group (37.3%; *P*=0.0554). A significantly higher proportion of patients receiving pramipexole ER or IR achieved a PGI-I response for early morning "off" symptoms compared to patients receiving placebo (34.8 and 40.4 vs 19.6%; *P*<0.05 for both).

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
			UPDRS Part I score and PDQ-39	A UPDRS Part II+III response to treatment was experienced by 64.0 and 68.5% of patients treated with pramipexole ER and IR, respectively compared to the placebo group (40.2%; *P*<0.0001 for both). There was no difference between either pramipexole formulation and placebo with regard to changes in UPDRS Part I score (*P*>0.05 for both). Statistically significant reductions from baseline in UPDRS Part II score were achieved by patients treated with pramipexole ER (*P*=0.0455) or IR (*P*<0.0001) compared to patients treated with placebo. Statistically significant improvements in UPDRS Part III scores compared to baseline occurred in patients treated with either pramipexole formulation compared to patients treated with placebo (*P*<0.0001 for both). There was a significant reduction from baseline in PDQ-39 scores with pramipexole IR compared to placebo (*P*=0.0038); however, no significant reduction was reported with pramipexole ER (*P*=0.2338).
Hauser et al[18] Pramipexole ER 0.375 mg QD increased as needed to 4.5 mg QD vs pramipexole IR 0.125 mg TID increased as needed to 1.5 mg TID vs placebo The dose was titrated	AC, DB, MC, PC, RCT Patients ≥30 years of age with Parkinson's disease for ≤5 years and were exhibiting at least two cardinal signs (bradykinesia, rigidity, and resting tremor) and were Hoehn and Yahr Stages I to III and in	N=259 18 weeks	Primary: Change from baseline in UPDRS Part II+III combined score Secondary: CGI-I and PGI-I responder rates, change from baseline in individual UPDRS Parts I, II and III, and PDQ-39 and EQ-5D scores	Primary: The mean reduction from baseline in UPDRS Part II+III score from baseline (including data from subjects receiving levodopa rescue medication) was -5.1 in the placebo group compared to -8.1 in the pramipexole ER group (*P*=0.0282) and -8.4 in the pramipexole IR group (*P*=0.0153). The mean reduction from baseline in UPDRS Part II+III score (carrying forward the last efficacy value before levodopa rescue) was -2.7 in the placebo group compared to -7.4 in the pramipexole ER group (*P*=0.0010) and -7.5 in the pramipexole IR group (*P*=0.0006). The difference between the two pramipexole groups in UPDRS Part II+III score was small and not statistically significant. Secondary: The percentage of patients considered to be PGI-I responders was 35.6% in the pramipexole ER group (*P*=0.0017) and 23.8% in the pramipexole IR group (*P*=0.0591) compared to the placebo group (10%).

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
weekly over seven weeks, as tolerated, to a response level judged satisfactory by the investigator and at which patients rated themselves as at least "a little better" on the PGI-I scale.	need of dopaminergic therapy			The percentage of responders according to the CGI-I was 37% in the ER group (*P*=0.0165) and 48% in the IR group (*P*=0.0004) compared to the placebo group (16%). Changes in UPDRS Part I scores were not significantly different from placebo for either pramipexole ER or IR. Changes in UPDRS Part II scores were significantly reduced from baseline for patients receiving pramipexole ER or IR formulations regardless of rescue levodopa use (*P*<0.05 for all). When the levodopa data was censored, there was a statistically significant reduction from baseline in UPDRS Part III scores with pramipexole ER (*P*=0.0039) and IR (*P*=0.0038) formulations compared to placebo; however, with the levodopa data was not censored, the difference was not statistically significant. Statistically significant improvements in PDQ-39 scores were reported in patients receiving pramipexole ER or IR compared to patients receiving placebo, regardless of levodopa data censoring (*P*<0.05 for all). No statistically significant difference was reported between either pramipexole group and the placebo group with regard to EQ-5D scores (*P*>0.05 for all).
Kieburtz et al[19] Pramipexole IR 0.5 mg TID vs pramipexole IR 0.75 mg BID	AC, DB, MC, PC, PG, RCT Patients ≥30 years of age with Parkinson's disease for <7 years with two of three cardinal signs	N=311 12 weeks	Primary: Change from baseline in UPDRS total score Secondary: Changes from baseline in the modified Schwab and England ADL score,	Primary: The mean reduction in the total UPDRS score, was comparable among patients receiving 0.5 mg BID (-4.4; 95% CI, -2.3 to -6.5), 0.75 mg BID (-4.7; 95% CI, -2.5 to -6.9) and 0.5 mg TID (-4.4; 95% CI, -2.3 to -6.5) compared to patients receiving placebo (*P*<0.0001 all compared to placebo). Secondary: Compared to placebo, Schwab and England scores for ADLs were improved by 2.0 points with 50 mg BID (P=0.01), 1.8 points with 0.75 mg BID (*P*=0.02) and 1.8 with 50 mg TID (*P*=0.02).

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
vs pramipexole IR 0.5 mg BID vs placebo Concomitant dopaminergic medications were not permitted; however, MAO-B inhibitors, anticholinergics, and amantadine could be maintained at a stable dosage throughout the study.	(resting tremor, bradykinesia and rigidity)		ESS, Montreal Cognitive Assessment, BDI-II, PDQ-39, Apathy Scale, PDSS, Snaith-Hamilton Pleasure Scale and the MMIDI	The mean ESS score improved among all three pramipexole groups compared to the placebo group ($P \leq 0.03$ for all). There was no statistically significant difference between both pramipexole regimens and placebo with regard to Montreal Cognitive Assessment scores at 12 weeks ($P \geq 0.16$ for all). Similarly, no statistically significant differences were observed between any pramipexole group and the placebo group in terms of improvements BDI-II scores ($P \geq 0.37$ for all) or Apathy scale scores ($P \geq 0.59$). Patients receiving pramipexole 0.75 mg BID or 0.50 mg TID experienced statistically significant improvements in PDQ-39 scores compared to patients receiving placebo ($P \leq 0.05$ for both); however, no significant difference occurred in the 0.50 mg BID group. No significant treatment effects were observed for any of the other secondary outcome variables.
Rascol et al[20] Pramipexole ER 0.375 mg QD increased as needed to 4.5 mg QD plus placebo BID vs pramipexole IR 0.125 mg TID increased as needed to 1.5 mg TID	DB, MC, PC, RCT Patients ≥30 years of age with Parkinson's disease for ≤5 years and at least two of three cardinal motor signs (resting tremor, bradykinesia, and rigidity) receiving pramipexole	N=169 9 weeks	Primary: Proportion of patients successfully switched, with or without any dosage adjustment (no worsening from baseline UPDRS Part II+III score by >15% and no withdrawal due to drug-related adverse events) Secondary: Proportion of patients successfully switched	Primary: At nine weeks in the full analysis set, 84.5% of subjects in the pramipexole ER group had been successfully switched to the opposite treatment, compared to 94.2% for the IR group. The absolute difference between groups was -9.76% (95% CI, -18.81 to 1.66). In the PPS, the rates were similar, at 85.0% for pramipexole ER and 93.9% for IR, an absolute difference of -8.88% (95% CI, -18.08 to 2.98). The lower limits of the 95% CIs exceeded the prespecified noninferiority margin of -15%, meaning noninferiority was not established. Secondary: At four weeks, 81.6% of subjects in the pramipexole ER group had been successfully switched to the opposite treatment compared to 92.3% of subjects for the IR group. The absolute difference between groups was -10.75% (95% CI, -20.51 to 1.48).

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
	IR continuously for at least three months		at week four, change in UPDRS Parts II, III and II+III scores, proportion of patients requiring dosage change, mean change in daily dosage, CGI-I and PGI-I	Following nine weeks of treatment, the mean reduction from baseline in UPDRS Part II+III score was not significantly different between the pramipexole ER and IR groups (1.6 vs 0.5; *P*=0.2061). Similarly, there was no statistically significant reduction from baseline between the pramipexole ER and IR groups with regard to UPDRS Part II (0.3 vs 0.1; *P*=0.4694) and III scores (1.2 vs 0.3; *P*=0.1804). Among patients successfully switched at week nine, the mean reduction in UPDRS Part II+III score was greater for the pramipexole ER group compared to the IR group (2.9 vs 0.8; *P*=0.0030). At nine weeks, the proportion of CGI-I responders was not significantly different between the pramipexole ER and IR groups (87.4 vs 78.8%; *P*=0.1623). Similar results were reported for PGI-I responders (81.6 vs 71.2%; *P*=0.1299).
Clarke et al[21] Pramipexole vs placebo	MA Patients with a Parkinson's disease and long-term complications of dyskinesia and/or end-of-dose deterioration	N=669 (4 trials) >4 weeks	Primary: "Off" time measurements, changes in dyskinesia rating scale, prevalence of dyskinesia, Parkinson's disease rating scales, levodopa dosage, withdrawals due to lack of efficacy and/or adverse events Secondary: Not reported	Primary: Pramipexole resulted in a greater reduction in "off" time compared to placebo (WMD, 1.8 hours; 95% CI, 1.2 to 2.3; *P*=0.00001). The incidence of dyskinesia was more frequent in the pramipexole group compared to the placebo group (OR, 2.10; 95% CI, 1.50 to 2.94; *P*=0.00002). A significant improvement in UPDRS complication score was noted in two of four trials, UPDRS ADL scores improved in all trials and UPDRS motor scores improved in three trials. Pramipexole showed a significant benefit in reducing the dose of levodopa (WMD, 115 mg; 95% CI, 87 to 143; *P*<0.00001) and a significantly lower withdrawal rate (OR, 0.64; 95% CI, 0.44 to 0.93; *P*=0.02). Secondary: Not reported

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
Clarke et al[22] Pramipexole vs bromocriptine	MA Patients with Parkinson's disease and long-term complications of dyskinesia and/or end-of-dose deterioration	N=163 (1 trial) >4 weeks	Primary: "Off" time measurements, changes in dyskinesia rating scale, prevalence of dyskinesia, Parkinson's disease rating scales, levodopa dosage, withdrawals due to lack of efficacy and/or adverse events Secondary: Not reported	Primary: Pramipexole therapy resulted in a greater reduction in "off" time compared to bromocriptine (WMD, 1.4 hours; 95% CI, 0.03 to 2.77; *P*=0.05). The difference in the prevalence of dyskinesia, change in the dyskinesia rating scale, or UPDRS complication score was not significant. Improvements in the UPDRS ADL and motor scores, as well as the levodopa dose reduction were comparable with both agents. There was no significant difference in the withdrawal rate. Secondary: Not reported
Marek et al[23] Pramipexole IR 0.5 mg TID increased as needed to maximum of 1.5 mg TID vs carbidopa/levodopa 25/100 mg TID increased as needed to a maximum of 150/600 mg daily Supplemental levodopa was prescribed as needed.	DB, MC, PG, RCT Patients with early Parkinson's disease requiring dopaminergic therapy	N=82 4 years	Primary: The mean change from baseline in striatal [^{123}I]β-CIT uptake (a useful marker of disease progression) after 46 months Secondary: The percentage and absolute changes from baseline in striatal, putamen, and caudate ^{123}I] β-CIT uptake (a useful marker of disease progression) after 22	Primary: Pramipexole was associated with a slower rate of decline from baseline in striatal [^{123}I]β-CIT uptake with a mean change from baseline of -16.0% compared to -25.5% with levodopa (*P*=0.01). Secondary: Pramipexole also demonstrated less of a decline in striatal [^{123}I] β-CIT uptake compared to levodopa at months 22 (-7.1 vs -13.5%; *P*=0.004) and 34 (-10.9 vs -19.6%; *P*=0.009). Results were similar for putamen [^{123}I]β-CIT uptake after 22 months (-7.9% for pramipexole compared to -16.9% for levodopa; *P*=0.005) and 34 months (-11.4% for pramipexole compared to -24.2% for levodopa; *P*=0.001), as well as caudate [^{123}I]β-CIT uptake after 22 months (-6.4% for pramipexole compared to -11.8% for levodopa; *P*=0.02) and 34 months (-10.3% for pramipexole compared to -17.2% for levodopa; *P*=0.04). A significant decrease in both the mean total and motor UPDRS scores from

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
			and 34 months, clinical severity of Parkinson's disease using the UPDRS 12 hours "off" medication	baseline was observed in the levodopa group (-3.3 vs 0.9 in the pramipexole group and -2.5 vs 0.0 in the pramipexole group respectively) at month 22. Differences between groups in UPDRS scores did not reach statistical significance at months 34 or 46.
Etminan et al[24] Pramipexole vs ropinirole vs levodopa vs placebo	MA Patients with Parkinson's disease	N=2,163 (13 trials) Duration not reported	Primary: Adverse events Secondary: Not reported	Primary: The dopamine agonists were associated with a significantly greater risk of somnolence (RR, 1.61; 95% CI, 1.21 to 2.13) and hallucinations (RR, 1.92; 95% CI, 1.08 to 3.24) than levodopa; however, there was no significant difference for dizziness (RR, 0.96; 95% CI, 0.61 to 1.51), hypotension (RR, 1.01; 95% CI, 0.67 to 1.51) and nausea (RR, 1.13; 95% CI, 0.92 to 1.39). Compared to placebo, the dopamine agonists were associated with an increased risk of dizziness (RR, 1.60; 95% CI, 1.17 to 2.20), hypotension (RR, 2.14; 95% CI, 1.02 to 4.48), nausea (RR, 2.15; 95% CI, 1.16 to 2.75), somnolence (RR, 3.16; 95% CI, 1.62 to 6.13) and hallucinations (RR, 4.24; 95% CI, 1.87 to 9.62). There was a significantly higher risk of developing hypotension with ropinirole (RR, 6.46; 95% CI, 1.47 to 28.28) compared to pramipexole (RR, 1.65; 95% CI, 0.88 to 3.08) when compared to placebo but not when the agents were compared to levodopa (RR, 1.03; 95% CI, 0.62 to 1.63 for ropinirole compared to RR, 1.12; 95% CI, 0.30 to 4.19 for pramipexole). The RR of somnolence reported with ropinirole was 5.73 (95% CI, 2.34 to 14.01) compared to 2.01 (95% CI, 2.17 to 3.16) for pramipexole relative to placebo although a significant difference was not demonstrated in comparison to levodopa. Pramipexole was associated with a higher risk of hallucinations than ropinirole compared to placebo (RR, 5.20; 95% CI, 1.97 to 13.72 compared to RR, 2.75; 95% CI, 0.55 to 13.73), but not when compared to levodopa. Secondary:

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
				Not reported
Inzelberg et al[25] Pramipexole vs ropinirole vs cabergoline vs levodopa	SR Patients with early Parkinson's disease	N=981 (3 trials) 2 to 5 years	Primary: Proportion of patients who developed dyskinesia, patient withdrawals, change from baseline in scores for motor function and ADL and adverse events Secondary: Not reported	Primary: Fewer patients developed dyskinesia with dopamine agonist use than with levodopa use (*P*<0.01 for all). The decrease in risk was similar among groups with an OR of 0.25 (95% CI, 0.13 to 0.47) for pramipexole, 0.31 (95% CI, 0.18 to 0.53) for ropinirole and 0.38 (95% CI, 0.19 to 0.78) for cabergoline all compared to levodopa. Differences in the incidence of withdrawals relative to levodopa did not reach statistical significance for ropinirole (OR, 1.13; 95% CI, 0.68 to 1.88), pramipexole (OR, 1.24; 95% CI, 0.64 to 2.39) or cabergoline (OR, 1.24; 95% CI, 0.71 to 2.14). Improvements in motor function were found to be greater with levodopa than both pramipexole (*P*=0.001) and ropinirole (*P*=0.008). The adjusted mean changes in the motor scores were reported as 3.90 for pramipexole and 4.48 for ropinirole with a difference of 0.58 (95% CI, -4.20 to 3.13; *P*=0.759), thus the difference between each dopamine agonist compared to levodopa was comparable. Levodopa demonstrated significant improvements in ADLs compared to pramipexole (*P*<0.001), but not ropinirole (*P*=0.08). The adjusted mean changes in the ADL scores were reported as 5.000 for pramipexole and 1.530 for ropinirole with a difference of 3.470 (95% CI, 0.363 to 6.580; *P*=0.029). Results of these two outcomes were not reported for cabergoline. The incidence of edema was reported more often with dopamine agonists compared to levodopa. OR were reported as 4.09 (95% CI, 1.61 to 10.41) for pramipexole, 2.73 (95% CI, 1.01 to 7.39) for ropinirole and 6.22 (95% CI, 2.55 to 15.21) for cabergoline. There were no significant differences in the absolute risk reduction. The frequency of other adverse events including anxiety, depression, headache, dizziness/hypotension and nausea did not differ significantly among each of the dopamine agonists or compared to levodopa (*P*>0.10).

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
				Somnolence was only reported in trials comparing pramipexole or ropinirole with levodopa and occurred more often with pramipexole (*P*=0.032) but not with ropinirole relative to levodopa (*P*=0.175). Secondary: Not reported
Clarke et al[26] Ropinirole vs placebo	MA Patients with Parkinson's disease and long-term complications of dyskinesia and/or end-of-dose deterioration	N=263 (3 trials) >4 weeks	Primary: "Off" time measurements, changes in dyskinesia rating scale, prevalence of dyskinesia, Parkinson's disease rating scales, levodopa dosage, withdrawals due to lack of efficacy and/or adverse events Secondary: Not reported	Primary: There was inadequate data available to determine the effect of ropinirole on "off" time. The incidence of dyskinesia was significantly more frequent with active treatment (OR, 2.90; 95% CI, 1.36 to 6.19). Ropinirole demonstrated significant reductions in the dose of levodopa (WMD, 180 mg; 95% CI, 106 to 253). There was no significant difference in the withdrawal rate reported (OR, 0.52; 95% CI, 0.24 to 1.09). More patients were likely to consider themselves to be "much/very much improved" with ropinirole compared to placebo (OR, 2.98; 95% CI, 1.53 to 5.80; *P*=0.001). Secondary: Not reported
Clarke et al[27] Ropinirole vs bromocriptine	MA Patients with Parkinson's disease and long-term complications of dyskinesia and/or end-of-dose	N=482 (3 trials) >4 weeks	Primary: "Off" time measurements, prevalence of dyskinesia, Parkinson's disease rating scales, levodopa dosage, withdrawals due to lack of efficacy	Primary: No significant difference was established between comparators in "off" time (WMD, 0.80; 95% CI, -0.80 to 1.69), prevalence of dyskinesia (OR, 1.51; 95% CI, 0.65 to 3.49), patients reporting "much/very much improved" on the CGI (OR,1.36; 95% CI, 0.87 to 2.13), levodopa dose reduction (WMD, 50.21; 95% CI, -49.40 to 149.81) or withdrawal rates (OR, 0.76; 95% CI, 0.45 to 1.27). Secondary: Not reported

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
	deterioration		and/or adverse events Secondary: Not reported	
Whone et al[28] Ropinirole 0.25 mg TID increased to a maxium of 24 mg daily as needed vs carbidopa/levodopa 12.5/50 mg daily increased to a maximum of 1,000 mg of levodopa as needed Supplemental levodopa was prescribed as needed. Fixed dose amantadine and anticholinergic antiparkinson medications were permitted.	DB, MC, PRO, RCT Patients 30 to 75 years of age with ^{18}F-dopa PET evidence and a clinical diagnosis of Parkinson's disease, who were experiencing symptoms for ≤2 years	N=162 2 years	Primary: Change in putamen ^{18}F-dopa uptake (a useful marker of disease progression) from baseline Secondary: Change from baseline in UPDRS motor scores, proportion of patients scoring one ("very much improved") or two ("much improved") on the CGI-I scale over one year, incidence and time to development of dyskinesias	Primary: A significantly greater reduction in putamen ^{18}F-dopa uptake was observed with levodopa treatment relative to ropinirole therapy (-20.30 vs -13.40%; *P*=0.022). Secondary: Ropinirole was associated with an increase in the UPDRS motor score (0.70 points), while levodopa demonstrated a reduction in the score (-5.64 points) and therefore an improvement in symptoms. The difference in the change in motor function between levodopa and ropinirole was significant (95% CI, 3.54 to 9.14). The percentage of patients reporting either a one or a two on the CGI-I scale was comparable between groups (67.80 and 74.70% for ropinirole and levodopa, respectively; OR, 0.72; 95% CI, 0.36 to 1.45; *P*=0.367). There was a significant reduction in the risk of developing dyskinesias with ropinirole (3.40%) relative to levodopa (26.70%; OR, 0.09; 95% CI, 0.02 to 0.29; *P*<0.001). The difference in time to development of dyskinesias was significant and favored ropinirole (*P*<0.001). Supplemental levodopa was required in 15 (17.0%) patients in the ropinirole group and seven (9.0%) patients in the levodopa group. The most common adverse events noted were nausea and somnolence, both occurred more often with ropinirole use (43.7 and 37.9% respectively vs 21.3 and 9.3% for levodopa).
Kim et al[29] Rotigotine transdermal patch 2 to 8 mg/24	MC, OL Patients ≥18 years of age	N=124 4 weeks	Primary: Change from baseline in UPDRS Part I, II, III and IV	Primary: Rotigotine treatment resulted in small mean decreases in scores from baseline on UPDRS Part I (-0.5), II (-0.9), III (-1.9) and IV -0.4) following a switch to rotigotine treatment (*P* values not reported).

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
hours Switching from oral ropinirole to rotigotine patch was proposed to be done as follows: 3 mg/day ropinirole to 2 mg/24 hours rotigotine, 6 mg/day to 4 mg/24 hours, 8 or 9 mg/day to 6 mg/24 hours and 12 mg/day to 8 mg/24 hours	with Parkinson's disease who were not controlled by ropinirole at a total daily dose of 3 to 12 mg		scores, mPDSS, ESS, NMSS, CGI-I, PGI and PDQ-8 Secondary: Not reported	The mean mPDSS score was 12.7 at baseline, and was -0.8 following four weeks of rotigotine therapy (*P* value not reported). The mean ESS score was reduced by 0.3 points from baseline following the switch to rotigotine (*P* value not reported). A reduction of 7.9 points in the total NMSS score was observed when patients switched from ropinirole to rotigotine (*P* value not reported). The CGI-I score assessed by investigators indicated that 54 subjects were considered improved, while 22 subjects were considered worsened and 37 subjects had no change. The mean CGI-I score for global improvement was 3.6, indicating an average assessment of minimally improved to no change (*P* values not reported). The PGI scores showed that 54 subjects reported improvement, while 27 subjects reported worsening. As part of this rating, 77 subjects reported having no adverse events, and 24 subjects reported adverse events that "did not significantly interfere" with functioning (*P* values not reported) The mean baseline PDQ-8 decreased from baseline by -3.9 points, indicating some improvement after switching to rotigotine (*P* value not reported). Secondary: Not reported
Giladi et al[30] Rotigotine transdermal patch 2 to 16 mg/24 hours Patients could receive levodopa (except levodopa CR or >5	MC, OL, PRO Patients with Parkinson's disease and self- reported unsatisfactory control of early morning motor	N=54 12 weeks	Primary: Change from baseline in UPDRS Part II, III and IV scores, TUaG, PDSS, NADCS and ESS Secondary:	Primary: The mean UPDRS Part III score decreased by 9.3 points from baseline following treatment with rotigotine (*P* value not reported). Following treatment with rotigotine, there was an improvement in the TUaG test of 1.4 seconds compared to baseline values (*P* value not reported). Compared to baseline, PDSS scores improved by 10.6 cm on the VAS scale following treatment with rotigotine (*P* value not reported).

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doses of levodopa IR daily), anticholinergic agents, entacapone, MAO-B inhibitors or amantadine if doses were stable for ≥28 days prior to baseline assessment.	impairments		Not reported	There was a reduction from baseline (improvement) in NADCS score for akinesia, dystonia and cramps compared to baseline scores (-2.13; *P* value not reported). Patients treated with rotigotine experienced a reduction from baseline in UPDRS Part II scores (4.4; *P* value not reported). In addition, a worsening of daytime sleepiness as measured by the ESS was not reported among individuals treated with rotigotine (-0.9; *P* value not reported). Secondary: Not reported
Trenkwalder et al[31] Rotigotine transdermal patch 2 to 16 mg/24 hours vs placebo Anticholinergic agents, MAO-B inhibitors, NMDA antagonists, entacapone, sedatives, hypnotics, selective serotonin reuptake inhibitors, anxiolytics, and other central nervous system medications were permitted if dose was	DB, MC, PC, PG, RCT Patients ≥18 years of age with Parkinson's disease and unsatisfactory control of early morning motor symptoms as determined by the investigator	N=287 Up to 22 weeks	Primary: Change from baseline in UPDRS Part III and PDSS-2 scores Secondary: Change from baseline in NADCS, NMS, BDI-II, PDQ-8, UPDRS Part II, III and IV scores	Primary: The improvement in UPDRS Part III score was significantly greater for patients treated with rotigotine compared to placebo (LS mean difference, -3.55; 95% CI, -5.37 to -1.73; *P*=0.0002). Similarly, an improvement PDSS-2 total score occurred with rotigotine compared to placebo (-4.26; 95% CI, -6.08 to -2.45; *P*<0.0001). Secondary: A significantly greater improvement in NADCS score was observed with rotigotine compared to placebo (LS mean difference, -0.41; 95% CI, -0.79 to -0.04; *P*=0.030). The mean NMS total score was significantly improved with rotigotine compared to placebo (LS mean difference, -6.65; 95% CI, -11.99 to -1.31; *P*=0.015). Statistically significant improvements with rotigotine compared to placebo were observed on the BDI-II (LS mean difference, -2.01; 95% CI, -3.55 to -0.47; *P*=0.011), PDQ-8 (LS mean difference, -5.74; 95% CI, -8.74 to -2.75; *P*=0.0002), UPDRS Part II (LS mean difference, -1.49; 95% CI, -2.32 to -0.65;

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stable for the 28 days prior to baseline.				*P*=0.0005) and Part III (LS mean difference, -3.55; *P*=0.0002). Minimal changes in UPDRS Part IV scores were reported between the treatment groups.
Watts et al[32] Rotigotine transdermal patch 6 mg/24 hours vs placebo Rotigotine was titrated from 2 mg/24 hour every week up to 6 mg/24 hour Subjects were permitted to take anticholinergic agents, a MAO-B inhibitor or amantadine if they were stable on dose for ≥28 days prior to study and maintained throughout study period.	DB, MC, PC, PG, RCT Patients ≥30 years of age with Parkinson's disease for ≤5 years, UPDRS Part III score ≥10 and, at least two cardinal signs (bradykinesia, resting tremor or postural instability) and MMSE ≥25	N=277 24 weeks	Primary: Change from baseline in UPDRS Part II+III combined score and responder rates (≥20% from baseline) Secondary: Not reported	Primary: Patients treated with rotigotine experienced improved UPDRS scores, compared to patients treated with placebo (-3.98, 95% CI, -7.60 to -2.96). Mean change in Part III motor scores was -3.50 and -0.30 on Part II. Part III resulted in greatest component of UPDRS improvement (*P* value not reported). The responder rates were greater for the rotigotine group compared to the placebo group. The percentage of patients achieving 25 and 30% improvement in UPDRS scores with rotigotine were 16 (*P*<0.0001) and 13%, respectively (*P*<0.0001). Secondary: Not reported
Jankovic et al[33] Rotigotine 6 mg/24 hours vs placebo	DB, MC, PC, RCT Patients ≥30 years of age with Parkinson's disease for ≤5 years in duration	N=277 24 weeks	Primary: UPDRS responder rates(patients achieving ≥20% reduction in UPDRS Parts II+III score) Secondary:	Primary: There was a significantly greater proportion of UPDRS responders in the rotigotine group compared to the placebo group (48 vs 19%, respectively; *P*<0.001). At study endpoint, the rotigotine group experienced a mean reduction of 15% in UPDRS Parts II+III compared to an increase in the placebo group (*P*<0.002). Secondary:

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Patients were started on 2 mg/24 hours and titrated up in increments of 2 mg weekly to a maximum of 6 mg/24 hours.	with at least two cardinal signs, (bradykinesia, resting tremor, rigidity, postural instability), UPDRS Part II score ≥10, Hoehn and Yahr stage ≤3, and MMSE ≥25		Change in prolactin concentrations and QOL measurements	Prolactin serum concentrations decreased from 6.8 to 5 ng/mL in the rotigotine group. However, the placebo group did not result in significant changes from baseline (*P* value not reported). The rotigotine group had a mean QOL index of 0.83 (range 0.31 to 1.00; *P*>0.05). The placebo group resulted in deterioration of QOL levels with a mean index of 0.77 (range, 0.38 to 1.00), which was significant compared to baseline (*P*=0.04).
Elmer et al[34] Rotigotine transdermal patch 2 to 6 mg/24 hours Medications allowed after one month of open-label rotigotine included levodopa, MAO-B inhibitors, anticholinergic agents, NMDA-antagonists, entacapone, olanzapine, ziprasidone, aripiprazole, clozapine, quetiapine and modafinil.	ES, MC, OL, PRO Patients ≥30 years of age with Parkinson's disease for ≥5 years, with UPDRS Part III score >10, and a Hoehn and Yahr stage score <3 who had completed previous studies by Watts et al[32] or Jankovic et al[33]	N=233 6 years	Primary: Safety, extent of exposure, changes in daytime sleepiness, vital signs, laboratory parameters and ECG Secondary: Time to adjunctive levodopa therapy, dyskinesias, UPDRS Part II+III total score and CGI-I item one score	Primary: The median exposure to rotigotine during the OL extension was 1,910 days. The mean rotigotine dose at the end of treatment was 7.2 mg. During OL rotigotine treatment, 159 (74%) patients started levodopa treatment. The median time from the beginning of OL treatment to start of levodopa usage was 374 days. Overall, 214 (99%) patients reported at least one adverse event during the OL treatment period. The most common adverse events were somnolence (23.4%), falls (16.5%), peripheral edema (14.2%), nausea (12.4%), and application site reactions (11.7%). The majority of adverse events experienced were either mild (57.0%) or moderate (38.0%) in intensity and 5.0% were severe. Overall, 74% of somnolence cases were reported to be mild in intensity, while 24% were moderate; three cases experienced by three patients were considered severe. Six cases of sleep attacks were reported in five patients; two were reported as serious. Overall, 101 application site reactions were reported in 70 (32%) patients. Other adverse events associated with dopaminergic stimulation included compulsive behaviors, hallucinations, and orthostatic hypotension. A total of 29 adverse events indicative of compulsive behavior were recorded. The

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				majority were reported to be mild (31%) or moderate (55%) in intensity and four were reported as severe. The majority of patients (75%) did not develop dyskinesias during up to six years of OL rotigotine treatment. Of the 53 (25%) patients who reported dyskinesias, 83% (i.e., 44 patients of the 53) reported dyskinesias after initiating concomitant levodopa. The mean ESS score increased from 5.7 at DB baseline to 9.0 at the end of maintenance. No clinically relevant changes were observed in vital signs, clinical laboratory measurements or ECGs. Secondary: At the start of OL maintenance, the mean UPDRS Part II+III total score improved relative to DB baseline by 5.6 points. Thereafter, there was a gradual decline to DB baseline value by two years of OL treatment, and mean score remained within four points of DB baseline value for a further four years. The mean CGI-I item one score increased slightly (indicating worsening) from 3.0 at DB baseline to 3.5 at the end of maintenance.
Babic et al[35] Rotigotine transdermal patch (fast titration with starting dose 4 mg/24 hours titrated up by 4 mg weekly) vs rotigotine transdermal patch (slow titration starting dose 4 mg/24 hours titrated up by 2	MC, OL, PG, RCT Patients with advanced Parkinson's disease who were on a stable dose of levodopa, with an "off" time ≥2.5 hours per day	N=34 84 days	Primary: Rate of adverse events, and discontinuation rate Secondary: Not reported	Primary: In the fast titration group, 8 mg was the dose at which the first reported nausea and/or vomiting occurred and 4 mg for the slow titration group. A total of eight patients in the fast titration group and six patients in the slow titration group reported adverse events considered treatment-related. All adverse events were mild to moderate in severity. Four patients discontinued treatment due to adverse events. Three were from the fast titration group and one from the slow titration group. Secondary: Not reported

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
mg weekly) Both groups titrated to target dose of 24 mg/24 hours or individual maximal achievable dose.				
Güldenpfennig et al[36] Rotigotine transdermal patch 4.5 mg/24 hours vs rotigotine transdermal patch 9 mg/24 hours vs rotigotine transdermal patch 13.5 mg/24 hours vs rotigotine transdermal patch 18 mg/24 hours All subjects were started at 4.5 mg/24 hours and titrated up weekly by 4.5 mg.	OL Patients with idiopathic Parkinson's disease for <5 years duration	N=31 28 days	Primary: Safety Secondary: Tolerability (number of patients who completed fixed escalating doses and dose-maintenance period), change in UPDRS Part I, II and III score	Primary: No abnormal, clinically significant laboratory findings were reported. No relevant changes in blood pressure, body temperature, or respiratory rate were recorded from baseline. There was a slight, non-dose dependent increase in mean heart rate, but did not result in any patient withdrawals. There were no significant changes in ECGs for patients receiving rotigotine. Secondary: Approximately 94% of patients completed the dose-escalation and dose-maintenance periods and 81% of patients completed the dose-escalation period at a maximum study dose of 18 mg. There was a statistically significant improvement in UPDRS Part I, II and III scores from baseline in those patients who completed the study (*P*=0.0078, *P*=0.0001 and *P*<0.0001, respectively).
LeWitt et al[37] Rotigotine transdermal	DB, PC, PG, RCT	N=351 24 weeks	Primary: Change in absolute time spent "off",	Primary: The absolute reduction from baseline in daily "off" time was -2.7 hours (*P*<0.001) in the rotigotine 8 mg group, -2.1 hours (*P*<0.001) in the rotigotine

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
patch 8 mg/24 hours vs rotigotine transdermal patch 12 mg/24 hours vs placebo	Patients ≥30 years of age with advanced Parkinson's disease for ≥3 years with bradykinesia plus at least one cardinal feature (resting tremor, rigidity, impaired postural reflex), Hoehn and Yahr stage II and IV in both the "on" and "off" states and MMSE ≥25		percentage of patients achieving ≥30% response in absolute time spent "off" Secondary: Change in time in the "on", "on without troublesome dyskinesia", "on with troublesome dyskinesia", number of "off" periods, change in UPDRS Part II and III scores in the "on" state	12 mg group, and -0.9 hours (*P*>0.05) in the placebo group. The difference between both treatment groups was not significant. There were significantly higher rates of patients achieving ≥30% decrease in absolute "off" time with rotigotine 8 and 12 mg compared to placebo (56.6, 55.1 and 34.5%, respectively; *P*<0.001 for both). Secondary: Patients in either the 8 or 12 mg rotigotine groups experienced significantly greater "on" time compared to the placebo group (*P*<0.0001 and *P*=0.0031, respectively). Similar results occurred with "on time without troublesome dyskinesias" (*P*<0.0001 and *P*=0.0078, respectively for the 8 and 12 mg rotigotine groups). The change in "on time with troublesome dyskinesias" was not significantly different compared to the placebo group for both the 8 and 12 mg groups (*P*=0.0871 and *P*=0.6499, respectively). The number of daily "off" periods was significantly reduced for patients receiving rotigotine 8 or 12 mg compared to the placebo group (*P*=0.001 and *P*=0.0195, respectively). Both the 8 and 12 mg groups achieved significant reductions in UPDRS Part II scores (*P*=0.0004 and *P*=0.0023, respectively) and UPDRS Part III scores (*P*=0.0185 and *P*=0.0006, respectively) compared to the placebo group.
Parkinson Study Group[38] Rotigotine transdermal patch 4.5 mg/24 hours vs rotigotine transdermal	DB, MC, PC, PG, RCT Patients >30 years of age with Parkinson's disease and a Hoehn and Yahr stage ≤3	N=242 11 weeks	Primary: Change from baseline in UPDRS Part II+III combined score Secondary: Change in UPDRS Part II and II scores	Primary: Changes from baseline in UPDRS Part II+III scores were statistically significant in comparison to placebo for the 13.5 and 18 mg groups. The 4.5 and 9 mg groups had a -0.91 and -2.78 difference from placebo (*P*=0.52 and *P*=0.06, respectively), whereas the 13.5 and 18.0 mg groups resulted in -4.83 (*P*=0.001) and *P*<0.001). Secondary: The only group to reach statistically significant differences from placebo in

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
patch 9 mg/24 hours vs rotigotine transdermal patch 13.5 mg/24 hours vs rotigotine transdermal patch 18 mg/24 hours vs placebo Subjects were permitted to take selegiline, amantadine, or anticholinergic agents if maintained at stable doses for 28 days before baseline and throughout trial.				UPDRS Part II score was the 18 mg group (*P*=0.003). The 4.5, 9 and 13.5 mg groups did not result in significant differences compared to placebo (*P*=0.94, *P*=0.11, and *P*=0.08, respectively). In regard to UPDRS Part III score, both the 4.5 and 9 mg groups did not result in statistically significant differences from placebo (*P*=0.44 and *P*=0.11, respectively); however, both the 13.5 and 18.0 mg groups did result in significant changes compared to placebo (*P*=0.001 and *P*=0.001, respectively).
Poewe et al[39] Rotigotine transdermal patch 16 mg/24 hours vs pramipexole 4.5 mg/day divided TID	DB, PC, PG, RCT, Patients ≥30 years of age with Parkinson's disease for >3 years, on stable treatment with levodopa and	N=506 16 weeks	Primary: Change in absolute time spent "off", responder rates (≥30% reduction in absolute time "off" from baseline) Secondary: Change in absolute	Primary: The mean change in time "off" from baseline compared to placebo was -1.58 hours (*P*<0.0001) for rotigotine and -1.94 hours (*P*<0.0001) for pramipexole. Responder rates were significantly greater with both groups compared to the placebo group (*P*<0.0001). Differences in responder rates between rotigotine and pramipexole was -7.3% (*P*=0.108). Secondary: Both groups resulted in significant differences compared to the placebo group

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
vs placebo Rotigotine doses were started at 4 mg/24 hours and titrated up by 2 mg weekly to a maximum of 16 mg/24 hours. Pramipexole was started at 0.375 mg/day, doubled in the first week, followed by weekly increases of 0.75 mg/day up to a maximum of 4.5 mg/day.	stable doses of any concomitant antiparkinsonian medication prior to enrollment and had motor fluctuations of the "wearing-off" type with average ≥2.5 hours daily spent in "off" state		time spent "on" without troublesome dyskinesias, number of "off" periods, motor status after morning wake-up (on with or without troublesome dyskinesias or "off"), UPDRS Part II and III scores	in all parameters. However, there were no significant differences between rotigotine and pramipexole in all measured parameters. Absolute "on" time without troublesome dyskinesias was significantly greater with rotigotine (*P*=0.0003) and pramipexole (*P*=0.0007) compared to placebo; however, there was no significant difference between active treatments (*P*=0.7980). The number of "off" periods was significantly lower with rotigotine (*P*=0.001) and pramipexole (*P*=0.0006) compared to placebo, although no differences between active treatments were reported (*P*=0.8478). Motor status after wake-up was significantly improved for both rotigotine (*P*=0.0101) and pramipexole (*P*=0.0242); however, there was no difference between active treatments (*P*=0.6710). Time "on" without troublesome dyskinesias was significantly improved in both the rotigotine (*P*=0.0139) and pramipexole groups compared to the placebo group (*P*=0.0429); however, there was no difference between active treatments (*P*=0.5825). There were statistically significant improvements in UPDRS Part II score in both the rotigotine group (*P*<0.0001) and pramipexole group (*P*<0.0001) compared to the placebo group, with no difference between the rotigotine and pramipexole groups (*P*=0.1874). Similarly, significant improvements in UPDRS Part III score occurred with both active treatments compared to placebo (*P*<0.0001for both); however, there was no difference between the two groups (*P*=0.0.0672).
Giladi et al[40] Rotigotine transdermal patch 8 mg/24 hours vs	DB, MC, PC, PG, RCT Patients with early-stage Parkinson's	N=561 24 weeks	Primary: UPDRS responder rates (≥20% improvement in UPDRS Part II+III scores)	Primary: Treatment with the rotigotine resulted in a significantly higher proportion of responders compared to treatment with placebo (52 vs 30%; *P*<0.0001). The responder rate in the ropinirole arm was 68% (*P*<0.0001 compared to placebo).

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
ropinirole 24 mg/day vs placebo Rotigotine doses were titrated up in 2 mg/24 hours weekly increments.	disease		Secondary: Change in UPDRS Part II+III score	Secondary: A significant improvement in absolute UPDRS Parts II+III combined score was observed for patients treated with rotigotine compared to placebo (-7.2 vs -2.2; *P*<0.0001). A mean decrease of -11.0 was observed for ropinirole (*P*<0.0001).
Stocchi et al[41] Ropinirole ER 2 to 24 mg QD vs ropinirole IR 0.75 to 24 mg divided TID	DB, MC, PG, RCT Patients ≥30 years of age with Parkinson's disease, and a lack of control with levodopa therapy	N=350 24 weeks	Primary: Proportion of patients with a ≥20% reduction in daily awake time spent ''off'' Secondary: Responder rates (rated ''very much'' or ''much'' improved) on CGI-I, proportion of patients requiring reinstatement of levodopa, change in percentage of awake time spent ''off', UPDRS Part II+III score, EQ-5D, PDSS, AIMS and the dose of levodopa at 24 weeks	Primary: The proportion of patients with a ≥20% maintained reduction in awake time spent ''off'' was 66% for ropinirole ER and 51% for ropinirole IR (OR, 1.82; 95% CI, 1.16 to 2.86; *P*=0.009). Secondary: A higher proportion of responders on the CGI-I scale was observed in the ropinirole ER group (55%) compared to the ropinirole IR group (43%; OR, 1.67; 95% CI, 1.06 to 2.63; *P*=0.027). The number of patients who required reinstatement of levodopa following a dose reduction was two in the ER group and three for the IR group, respectively. There was no statistically significant difference in the reduction in time spent "off" while awake between patients in the ER and IR groups (16.6 vs 14.9%, respectively; *P*=0.379). Patients treated with ER experienced a statistically significant reduction in UPDRS total motor score compared to patients receiving the IR (10.2 vs 7.9; *P*=0.022). No statistically significant difference was reported between the groups with regard to scores for activities of daily living while "on" or "off" (*P*=0.10 and

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
				P=0.27, respectively). Similarly, no significant difference in EQ-5D utility score or AIMS total movement severity score was reported between the treatments (*P*=0.165 and *P*=0.866, respectively).
Stowe et al[42] Dopamine agonists with or without levodopa vs levodopa or dopamine agonists with or without levodopa vs placebo or dopamine agonists with or without levodopa vs levodopa and placebo	MA Patients of any age with early idiopathic Parkinson's disease, no history of motor complications, either untreated or with limited exposure to antiparkinsonian medications	N=5,247 (29 trials) 8 weeks to 10 years	Primary: Symptom control, motor complications, side effects and withdrawals Secondary: Not reported	Primary: Levodopa was reported to be of benefit over dopamine agonists in overall symptom control, although there was insufficient data available to meta-analyze results. Freezing was noted more often with dopamine agonist therapy relative to levodopa therapy (OR, 1.58; 95% CI, 1.14 to 2.18; *P*=0.005); however, this outcome was only reported in five trials. The risk of developing motor complications was reduced in patients receiving agonist therapy compared to patients receiving levodopa, including dyskinesia (OR, 0.51; 95% CI, 0.43 to 0.59; *P*<0.00001), dystonia (OR, 0.64; 95% CI, 0.51 to 0.81; *P*=0.0002) and motor fluctuations (OR, 0.75; 95% CI, 0.63 to 0.90; *P*=0.002). Edema (OR, 3.68; 95% CI, 2.62 to 5.18; *P*<0.00001), somnolence (OR, 1.49; 95% CI, 1.12 to 2.00; *P*=0.007), constipation (OR, 1.59; 95% CI, 1.11 to 2.28; *P*=0.01), dizziness (OR, 1.45; 95% CI, 1.09 to 1.92; *P*=0.01), hallucinations (OR, 1.69; 95% CI, 1.13 to 2.52; *P*=0.01) and nausea (OR, 1.32; 95% CI, 1.05 to 1.66; *P*=0.02) were all more frequently reported in patients taking dopamine agonists than with levodopa. Subsequently, a greater number of patient in the dopamine agonist group discontinued treatment secondary to adverse events (OR, 2.49; 95% CI, 2.08 to 2.98; *P*<0.00001). Analysis between individual agonists was reported with regard to reduction in dyskinesia. There was a 59% decrease in dyskinesia for both cabergoline and pergolide, 71% for both pramipexole and ropinirole and 35% decrease with bromocriptine (*P*=0.008). Secondary:

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
				Not reported
Restless Legs Syndrome				
Ma et al[43] Pramipexole 0.125 mg QHS titrated to efficacy and tolerability vs placebo	DB, MC, PC, PG, RCT Patients 18 to 75 years of age with moderate-to-severe RLS, IRLS score >15 with symptoms persistent for two or more days per week for the three months prior to study entry	N=387 6 weeks	Primary: Change from baseline in IRLS scores and proportion of CGI-I responders Secondary: IRLS responder rate, PGI responder rate, ESS, RLS-6 rating scales and VAS	Primary: The mean change in IRLS scores from baseline was significantly greater for patients receiving pramipexole compared to patients receiving placebo (-15.87 vs -11.35; *P*<0.0001). The proportion of patients with a CGI-I assessment of ‘‘much improved’’ and ‘‘very much improved’’ was 81.9% in the pramipexole group 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 patients treated with placebo were considered to be PGI responders (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 ADL (-2.78 vs -3.22; *P*=0.3294). Greater improvements were reported in the pramipexole group compared to the placebo group 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 vs -2.8, respectively; *P*<0.0001).
Högl et al[44] Pramipexole 0.125 to 0.750 mg QHS	DB, MC, PC, RCT Patients with	N=331 26 weeks	Primary: Change from baseline in IRLS score	Primary: Patients randomized to receive pramipexole reported a significantly greater reduction from baseline in IRLS score compared to patients receiving placebo. Treatment differences between groups occurred as early as week

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
vs placebo The dose could be titrated weekly to a maximum of 0.750 mg QHS.	RLS and a baseline IRLS score >15 who were experiencing symptoms at least twice per week in three months prior to study entry and ferritin >30 ng/mL		Secondary: IRLS, PGI and CGI-I responder rates, RLS-QOL and RLS-6 scores	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: The IRLS responder rate was 58.6% for patients treated with pramipexole compared to 42.8% for patients treated with placebo (*P*=0.0044). More patients randomized to pramipexole compared to placebo were CGI-I responders (68.5 vs 50.3%; *P*=0.0010) and PGI responders (62.3 vs 44.0%; *P*=0.0011). Pramipexole treatment was associated with a significantly greater improvement in RLS-6 score compared to placebo treatment 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[45] 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 RLS and a baseline IRLS score >15, who were experiencing symptoms at least twice per week 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 on item 10 of IRLS Secondary: Responder rates on CGI-I, PGI, IRLS and BDI-II, change from baseline in HADS, 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 on item 10 of the IRLS was reported in the pramipexole group compared to the placebo group (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 patients receiving 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 (day one for PGI, day nine for CGI-I) in the pramipexole

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
				group compared to the placebo group (*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). Similarly, higher responder rates were observed for PGI at week 12 (62.9 vs 38.0%, respectively; *P*<0.0001). The median reduction in depression score on the HADS scale was significantly greater in the pramipexole group compared to the placebo group (three vs two; *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). On RLS-6 scales, the improvements 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[46] 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 RLS and a baseline IRLS score >15 and more than five PLM/hour while in bed	N=41 6 weeks	Primary: Change from baseline in PLMI Secondary: Change in PLMSI, total number of PLM, 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	Primary: The median change in PLMI was -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).

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
			scores	Patients randomized to receive pramipexole reported significantly lower IRLS scores compared to patients randomized to placebo at week one, two, four and six (*P*<0.001 for all). 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 on CGI-I was significantly higher in the pramipexole group compared to the placebo group (80.0 vs 52.4%; *P*=0.0488). There were no significant differences in ESS scores between patients treated with pramipexole or patients treated with placebo (*P*=0.2274). The mean change in PSQI score from baseline was significantly greater for patients treated with pramipexole compared to patients treated with placebo at week six (*P*=0.0016).
Manconi et al[47] Pramipexole 0.25 mg QHS vs placebo	DB, PC, PRO, RCT Patients 18 to 70 years of age with RLS and IRLS score >20, who were experiencing symptoms at least twice per week in the six months prior to study entry and PLMS >10 during baseline	N=32 2 days	Primary: Changes in VAS scores for symptom severity Secondary: PLMSI of entire night, during REM and nREM sleep, total number of leg movements and total number of PLMS sequences	Primary: Following a single dose of pramipexole, the mean VAS score changed from 7.4 to 1.3 (*P*<0.00001). In the placebo group, no change in VAS score from baseline was reported (*P*=NS). Secondary: Mean PLMSI scoring for the entire night following treatment was significantly lower for patients treated with pramipexole compared to patients treated with placebo (9.4 vs 48.8; *P*=0.0002). The PLMSI was lower during REM sleep for patients treated with pramipexole compared to patients treated with placebo (17.4 vs 32.0; *P* value not reported). Compared to placebo the mean PLMSI 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

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
	PSG			receiving treatment with pramipexole (7.1 vs 10.5; *P* value not reported).
Hornyak et al[48] Pramipexole 0.125 to 0.750 mg QHS vs placebo The dose could be titrated to a maximum of 0.750 mg.	DB, MC, PC, RCT, SA SA of two studies including patients with RLS symptoms on two or more days per week throughout the prior three months and a baseline IRLS score >15	N=973 12 weeks	Primary: Change from baseline in VAS scores for RLS-related limb pain Secondary: Not reported	Primary: In first trial, 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 ≥30% occurred in 72.5% pramipexole-treated patients compared to 51.4% placebo-treated patients (OR, 2.49; *P*<0.0001). In the second trial, the median 12-week reduction in VAS limb-pain score was -31.0 in the pramipexole treatment group and -11.0 in the placebo group (*P*<0.0001). A reduction of VAS score by ≥30% occurred in 68.7% of the pramipexole group, compared to 45.7% of the placebo group (*P*<0.0001). Secondary: Not reported
Oertel et al[49] 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 RLS and a baseline IRLS score >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 greater in the pramipexole group compared to the placebo group (12.3 vs 5.7; *P*<0.001). More patients receiving pramipexole were CGI-I responders compared to patients receiving placebo (62.9 vs 32.5%; *P*<0.0001). Secondary: A greater proportion of patients were determined to be both IRLS (52.5 vs 28.9%; *P*<0.00010) and PGI responders (61.6 vs 31.6%; *P*<0.0001) in the pramipexole group compared to the placebo group. Pramipexole demonstrated a benefit over placebo in severity of symptoms while going 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 treatment included nausea (9.6 vs 5.2%), fatigue (9.1 vs 4.3%) and headache (7.0 vs 6.1%).

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
Winkelman et al[50] 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 ≥15 and symptoms least two days per week	N=344 12 weeks	Primary: Change from baseline in IRLS score and CGI-I responder rate Secondary: IRLS and PGI responder rates, VAS scores, ESS and RLS-QOL	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 and 14.0 for 0.75 mg compared to 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). 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 going 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; however, the difference in daytime somnolence was not significant (*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).
Partinen et al[51] Pramipexole 0.125 mg QHS	DB, PC, PG, RCT Patients 27 to	N=109 3 weeks	Primary: Change from baseline in PLMI	Primary: Compared to placebo, all doses of pramipexole demonstrated significant reductions from baseline in PLMI (52.70, 31.05, 26.55 and 30.00 vs 3.00 for pramipexole 0.125, 0.25, 0.50, 0.75 mg and placebo, respectively; *P*<0.05 for

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
vs pramipexole 0.25 mg QHS vs pramipexole 0.50 mg QHS vs pramipexole 0.75 mg QHS vs placebo	76 years of age with moderate-to-severe RLS with a baseline IRLS score >15 and at least five PLMS/hour and weekly RLS symptoms that disrupted sleep within previous three months		Secondary: IRLS, CGI-I and PGI responders, quality of sleep, daytime well being, PLMSI, PLMWI, PLMAI, PLM, total number of PLMS, total number of awakenings/ arousals during sleep, sleep latency, sleep efficiency, total sleep time, percentage of delta sleep and percentage of stage REM sleep	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, 50.0 and 33.3% of patients were classified as “much better,” compared to 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 groups were CGI-I responders following three weeks of therapy, compared to 42.9% of patients in the placebo group. There was no difference in responder rate 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 groups and the placebo group 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 was significantly greater with pramipexole 0.125 (41.30), 0.25 (36.50) and 0.50 mg (36.50) compared to placebo (11.00; *P*<0.05 for all) 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).

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
				Significant improvements in sleep latency scores were reported with pramipexole 0.125, 0.50 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 REM sleep were reported between any of the pramipexole groups and the placebo group. 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 the placebo group. 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 pramipexole 0.125, 0.25, 0.50 and 0.75 mg, respectively (*P*<0.05 for all strengths compared to placebo.
Manconi et al[52] Pramipexole 0.25 mg QHS vs bromocriptine 2.5 mg QHS vs placebo	AC, PC, PG, PRO, RCT, SB Treatment naïve patients 18 to 70 years of age with RLS for at least six months with symptoms more than twice-weekly and an IRLS score ≥20	N=45 2 days	Primary: PLMSI during entire night, REM and nREM sleep, total leg movement index, total number of PLMS sequences and periodicity index Secondary: Not reported	Primary: The PLMSI 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 was also associated with greater reductions in PLMSI 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 PLMSI between the groups during REM sleep (*P*=NS). Pramipexole was associated with a significant reductions in lower total leg movement index for the total duration of sleep compared to both bromocriptine and placebo (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 groups (*P*=NS). Secondary: Not reported

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
Inoue et al[53] Pramipexole 0.25 to 0.75 mg QHS The dose could be titrated every two weeks to a maximum of 0.75 mg or decreased to 0.125 mg according to the needs of the patient.	ES, OL Patients 20 to 80 years of age with RLS and baseline IRLS score >15 who had completed a prior six-week DB trial	N=141 46 weeks	Primary: Change in IRLS score and responder rates, CGI-I and PGI responder rates, PSQI and ESS scores Secondary: Not reported	Primary: During the OL treatment period, the mean IRLS score decreased from 10.1 at baseline 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 OL period was -3.1 points (95% CI, -3.8 to -2.5). By week 52, the mean ESS score decreased by -4.0 points from baseline (95% CI, -4.9 to -3.1). Of 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 ECGs were reported. Secondary: Not reported
Winkelman et al[54] Pramipexole 0.125 mg QHS The dose could be	RETRO Patients with RLS who were maintained on pramipexole for	N=59 Median duration of 21.2 months	Primary: Rates of augmentation and pramipexole tolerance	Primary: Augmentation developed in 32% of patients treated with pramipexole. The mean time to onset of augmentation was 8.8 months. Patients treated with pramipexole were significantly more likely to develop augmentation if the patient experienced augmentation to prior levodopa therapy (P<0.05).

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
titrated by 0.125 to 0.25 mg every week until symptoms were eliminated.	at least six months		Secondary: Not reported	Pramipexole tolerance occurred in 46% of patients. In these patients, mean total daily dose increased from 0.43 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). Secondary: Not reported
Inoue et al[55] 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 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, ESS, PSQI and laboratory parameters	Primary: Pramipexole was associated with a reduction in IRLS score from baseline with the 0.25 mg dose (-12.3; 95% CI, -14.5 to -10), 0.50 mg dose (-12.5; 95% CI, -14.6 to -10.4) and 0.75 mg dose (-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, 0.50 and 0.75 mg of pramipexole, respectively. The PGI responder rates at week six were 72.9, 79.3 and 67.9% for patients receiving pramipexole doses of 0.25, 0.50 and 0.75 mg, respectively. 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, 0.50 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). A reduction from baseline in PSQI occurred in all 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: -

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
				2.5; 95% CI, -3.3 to -1.8). Patients in all three pramipexole groups experienced an improvement in 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 groups.
Manconi et al[56] Pramipexole 0.25 mg QHS vs ropinirole 0.50 mg at QHS 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 ≥20	N=45 2 days	Primary: PLMSI during entire night, REM and nREM sleep, total leg movement index and total number of PLMS sequences Secondary: Not reported	Primary: The PLMSI 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 leg movement 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). Secondary: Not reported
Bassetti et al[57] Pramipexole 0.125 mg to 0.750 mg QHS vs levodopa/benserazide ER 125 to 375 mg QHS	DB, MC, RCT, XO Patients 25 to 85 years of age with RLS and more than five PLM/hour during bedtime on three consecutive	N=39 10 weeks	Primary: Change from baseline in PLMI Secondary: Change in IRLS score, VAS scores during the day, at sleep onset and at night, SF-36 scores, daytime sleepiness,	Primary: Pramipexole was noninferior to levodopa/benserazide with regard to the mean change from baseline in PLMI (-11.5 vs -7.7; *P*=0.00015). Secondary: There was a trend towards lower IRLS scores with pramipexole compared to levodopa/benserazide; however, the 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

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
The dose of pramipexole could be increased every three to five days to a maximum of 0.750 mg QHS.	nights		mood, ESS and HADS scores	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). 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 groups. Reported HADS scores were similar between patients in both 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).
Benes et al[58] Ropinirole 0.50 to 4.0 mg QHS vs placebo	DB, MC, PC, PG, RCT Patients 18 to 80 years of age with moderate-to-severe RLS, baseline IRLS score >15, RLS diagnostic index score ≥11, MADRS score ≥12 at baseline and RLS symptoms ≥15 nights in the four weeks preceding enrollment	N=266 12 weeks	Primary: Change from baseline in MADRS Secondary: BDI-II, HAMD, IRLS scores, CGI-I and CGI-S responder rates, MOS sleep scale, 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 and 5.4 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 and 6.5 points in the ropinirole and placebo groups, respectively (treatment 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 (treatment 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

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
				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 scales, 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[59] Ropinirole 0.50 to 6.0 mg divided BID vs placebo	DB, MC, PC, RCT Patients 18 to 79 years of age with RLS and a baseline IRLS score ≥20 and >15 on the insomnia severity index with ≥15 nights of RLS symptoms within the previous month	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 receiving ropinirole were classified as CGI-I responders at all assessment points compared to patients receiving placebo (OR, 2.43; 95% CI, 1.57 to 3.76; *P*<0.001). 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 at week 12 (OR, 3.24; 95% CI, 2.05 to 5.12; *P*<0.001). Secondary: Not reported

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
Montplaisir et al[60] 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 RLS and a baseline IRLS score ≥15 and a history ≥15 nights of RLS symptoms in previous month	N=202 36 weeks	Primary: Proportion of patients relapsing 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 DB treatment phase, 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 compared to the ropinirole group (OR, 0.40; 95% CI, 0.1 to 0.9; *P*=0.0372). Twelve weeks after randomization, more patients in the ropinirole group compared to the placebo group were CGI-I responders (OR, 2.6; 95% CI, 1.1 to 6.3; *P*=0.0298). The treatment difference in IRLS score favored ropinirole over placebo (-4.6 points; 95% CI, -8.6 to -0.6; *P*=0.0246). 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) and sleep quantity (treatment difference, 60 minutes; 95% CI, 6 to 120; *P*=0.0346). Scores for sleep adequacy were not significantly different between the 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[61] Ropinirole 0.50 to 4.0 mg QHS	DB, MC, PC, PG, RCT Patients 18 to	N=65 12 weeks	Primary: Change In PLMS/hour	Primary: The adjusted treatment difference in PLMS/hour significantly favored ropinirole over placebo (-27.2; 95% CI, -39.1 to -15.4; *P*<0.0001).

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
vs placebo	79 years of age with RLS and had five PLMS/hour on PSG screening		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 sleep scale, IRLS total score	Secondary: After 12 weeks of treatment the PLMA/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 significant difference in PLMW/hour favoring ropinirole 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 (-9.8 minutes; 95% CI, -17.2 to -2.4; *P*=0.0106). There were significant differences between the 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 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[62] Ropinirole 0.50 to 6.0 mg divided BID vs placebo	DB, PC, XO Patient ≥18 years of age with RLS and a baseline IRLS score ≥10	N=22 9 weeks	Primary: Change from baseline IRLS score Secondary: Global change score, ESS, RLS symptom diary and adverse events	Primary: The mean IRLS score was lower at the end of the ropinirole treatment period compared to the placebo treatment period (13 vs 25; *P*<0.001). Secondary: Global change scores for improvement in symptoms were higher in the ropinirole group compared to the placebo group (*P*<0.001). There was no difference between the groups with regard to ESS scores (*P*=0.31).

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
				Diary scores for symptoms were significantly lower for patients treated with ropinirole compared to the placebo treatment group (0.12 vs 0.23; *P*=0.008). Adverse events with onset during ropinirole treatment were significantly more frequent compared to placebo treatment, notably dizziness and nausea (*P*<0.05). Two patients discontinued treatment during ropinirole treatment (one due to lack of efficacy, one with dizziness, nausea, and vomiting) and one during placebo treatment (syncope).
Trenkwalder et al[63] Ropinirole 0.25 to 4.0 mg QHS vs placebo	DB, PC, MC, RCT Patients 18 to 79 years of age with RLS and a baseline IRLS score >15 while experiencing symptoms at least 15 nights/month in the previous month or prior to treatment	N=284 12 weeks	Primary: Change from baseline in IRLS score Secondary: CGI-I responder rate, change from baseline in the total IRLS score at week one, impact of treatment on sleep, RLS-QOL and safety	Primary: The mean reduction in total IRLS score was significantly greater in the ropinirole group compared to the placebo group (-11.04 vs -8.03; *P*=0.0036). Secondary: A significantly greater proportion of patients met CGI-I criteria in the ropinirole group compared to the placebo group (53.4 vs 40.9%; *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), sleep quantity (*P*=0.0331), daytime somnolence (*P*=0.0064) and sleep disturbance (*P*=0.0245) with ropinirole relative to placebo. Similarly, significant improvements in RLS-QOL scores occurred with ropinirole 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[64] Ropinirole 0.125 to 4 mg daily vs	DB, MC, RCT Patients 18 to 79 years of age with primary RLS and baseline IRLS	N=267 12 weeks	Primary: Change from baseline in IRLS score Secondary: CGI-I responder rate	Primary: The mean reduction total IRLS score was significantly greater in the ropinirole group compared to the placebo group (-11.2 vs -8.7; *P*=0.0197). Secondary: A significantly greater proportion of patients were CGI-I responders in the ropinirole group compared to the placebo group at week 12 (59.5 vs 39.6%;

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
placebo	score ≥15 while experiencing symptoms ≥15 nights/month in the previous month or prior to treatment		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 questionnaire, SF-36 and WPAI	*P*=0.001). Similar results were found concerning 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 placebo (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 patients treated with 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). Ropinirole 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 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 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 the placebo group (39.7 and 15.3 vs 8.1 and 6.6%). Headache was also common but more frequent in the placebo group (25.7 vs 22.1%).
Garcia-Borreguero et al[65] Ropinirole 0.50 to 4.0 mg QHS	ES, MC, OL, Subjects 18 to 79 years of age, with RLS and ≥15 nights of RLS symptoms during the previous month	N=310 52 weeks	Primary: Adverse events, blood pressure and heart rate, weight and laboratory assessments Secondary: Changes in IRLS	Primary: During OL 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. Adverse events deemed related or possibly related to the study drug were

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
	and a have total score ≥15 based on the IRLS rating scale in addition to experiencing a relapse while enrolled in one of three previous studies		score, CGI-I responder rate, MOS sleep scale, WPAI, RLS-QOL and SF-36	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 importance. Two patients had a low (<50 mm Hg) and significant decrease (≥20 mm Hg). Twelve patients (3.9%) had a sitting systolic blood pressure value of clinical importance at 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 LOCF analysis, respectively. The CGI-I responder rates at week 52 were reported as 82.8 and 71.9% for the observed case analysis and LOCF 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[66] Gabapentin 300 to 1,200 mg QHS vs ropinirole 0.25 to 1.50 mg QHS	AC, OL, RCT Patients with a diagnosis of RLS	N=16 4 weeks	Primary: Number of PLMS, PLMSI, PLMSAI, IRLS and ESS scores Secondary: RLS-QOL and PSQI scores	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 were associated with significant reductions in the PLMI (*P*=0.012 and *P*=0.018, respectively). There was no difference between gabapentin and ropinirole in PLMSI after four weeks (22.6 vs 13.2; respectively; *P*=0.752).

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
Gabapentin doses greater than 300 mg daily were administered BID.				There was no difference in PLMSAI for patients treated with either gabapentin or ropinirole for four weeks (2.4 vs 9.3; respectively; *P*=0.831). The difference in IRLS score between gabapentin and ropinirole was not significant following four weeks of treatment (6.8 vs 8.1; respectively; *P*=0.489). Patients randomized to gabapentin experienced a similar reduction in ESS compared to patients randomized to ropinirole following four weeks of treatment (6.0 vs 7.3; 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 the ropinirole group. The differences in RLS-QOL scores were not significantly different between the groups.
Oertel et al[67] Rotigotine transdermal patch 1 to 3 mg/24 hours vs placebo All patients randomized to rotigotine started the titration period with rotigotine 1 mg/24 hours and increased in weekly increments of 1 mg/24 hours until they reached their optimal dose (absence of or	DB, MC, PC, PG, RCT Patients 18 to 75 years of age with idiopathic RLS based on IRLS study group criteria and a PLMI score ≥15 PLM/h in bed, a baseline sum score ≥15 on the IRLS and score ≥4 at baseline on CGI-I item one	N=67 4 weeks	Primary: Change from baseline in PLMI Secondary: Change from baseline in PLMSAI, sleep efficiency, PLMSI, PLMWI, TST, total time in sleep stages, and sleep onset latency, and scores on IRLS, CGI-I item one and RLS-6	Primary: After four weeks of treatment, the PLMI was significantly lower following treatment with rotigotine compared to treatment with placebo (8.1 vs 27.1; *P*<0.0001). Secondary: There was a statistically significant reduction from baseline in PLMSAI for patients randomized to rotigotine compared to patients randomized to placebo (5.63 vs 2.51; *P*=0.0072). There was no statistically significant difference between the rotigotine and placebo groups with regard to sleep efficiency (*P*=0.3618). Significantly greater improvements in PLMSI scores were achieved with rotigotine compared to placebo (-38.05 vs -7.7; *P*<0.0001). Similarly, improvements in PLMWI significantly favored the rotigotine treatment group compared to patients receiving placebo (-46.44 vs -18.34; *P*=0.0010).

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
maximal reduction in RLS symptoms without intolerable side effects).				The total sleep time, sleep onset latency and time spent in sleep stages was not significantly different between patients receiving rotigotine or patients receiving placebo (*P*>0.05 for all). There was a greater reduction from baseline in IRLS (LS mean difference, -6.09; 95% CI, -10.71 to -1.47; *P*=0.0107) and CGI-I item one score (LS mean difference, -0.89; 95% CI, -1.62 to -0.17; *P*=0.0168) compared to placebo. Similarly, the proportion of IRLS and CGI-I responders were higher in the rotigotine group when compared to patients randomized to receive placebo. The improvements in RLS-6 symptom severity scores were greater in the rotigotine group compared to the placebo group for all time of the day (*P* values not reported).
Hening et al[68] Rotigotine transdermal patch 0.5 mg/24 hours vs rotigotine transdermal patch 1 mg/24 hours vs rotigotine transdermal patch 2 mg/24 hours vs rotigotine transdermal patch 3 mg/24 hours	DB, MC, PC, RCT Patients 18 to 75 years of age with RLS, a baseline IRLS score ≥15 and CGI-I item one score ≥4	N=505 6 months	Primary: Change from baseline in IRLS and in CGI-I item one scores Secondary: Proportion of treatment responders for IRLS and CGI-I item one (≥50% improvement from baseline), CGI-I item two responder rate (‘‘much improved’’ or ‘‘very much improved”), IRLS remitter rates (IRLS score ≤10), RLS-6 rating scales, CGI-I	Primary: After six months, there were statistically significant improvements in scores on both the IRLS and CGI-I item one compared to placebo for patients receiving 2 and 3 mg of rotigotine (*P*<0.001). Improvements also occurred in the rotigotine 0.5 and 1 mg groups; however, these differences were not statistically significant compared to the placebo group. Secondary: A total of 56.6% of patients receiving rotigotine were considered IRLS responders and 49.8% were considered CGI-I item one responders. In all rotigotine groups, response rates were significantly higher compared to the placebo group with the exception of the 0.5 mg group (*P*<0.05 for all groups except 0.5 mg). There was a statistically significant response on CGI-I item-two responder rate for the 3 mg rotigotine dose compared to placebo (80.0 vs 57.1%; *P*<0.005); however, no differences were reported between the other rotigotine groups and the placebo group. Significantly more patients were considered to be IRLS remitters following

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
vs placebo			items two and three and SDS	treatment with rotigotine 3, (62.1%; *P*<0.001), 2(57.3%; *P*<0.005) and 1 mg (49.5%; *P*<0.05) compared to treatment with placebo (32.3%). No significant difference was reported for rotigotine 0.5 mg (40.8%). Daytime sleepiness on the RLS-6 and ESS improved across all treatment groups with no significant difference between rotigotine and placebo. Changes in ESS and SDS index at end of the maintenance treatment phase were comparable between the rotigotine and placebo groups.
Oertel et al[69] Rotigotine transdermal patch 0.5 mg/24 hours vs rotigotine transdermal patch 1 mg/24 hours vs rotigotine transdermal patch 2 mg/24 hours vs rotigotine transdermal patch 3 mg/24 hours vs rotigotine transdermal patch 4 mg/24 hours vs	DB, MC, PC, PG, RCT Patients 18 to 75 years of age with RLS and an IRLS score of ≥15 at baseline	N=371 6 weeks	Primary: Change from baseline in IRLS score Secondary: CGI-I scores, responder rates on IRLS, and CGI-I (≥50% improvement from baseline for IRLS score and ratings of “much improved” or “very much improved” on CGI-I), IRLS remitter rates (score ≤10) and, RLS-6 RLS-QOL	Primary: Compared to placebo, the changes from baseline in IRLS total scores were significantly greater for patients randomized to receive rotigotine 1 (-15.3; *P*=0.0004), 2 (-15.7; *P*=0.003), 3 (-17.3; *P*<0.0001) and 4 mg (-14.9; *P*=0.0013). There was no statistically significant difference compared to placebo for patients receiving the 0.5 mg dose (*P*=0.2338). Secondary: Patients receiving the lowest rotigotine dose of 0.5 mg did not experience a statistically significant improvement in RLS-6 score compared to patients receiving placebo. With all four other rotigotine doses, clear improvements of ‘‘severity of RLS symptoms at bedtime’’ and ‘‘during the night’’ were reported (*P*<0.05 for all). Statistically significant improvements in CGI-I scores occurred in all active treatment groups compared to the placebo group with the exception of the 0.5 mg group. The proportions of IRLS responders were greater in the 1, 2, 3 and to 4 mg rotigotine groups compared to the placebo group (59.4, 61.2, 68.8 and 58.5 vs 41.5%, respectively), while the rate in the 0.5 mg group was similar to the placebo group (40.0%; *P* values not reported). Remitter responder rates were higher for patients receiving all doses of rotigotine compared to patients receiving placebo with the exception of the 0.5 mg dose.

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
placebo				An improvement in RLS-QOL score occurred in all rotigotine groups compared to the placebo group with the exception of the 0.5 mg group; however, the difference was only significant for the 3 mg group (*P*<0.05).
Oertel et al[70] Rotigotine transdermal patch 0.5 to 4 mg/24 hours Patients were titrated down at the completion of the six-week study and began a four-week titration period at the beginning of the OL period.	ES, MC, OL Patients completing the six-week study by Oertel et al[69] who had not experienced serious adverse events	N=295 1 year	Primary: Change from baseline in IRLS total score Secondary: CGI-I scores, responder rates on IRLS, RLS-6, CGI-I (≥50% improvement from baseline for IRLS score and ratings of "much improved" or "very much improved" on CGI-I), IRLS remitter rates (IRLS score ≤10) and RLS-QOL	Primary: Among patients continuing to receive rotigotine in the extension phase, there was a statistically significant reduction in IRLS total score from baseline after one year (-17.4; *P*<0.001). Secondary: All components of the RLS-6 symptom severity scale were significantly improved following one year in the ES compared to baseline (*P*<0.001). Similarly, statistically significant improvements in CGI-I item one scores occurred at one year of the ES compared to baseline (-2.9; *P*<0.001). Compared to baseline, there were a higher proportion of IRLS responders after one year of treatment with rotigotine (74.5 vs 68.1%; *P* value not reported). There were a greater proportion of RLS-6 responders and CGI-I responders after one year of rotigotine therapy compared to baseline (*P* values not reported). After one year of rotigotine treatment, 60% of patients were considered remitter responders compared to the proportion of patients at baseline of the OL period (60.0 vs 53.2%; *P* value not reported). There was a statistically significant reduction in RLS-QOL scores following one year of rotigotine treatment compared to baseline (-18.0; *P*<0.001).
Oertel et al[71] Rotigotine transdermal patch 0.5 to 4 mg/24 hours	ES, MC, OL Patients completing the six-week study	N=295 5 years	Primary: Adverse events and dropouts Secondary:	Primary: In total, 169 patients (57%) discontinued treatment before the end of maintenance, 31 (11%) because of lack of efficacy and 89 (30%) due to adverse events.

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
	by Oertel et al[69] who had not experienced serious adverse events		IRLS total score, RLS-6 scale, CGI-I item one and two, response rates on IRLS, CGI-I and remitter rates	Overall, 273 patients (93%) had one or more treatment-emergent adverse events. The most common dopaminergic adverse events were nausea, fatigue, headache and dizziness. Five patients (2%) had a sleep attack or sudden onset of sleep. Most patients had adverse events that were mild or moderate in intensity. There were 117 treatment-emergent serious adverse events reported by 79 patients. The adverse events most often reported as reasons for discontinuation were application site reactions in 56 patients (19%), insomnia in four patients (1%) and depression in three patients (1%). Of the 172 patients who reported application site reactions, most had reactions that were mild (30%) or moderate (52%) in intensity and 17% had a severe reaction. No clinically relevant changes in vital signs, clinical laboratory measurements, or electrocardiograms were reported. Four patients developed orthostatic hypotension. Secondary: The mean IRLS total score was 27.8 at baseline of the DB trial, decreasing to 8.9 after titration, and ranged between 8.5 and 10.5 throughout the five-year extension period. Overall, 67% of the patients who completed the trial were considered responders, 59% were considered remitters and 39% were symptom free according to the IRLS score. Mean CGI-I item one scores decreased by 2.8 points from baseline and 76% of patients who completed the trial were classified as responders on CGI-I item one. At the end of five years, 85% of patients had “low severity illness,” 32% had “normal severity illness,” 35% were “borderline ill” and 19% were “mildly ill” based on CGI-I item assessment. The reductions in mean RLS-6 scores were 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

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
				satisfaction (-4.5), severity of symptoms falling asleep (-4.3), and severity of symptoms during the night (-5.1). Scores for daytime symptoms decreased by a mean of 2.9 points while resting and 1.3 points while active.
Baker et al[72] 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 Patients with a mean age of 51 to 76 years of age with moderate-to-severe RLS	N=3,197 (14 trials) Up to 12 weeks	Primary: Percentage of responders to medications determined by the CGI-I score 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 WMD 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).
Trenkwalder et al[73] Dopamine agonists (doses and formulations not specified) vs	SR Patients ≥18 years of age with primary or secondary RLS receiving treatment with a dopamine	N=7,365 (38 trials) ≥7 days	Primary: Change in IRLS score, PLMSI, sleep efficiency and number of dropouts due to adverse events Secondary:	Primary: The mean reduction on the IRLS was -5.7 points greater with dopamine agonist treatment compared to placebo treatment (95% CI, -6.7 to -4.7). Trials using transdermal systems such as lisuride (-8.0; 95% CI, -10.28 to -5.70) and rotigotine showed high treatment effects (-6.98; 95% CI, -8.99 to -4.96). Lower effects were reported for pramipexole (-5.16; 95% CI, -6.88 to -3.43), followed by ropinirole (-4.19; 95% CI, -5.40 to -2.97). One study with sumanirole demonstrated a treatment difference of -1.83 points (95% CI, -4.71 to 1.05).

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
placebo The following dopamine agonists were included: cabergoline, lisuride*, pergolide, pramipexole, ropinirole, rotigotine and sumanirole.	agonist		CGI-I, self-rated quality of sleep and disease-specific QOL	The PLMSI was -22.4/hour lower with dopamine agonist treatment compared to placebo treatment (95% CI, -27.8 to -16.9). The improvement in PLMSI with pramipexole was -30.47/hour (95% CI, -51.58 to -9.35), -30.35/hour with rotigotine (95% CI, -43.74 to -16.96) and -14.11/hour with ropinirole (95% CI, -18.79 to -9.43). There was no difference in sleep efficiency for patients treated with pramipexole, ropinirole or rotigotine compared to placebo. Treatment with a dopamine agonist was associated with self-rated quality of sleep improvements compared to placebo treatment (SMD, 0.40; 95% CI, 0.33 to 0.47). Improvements with pramipexole (SMD, 0.44; 95% CI, 0.33 to 0.54), ropinirole (SMD, 0.30; 95% CI, 0.16 to 0.43) and rotigotine (SMD, 0.42; 95% CI, 0.28 to 0.56) were greater compared to placebo. Secondary: Dopamine agonist treatment improved disease specific QOL compared to placebo (SMD, 0.34; 95%CI, 0.23 to 0.44). Statistically significant changes in QOL were reported with pramipexole (SMD, 0.30; 95% CI, 0.13 to 0.47), ropinirole (SMD, 0.23; 95% CI, 0.09 to 0.36) and rotigotine (SMD, 0.50; 95% CI, 0.23 to 0.76) compared to placebo. Patients were more likely to discontinue treatment (OR, 1.82; 95%CI, 1.35 to 2.45) and experienced more adverse events when receiving treatment with a dopamine agonist compared to receiving treatment with placebo (OR, 1.82; 95% CI, 1.59 to 2.08). Compared to placebo, dropout rates were significantly greater with ropinirole (OR, 1.76; 95% CI, 1.31 to 2.38); however, no differences were reported with the other dopamine agonists compared to placebo. Patients treated with dopamine agonists responded more on the CGI-I compared to those on placebo treatment (RR, 1.44; 95% CI, 1.34 to 1.54). Patients were more likely to achieve a CGI-I response while receiving pramipexole (RR, 1.53; 95% CI, 1.30 to 1.80), ropinirole (RR, 1.36; 95% CI, 1.27 to 1.46) or rotigotine (RR, 1.48; 95% CI, 1.31 to 1.67) compared to

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
				placebo.

*Agent is not currently available in the United States.
Drug regimen abbreviations: BID=twice daily, CR=controlled-release, ER=extended-release, IR=immediate-release, QAM=every morning, QD=once daily, QHS=bedtime, TID=three times daily
Study abbreviations: AC=active control, DB=double-blind, CI=confidence interval, MA=meta-analysis, MC=multicenter, OL=open-label, OR=odds ratio, PC=placebo controlled, PG=parallel group, PRO=prospective, RCT=randomized controlled trial, RR=relative risk, SA=subanalysis, SR=systematic review, XO=crossover
Miscellaneous abbreviations: ADL=activities of daily living, AIMS=abnormal involuntary movement scale, BDI-II=Beck depression inventory, CIT=Carbomethoxy-3β-(4-iodophenyl) tropane, CGI=clinical global impression, CGI-I=clinical global impressions-improvement, EQ-5D=European quality of life-five domain questionnaire, ECG=electrocardiogram, ESS=Epworth sleepiness scale, HADS=hospital anxiety and depression score, HAMD=Hamilton depression rating scale, IRLS=international RLS study group rating scale, LOCF=last observation carried forward, LS=least square, MADRS=Montgomery–Asberg depression rating scale, MAO-B=monoamine oxidase type B, MMIDI=modified Minnesota disorders interview, MMSE=mini-mental state examination, MOS=medical outcomes study, mPDSS=modified Parkinson's disease sleep scale, NADCS= nocturnal dystonia cramp score, NMDA=N-methyl D-aspartate, NMS=nonmotor symptoms, NMSS=nonmotor symptom scale, NS=not significant, PDQ-8=Parkinson's disease questionnaire 8 items, PDQ-39=Parkinson's disease questionnaire 39 items, PDSS=Parkinson's disease sleep scale, PET=positron emission tomography, PGI=patient global impression, PGI-I=patient global impression of improvement, PLM=periodic limb movements, PLMAI=periodic limb movements associated with arousal index, PLMI=periodic limb movements index , PLMS=periodic limb movements of sleep, PLMSAI=periodic limb movement during sleep with arousal index, PLMSI= periodic limb movements during sleep index , PLMWI=periodic limb movements during wakefulness index , PPS=per-protocol set, PSG=polysomnogram, PSQI=Pittsburgh sleep quality index, QOL=quality of life, REM=rapid eye movement, nREM=nonrapid eye movement, RLS=restless legs syndrome, SDS=Zung Self-Rating Depression, SF=Short Form, SIT=suggested immobilization test, SMD=standardized mean difference, TST=total sleep time, TUaG=timed up- and-go test, UPDRS=unified Parkinson disease rating scale, VAS=visual analogue scale, WMD=weighted mean difference, WPAI=work productivity and activity impairment

Special Populations

Table 5. Special Populations[1-5,15]

Generic Name	Population and Precaution				
	Elderly/ Children	Renal Dysfunction	Hepatic Dysfunction	Pregnancy Category	Excreted in Breast Milk
Pramipexole	No evidence of overall differences in safety or efficacy observed between elderly and younger adult patients. Safety and efficacy in children have not been established.	Renal dose adjustment is required; for creatinine clearances >50 mL/minute, a dose of 0.125 to 1.5 mg three times daily is recommended. For creatinine clearances 30 to 50 mL/minute, a dose of 0.125 to 0.75 mg two or three times daily is recommended. For creatinine clearances 15 to 30 mL/minute, a dose of 0.125 to 1.5 mg once daily is recommended. Not adequately studied in patients with a creatinine clearance <15 mL/minute and hemodialysis patients.	Not studied in hepatic dysfunction.	C	Unknown; use caution.
Ropinirole	No dosage adjustment required in elderly, as the dose is individually titrated to clinical response. Safety and efficacy in children have not been established.	No dosage adjustment required.	Not studied in hepatic dysfunction.	C	Unknown; use caution.
Rotigotine	No evidence of overall differences in	No dosage adjustment required.	No dosage adjustment required.	C	Unknown; use caution.

Generic Name	Population and Precaution				
	Elderly/ Children	Renal Dysfunction	Hepatic Dysfunction	Pregnancy Category	Excreted in Breast Milk
	safety or efficacy observed between elderly and younger adult patients. Safety and efficacy in children have not been established.				

Adverse Drug Events

Table 6. Adverse Drug Events (%)[1-5,15]

Adverse Event	Pramipexole		Ropinirole		Rotigotine
	IR	ER	IR	XL	
Cardiovascular					
Abnormal T waves	-	-	-	-	<3
Atrial fibrillation	-	-	2	-	-
Chest pain	3	-	4	-	-
Extrasystoles	-	-	2	-	-
General edema	4 to 5	-	6	-	-
Hot flushes	-	-	3	-	<4
Hypertension	-	-	5	3	3 to 5
Hypotension	-	-	2	2	-
Orthostatic symptoms	-	3	6	5	-
Palpitations	-	-	3	-	-
Peripheral edema	2 to 5	5	2 to 7	4	<14
Peripheral ischemia	-	-	3	-	-
Postural hypotension	53	-	-	-	-
Syncope	-	-	3 to 12	-	-
Tachycardia	-	-	2	-	-
Central Nervous System					
Abnormal dreams	2	-	-	-	1 to 7
Akathisia	2 to 3	-	-	-	-
Amnesia	4 to 6	-	3 to 5	-	-
Anxiety	-	-	6	2	-
Balance disorder	-	2	-	-	<3
Confusion	4 to 10	-	5 to 9	7	-
Delusions	1	-	-	-	-
Depression	-	-	-	-	<5
Dizziness	25 to 26	12	11 to 40	8 to 10	5 to 23
Dizziness, postural	3	2	-	-	1 to 2
Dream abnormalities	11	-	-	-	-
Dry mouth	3 to 7	5	3 to 5	2	3 to 7
Dyskinesia	47	17	34	13	14 to 17
Dystonia	2 to 8	-	-	-	-
Early morning awakening	-	-	-	-	<3
Extrapyramidal syndrome	28	-	-	-	-
Fatigue	3 to 9	6	8 to 11	-	6 to 18

Adverse Event	Pramipexole		Ropinirole		Rotigotine
	IR	ER	IR	XL	
Gait abnormalities	7	-	-	-	-
Hallucinations	9 to 17	9	5 to 10	6 to 8	7 to 14
Headache	16	7	17	5	8 to 10
Hyperkinesia	-	-	2	-	-
Hypertonia	7	-	-	-	-
Hypesthesia	-	-	4	-	-
Hypokinesia	-	-	5	-	-
Impaired concentration	2	-	2	-	-
Insomnia	9 to 27	4	-	-	5 to 11
Lethargy	-	-	-	-	1 to 2
Nervousness	-	-	5	-	-
Nightmare	-	-	-	-	3 to 5
Paranoid reaction	2	-	-	-	-
Paresthesia	-	-	3 to 5	-	-
Pyrexia	1	-	-	-	-
Sleep attacks	6	3	-	-	<2
Sleep disturbances	1	2	-	-	2 to 14
Somnolence	6 to 22	36	12 to 40	7 to 12	5 to 32
Tinnitus	-	-	-	-	<3
Tremor	3	3	6	-	3 to 4
Twitching	2	-	-	-	-
Vertigo	2	4	2	4	1 to 4
Yawning	-	-	3	-	-
Gastrointestinal					
Abdominal pain/discomfort	-	2 to 3	3 to 9	6	-
Constipation	4 to 14	7 to 14	6	4	2 to 9
Diarrhea	1 to 7	2	5	3	5 to 7
Dyspepsia	1 to 7	3	4 to 10	-	<3
Dysphagia	2	-	2 to 4	-	-
Flatulence	-	-	2	-	-
Increased salivation	-	2	2	-	-
Nausea	11 to 27	11 to 22	30 to 60	11 to 12	15 to 41
Vomiting	-	4	7 to 12	-	2 to 20
Musculoskeletal					
Arthralgia	-	-	4 to 7	-	8 to 11
Arthritis	3	-	3	-	-
Asthenia	10 to 14	3	6	-	7 to 14
Back pain	3	2	-	2	-
Bursitis	2	-	-	-	-
Contusion	-	-	-	-	<4
Muscle cramps	-	-	3	-	-
Muscle spasms	3	5	-	-	2 to 4
Myasthenia	1	-	-	-	-
Pain	3 to 7	-	3 to 8	-	2
Ophthalmic					
Abnormal vision	3	-	6	-	-
Accommodation abnormalities	4	-	-	-	-
Anemia	-	-	2	-	-
Diplopia	1	-	2	-	-
Eye abnormality	-	-	3	-	-

Adverse Event	Pramipexole		Ropinirole		Rotigotine
	IR	ER	IR	XL	
Xerophthalmia	-	-	2	-	-
Other					
Accidental injury	17	-	-	-	-
Anorexia	4	5	4	-	<8
Application site reactions	-	-	-	-	21 to 46
Decreased appetite	-	-	-	-	<3
Erythema	-	-	-	-	1 to 6
Falls	4	4	10	2	-
Hiccups	-	-	-	-	2 to 3
Hyperhidrosis	-	-	3 to 7	5	<11
Impotence	2	-	3	-	<3
Increased alkaline phosphatase	-	-	3	-	-
Increased appetite	2	3	-	-	-
Increased creatinine phosphokinase	1	-	-	-	-
Increased drug level	-	-	7	-	-
Influenza	3	-	3	-	-
Libido decreased	1	-	-	-	-
Malaise	2 to 3	-	3	-	-
Myoclonus	1	-	-	-	-
Paresthesia/dysesthesia	-	-	-	-	5 to 6
Pruritus	-	-	-	-	3 to 9
Pyuria	-	-	3	-	-
Rash, pruritic	-	-	-	-	<3
Serum ferritin decreased	-	-	-	-	<2
Skin disorders	2	-	-	-	-
Urinary frequency	6	-	-	-	-
Urinary incontinence	2	-	2	-	-
Upper respiratory tract infection	4	-	6 to 9	-	<5
Urinary tract infection	-	-	5 to 6	-	-
Viral Infection	-	-	11	-	-
White blood cells urine positive	-	-	-	-	1 to 3
Weight decreased	2	-	2	-	<3
Respiratory					
Bronchitis	-	-	3	-	-
Cough	3	3	3	-	3
Dyspnea	4	-	3	-	-
Nasal congestion	3 to 6	-	2	-	3
Nasopharyngitis	-	-	9	-	5 to 10
Pharyngeal pain	-	-	-	-	<2
Pharyngitis	-	-	6 to 9	-	-
Pneumonia	2	-	-	-	-
Rhinitis	3	-	4	-	-
Sinusitis	-	-	4	-	<3
Sinus congestion	-	-	-	-	2 to 3

IR=immediate-release, ER, XL=extended-release
- Event not reported or incidence <5%.

Contraindications

Table 7. Contraindications[1-5,15]

Contraindication	Pramipexole		Ropinirole		Rotigotine
	IR	ER	IR	XL	
Hypersensitivity reaction (including urticaria, angioedema, rash, pruritus) to the active ingredient or to any components of the formulation	-	-	✔	-	-
Hypersensitivity to rotigotine or components of the transdermal patch	-	-	-	-	✔

IR=immediate-release, ER, XL=extended-release

Warnings/Precautions

Table 8. Warnings and Precautions[1-5,15]

Warnings and Precautions	Pramipexole		Ropinirole		Rotigotine
	IR	ER	IR	XL	
Application site reactions; if reaction persists or an increase in severity occurs, an assessment of the patient should be conducted	-	-	-	-	✔
Augmentation and rebound in restless legs syndrome; a worsening of symptoms or increase in overall symptom severity or earlier time of symptom onset may occur	✔	-	✔	-	✔
Dyskinesias; treatment may potentiate the dopaminergic adverse events of levodopa and may cause or exacerbate preexisting dyskinesia	✔	✔	✔	✔	✔
Elevated blood pressure and changes in heart rate; consider these events when treating patients with cardiovascular disease	-	-	-	✔	✔
Events reported with dopaminergic therapy; withdrawal-emergent hyperpyrexia, confusion, fibrotic complications and melanoma have been reported	✔	✔	✔	✔	✔
Excessive drowsiness; patients should use caution when receiving concomitant sedative medications, alcohol or in the presence of other sleep disorders	✔	✔	✔	✔	-
Falling asleep while engaging in activities of daily living; some patients report no advanced symptoms or warnings	✔	✔	✔	✔	✔
Hallucinations have been reported with treatment	✔	✔	✔	✔	✔
Heat application; avoid direct exposure of application site to external sources of heat such as heating pads, electric blankets or heat lamps due to the	-	-	-	-	✔

Warnings and Precautions	Pramipexole		Ropinirole		Rotigotine
	IR	ER	IR	XL	
potential for increase absorption					
Impulse control and/or combative behaviors; prescribers should alert patients or caregivers to report the development of any new or increased gambling urges, sexual urges, uncontrolled spending or other urges while taking this agent	✔	✔	✔	✔	✔
Magnetic resonance imaging and cardioversion; the back layer of this product contains aluminum and may result in skin burns if not removed prior to procedure	-	-	-	-	✔
Major psychotic disorders; due to the risk of exacerbating the psychosis, these patients should not receive this agent	-	-	-	✔	-
Melanoma; epidemiologic studies have demonstrated that Parkinson's patients have a higher risk of developing melanoma than the general population	-	-	-	-	✔
Renal impairment; use with caution in this patient population	✔	✔	✔	-	-
Sulfite sensitivity; this product contains sodium metabisulfite, which may cause allergic-type reactions in susceptible individuals	-	-	-	-	✔
Symptomatic orthostatic hypotension; patients should be monitored for signs and symptoms, especially during dose titration	✔	✔	✔	✔	✔
Syncope, sometimes associated with bradycardia has been observed in patients receiving treatment	-	-	✔	✔	✔
Weight gain and fluid retention have been reported in clinical trials at a higher rate compared to placebo	-	-	-	-	✔

IR=immediate-release, ER, XL=extended-release

Drug Interactions[1-5]

There are no significant drug interactions listed for pramipexole. Ropinirole is metabolized by the enzyme cytochrome P450 1A2 (CYP1A2), therefore, there is the potential for an alteration in clearance of this agent with inhibitors (e.g., ciprofloxacin, fluvoxamine) and inducers (e.g., omeprazole, cigarette smoking) of CYP1A2. Dopamine agonists such as antipsychotics may diminish the effectiveness of rotigotine transdermal patch.

Dosage and Administration

Table 9. Dosing and Administration[1-5,15]

Generic Name	Adult Dose	Pediatric Dose	Availability
Pramipexole	Treatment of the signs and symptoms of idiopathic Parkinson's disease:	Safety and efficacy in	Extended-release tablet:

Generic Name	Adult Dose	Pediatric Dose	Availability
	Extended-release tablet: initial, 0.375 mg orally once daily and increased gradually every five to seven days; maintenance, 0.375 to 4.5 mg orally once daily; maximum, 4.5 mg once daily Tablet: initial, 0.125 mg orally three times daily and increased by 0.25 mg every five to seven days; maintenance, 1.5 to 4.5 mg in three divided doses and should not be increased more frequently than every five to seven days Treatment of moderate-to-severe primary restless legs syndrome: Tablet: initial, 0.125 mg orally once daily two to three hours before bedtime and titrated every four to seven days; maintenance, 0.5 mg orally once daily; there is no evidence that the 0.75 mg dose provides additional benefit beyond the 0.5 mg dose	children have not been established.	0.375 mg 0.75 mg 1.5 mg 2.25 mg 3 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 the signs and symptoms of idiopathic Parkinson's disease: Extended-release tablet: initial, 2 mg orally once daily for one to two weeks followed by increases of 2 mg/day at weekly or longer intervals as appropriate; maintenance, 2 to 24 mg orally once-daily Tablet: initial, 0.25 mg orally three times daily, based on individual patient response, dosage should then be titrated with weekly increments; after week four, if necessary, daily dosage may be increased by 1.5 mg/day on a weekly basis up to a dose of 9 mg/day, and then by up to 3 mg/day weekly to a total dose of 24 mg/day; maximum, 24 mg/day Treatment of moderate-to-severe primary restless legs syndrome: Tablet: initial, 0.25 mg once daily, one to three hours before bedtime, after two days, the dosage can be increased to 0.5 mg once daily and to 1 mg once daily at the end of the first week of dosing; maintenance, 0.25 to 4 mg orally once daily; maximum, 4 mg orally once daily	Safety and efficacy in children have not been established.	Extended-release tablet: 2 mg 4 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 the signs and symptoms of idiopathic Parkinson's disease: Transdermal patch: initial, 2 mg/24 hours for early stage disease applied once daily or 4 mg/24 hours for advanced-stage disease applied once daily; maintenance, 2 to 6 mg/24 hours applied once daily; maximum, 6 mg/24 hours for early-stage disease applied once daily and 8 mg/24 hours for advanced-stage disease applied once daily	Safety and efficacy in children 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

Generic Name	Adult Dose	Pediatric Dose	Availability
	Treatment of moderate-to-severe primary restless legs syndrome: Transdermal patch: initial, 1 mg/24 hours applied once daily; maintenance, 1 to 3 mg/24 hours applied once daily and titrated in weekly intervals; maximum, 3 mg/24 hours applied once daily		

Clinical Guidelines

Table 10. Clinical Guidelines

Clinical Guideline	Recommendation(s)
European Federation of Neurological Societies/Movement Disorder Society: **Early (Uncomplicated) Parkinson's Disease (2011)**[9]	Early untreated patients may start treatment with • Monoamine oxidase type B (MAO-B) inhibitors, (selegiline or rasagiline) have a more modest symptomatic effect than that of levodopa and (probably) dopamine agonists, but they are easy to administer and well tolerated. • Amantadine or anticholinergics have a smaller impact on symptoms than levodopa. Anticholinergics are poorly tolerated in the elderly and their use is generally restricted to young patients. • Levodopa is the most effective symptomatic antiparkinsonian drug. Within a few years of treatment, motor complications frequently develop with levodopa. As older patients are more sensitive to neuropsychiatric adverse reactions and are less prone to developing motor complications, the early use of levodopa is recommended in the older population. Early use of controlled-release (CR) levodopa is not effective in the prevention of motor complications. • The oral dopamine agonists pramipexole and ropinirole immediate-or controlled- release are effective as monotherapy in early Parkinson's disease, with a lower risk of motor complications than levodopa. • Older drugs like bromocriptine are supported by lower class evidence; however, there is no convincing evidence that they are less effective in managing patients with early Parkinson's disease. • The benefit of dopamine agonists in preventing motor complications must be balanced with the smaller effect on symptoms and the greater incidence of hallucinations, impulse-control disorders, somnolence, and leg edema compared to levodopa. • Younger patients are more prone to developing levodopa-induced motor complications, and therefore initial treatment with a dopamine agonist may be recommended in this population. • Ergot derivatives such as pergolide, bromocriptine and cabergoline are not first-line treatments due to the risk of fibrotic reactions. • Subcutaneous apomorphine is not appropriate at this stage of the disease. The early combination of low doses of a dopamine agonist with low doses of levodopa is another option, although the benefits of such a combination have not been properly documented.
European Federation of Neurological Societies/Movement Disorder Society: **Late (Complicated)**	Motor fluctuations • In an early phase, when motor fluctuations are becoming apparent, adjustments in the frequency of levodopa dosing during the day, tending to achieve four to six daily doses may attenuate "wearing-off". • Add catechol-o-methyltransferase (COMT) inhibitor or MAO-B inhibitors. Neither is recommended over the other for initial treatment. All reduce "off"

Clinical Guideline	Recommendation(s)
Parkinson's Disease (2011)[10]	time by about one- to one and a half hours daily. • Tolcapone is only recommended in patients failing all other available medications. Rasagiline should not be added to selegiline because of cardiovascular safety issues. • Non-ergot dopamine agonists are considered first-line treatment. Ergot-derived agonists are second-line treatment, due to their association with lung, retroperitoneal and heart valve fibrosis. • Oral dopamine agonists reduce "off" time in patients experiencing "wearing-off". No dopamine agonist is more effective than another; however, switching from one agonist to another can be helpful in some patients. • Switch from standard levodopa to the CR formulation can also improve "wearing-off". This formulation is useful for the treatment of nighttime akinesia. • In patients with disabling recurrent "off" symptoms that fail to improve with recommended therapies, the addition of an anticholinergic (in younger patients), or amantadine, may improve symptoms in some cases. <u>Dyskinesias</u> • Reduce individual levodopa dose size, at the risk of increasing "off" time. This can be compensated for by increasing the number of daily doses of levodopa or increasing the doses of a dopamine agonist. • Discontinue or reduce dose of MAO-B inhibitors or COMT inhibitors at the risk of worsening "wearing-off." • The benefit of adding amantadine may last □<8 months. • Discontinuation of oral levodopa for a short period of time (three days) with simultaneous continuous intravenous infusion of amantadine may temporarily improve dyskinesia. • Add the atypical antipsychotics clozapine or quetiapine. Clozapine is associated with potential serious adverse events (agranulocytosis and myocarditis), which limits its use. • Apomorphine continuous subcutaneous infusion, allows for a reduction in levodopa therapy. • Intrajejunal levodopa infusion in patients with marked peak dose dyskinesia and motor fluctuations. <u>Off-period and early morning dystonias</u> • Usual strategies for "wearing-off" can be applied in cases of "off" period dystonia. • Additional doses of levodopa or dopamine agonist therapy at night may be effective for the control of dystonia appearing during the night or early in the morning. • Botulinum toxin can be employed in both "off" period and early morning dystonia.
National Institute for Health and Clinical Excellence: **Parkinson's Disease: Diagnosis and Management in Primary and Secondary Care (2006)**[11]	• There is no universal first-choice therapy for patients with Parkinson's disease. Clinical and lifestyle characteristics of the patient should be taken into account. • Levodopa may be used in patients with early Parkinson's disease for symptomatic treatment with doses kept as low as possible to reduce the development of motor complications. • Dopamine agonists may be used in patients with early Parkinson's disease for symptomatic treatment. Dopamine agonists should be titrated to a clinically efficacious dose and another agent in the class may be used if the

Clinical Guideline	Recommendation(s)
	patient fails therapy or adverse events prevent titration. • MAO-B inhibitors may be used in patients with early Parkinson's disease for symptomatic treatment. • Beta-blockers may be used for symptomatic treatment of selected people with postural tremor, but are not considered first-line agents. • Amantadine may be used in patients with early Parkinson's disease, but is not considered a first-line agent. • Anticholinergics may be used in young patients with early Parkinson's disease for symptomatic treatment associated with severe tremor. These agents are not considered first-line due to limited efficacy and the propensity to cause neuropsychiatric side effects. • Extended-release levodopa should not be used to delay the onset of motor complications in patients with early Parkinson's disease. • Most patients with Parkinson's disease will develop motor complications over time and will require levodopa therapy. Adjuvant medications have been developed to take concomitantly with levodopa to help reduce the motor complications and improve quality of life associated with late stage Parkinson's disease. • There is no single agent of choice for late stage Parkinson's disease. • Extended-release levodopa may help reduce motor complications in patients with late stage Parkinson's disease, but is not considered a first-line agent. • Dopamine agonists may be used to reduce motor fluctuations in patients with late stage Parkinson's disease. Dopamine agonists should be titrated to a clinically efficacious dose and another agent in the class may be used if side effects prevent titration. • MAO-B inhibitors may be used to reduce motor fluctuations in patients with late stage Parkinson's disease. • COMT inhibitors may be used to reduce motor fluctuations in patients with late stage Parkinson's disease. This class of medication is taken concomitantly with levodopa. • Amantadine may be used to reduce dyskinesias in patients with late stage Parkinson's disease. • "Drug holidays" should be avoided because of the risk of developing neuroleptic malignant syndrome.
American Academy of Neurology Practice Parameter: **Initiation of Treatment for Parkinson's Disease: An Evidence Based Review (2002)**[74]	• Patients with Parkinson's disease, who require symptomatic treatment, may be started with selegiline prior to the administration of dopaminergic therapy. • Selegiline has mild symptomatic benefits in Parkinson's disease, and no convincing evidence of neuroprotective benefits. • Levodopa, cabergoline, ropinirole and pramipexole are effective in ameliorating motor complications and impairment in the activities of daily living in patients with Parkinson's disease who require dopaminergic therapy. Of these agents, levodopa is more effective in treating motor complications and activities of daily living disability and is associated with a higher incidence of dyskinesias than dopamine agonists. • Levodopa or a dopamine agonist may be initiated in patients with Parkinson's disease who require dopaminergic therapy. • Cabergoline, ropinirole and pramipexole resulted in fewer motor complications (e.g., "wearing-off", dyskinesias and "on-off" fluctuations) compared to levodopa. • Treatment with a dopamine agonist was associated with more frequent

Clinical Guideline	Recommendation(s)
	adverse drug reactions (hallucinations, somnolence and edema in the lower extremities) than levodopa. • When initiating treatment with levodopa in patients with Parkinson's disease, either an immediate-release or sustained-release formulation may be used. In clinical trials, there was no difference in the rate of motor complications between the two formulations.
American Academy of Neurology Practice Parameter: **Treatment of Parkinson's Disease with Motor Fluctuations and Dyskinesia (2006)**[75]	• Rasagiline and entacapone have demonstrated statistically significant reductions in "off" time compared to placebo. It is recommended that these two agents should be offered to reduce "off" time. • Pergolide has demonstrated some improvement in the reduction in "off" time as compared to placebo. Pramipexole demonstrated some reduction in "off" time in placebo controlled trials. Ropinirole and tolcapone reduced "off" time compared to placebo. It is recommended that pergolide, pramipexole, ropinirole and tolcapone can be considered to reduce "off" time. Due to adverse events and the strength of the studies, entacapone and rasagiline are preferred over pergolide, pramipexole, ropinirole and tolcapone. • Apomorphine, cabergoline and selegiline were studied in clinical trials that lacked proper enrollment and methods to provide conclusive evidence of reducing "off" time. It is recommended that these agents may be considered to reduce "off" time. • Bromocriptine and carbidopa/levodopa CR do reduce "off" time. • Amantadine demonstrated reductions in dyskinesia compared to placebo in clinical trials. It is recommended that amantadine may be considered for patients with Parkinson's disease for reducing dyskinesias. • Deep brain stimulation of the subthalamic nucleus may be considered as a treatment option in Parkinson's disease patients to help improve motor function and to reduce motor fluctuations, dyskinesias and medication usage.
European Federation of Neurological Societies/European Neurological Society/European Sleep Research Society: **European Guidelines on Management of Restless Legs Syndrome (2012)**[12]	<u>Nonergot-derived dopamine agonists</u> • Rotigotine transdermal patch (1 to 3 mg) is effective for the short- and long-term treatment of primary restless legs syndrome (RLS). • Ropinirole is effective for improving symptoms in primary RLS when given at a mean dose of between 2.1 and 3.1 mg/day over the short-term and possibly over the long-term. • Pramipexole is considered effective in the short-term and possibly effective for the long-term treatment for RLS at doses between 0.25 and 0.75 mg. • Sumanirole at the investigated doses (0.5 to 4 mg) is ineffective for the treatment of primary RLS. <u>Ergot derived dopamine agonists</u> • In primary RLS, no new studies have been published on pergolide. Although the previous conclusion of effectiveness at mean dosages of 0.40 to 0.55 mg/day and possible effectiveness in the long-term remains possible, toxicity and adverse events outweigh the benefits of use. • For cabergoline, the same precaution as for pergolide applies. There is insufficient evidence to make any recommendations on terguride. • There are no new studies on bromocriptine and, therefore, the previous conclusion of probably effective at 7.5 mg for primary RLS remains. The most frequent adverse events of ergot-derived dopamine agonists are nausea, headache, nasal congestion, dizziness and orthostatic hypotension. • Augmentation remains an open issue for all ergot derivatives and requires further extensive investigation.

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	• Furthermore, owing to the negative adverse event profile, especially the potential to induce fibrosis, ergot derivatives cannot be recommended for the first-line treatment for RLS. Levodopa • There is high-quality evidence that shows that levodopa improves RLS symptoms. • Given the higher risk of augmentation compared to dopamine agonists, levodopa should not be given at a dosage higher than 200 mg/day. • In clinical practice, levodopa is now better established as a diagnostic test for RLS and as on-demand treatment in sporadic RLS, and therefore, there is a low recommendation for the use of levodopa compared to other available agents. Antiepileptics • Pregabalin and gabapentin enacarbil can be considered effective for the short-term treatment of primary RLS. In addition, gabapentin enacarbil can be considered probably effective for the long-term treatment of RLS. • Gabapentin continues to be considered effective in the short-term treatment of primary RLS and probably effective in secondary RLS after hemodialysis. • There is insufficient evidence to make any efficacy conclusions on oxcarbazepine. There is insufficient evidence to conclude on the efficacy of lamotrigine or levetiracetam for the treatment of RLS. Other agents • Clonidine is probably effective short-term in reducing symptoms and sleep latency in primary RLS. • Clonazepam is probably effective for treating primary RLS. • Iron sucrose is not effective for the treatment of primary RLS; however, oral ferrous sulfate and intravenous ferric carboxymaltose are probably effective. • There is insufficient evidence to recommend the use of onabotulinumtoxin A, bupropion, infrared light, aerobic training, folate, magnesium, vitamin E, physiotherapy or valerian for the management of RLS.
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 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 adverse event profile, these agents are not recommended

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	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, but it is 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 international restless leg scale, 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 • 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 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 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 investigational. N-Methyl-D-aspartic acid 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

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	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 investigation in RLS.
American Academy of Sleep Medicine: **The Treatment of Restless Legs Syndrome and Periodic Limb Movement Disorder in Adults-an Update for 2012 (2012)**[14]	Therapies for RLS • Patients with moderate to severe RLS should be treated with pramipexole. • Patients with moderate to very severe RLS should be treated with ropinirole. • Patients with RLS may be treated with levodopa; however, treatment carries the risk of augmentation. • Pergolide is effective in the treatment of RLS but has been withdrawn in the U.S. because of the risk of cardiac valvulopathy. • Cabergoline is more effective in the treatment of RLS than levodopa, but is not as well tolerated. Given the potential of adverse events, including heart valve damage, RLS patients should be treated with cabergoline only if other recommended agents have been tried first and failed, and close clinical follow-up is provided. • Opioids are effective in the treatment of RLS, especially for patients with RLS that is not relieved by other treatments. • Gabapentin enacarbil is effective in the treatment of moderate to severe RLS. • Gabapentin is effective in the treatment of mild to moderate RLS. • Pregabalin is effective in the treatment of moderate to severe RLS. • Carbamazepine is effective in the treatment of RLS. • Clonidine is effective in the treatment of RLS. • Iron supplementation has not been shown to be effective in the treatment of RLS, except perhaps in patients with iron deficiency or refractory RLS. • Clinicians may use supplemental iron to treat RLS patients with low ferritin levels. • Rotigotine transdermal patch is effective in the treatment of moderate to severe RLS, but was withdrawn from the United States in 2008 (NOTE: This product was reintroduced to the market in 2012). • There is insufficient evidence to support the use of lisuride in the treatment of RLS, and it is not Food and Drug Administration (FDA)-approved. • There is insufficient evidence to support the use of talipexole, peribedil, and alpha-dihydroergocryptine in the treatment of RLS. • There is insufficient evidence on the effect of benzodiazepines on the treatment of RLS. • There is insufficient evidence to evaluate the use of valproic acid for RLS. • There is insufficient evidence to evaluate the use of valerian for RLS. • There is conflicting evidence regarding whether or not antidepressant therapy can cause or exacerbate RLS symptoms. • There is insufficient evidence to evaluate the use of non-pharmacological therapy for RLS, including accommodative strategies, sleep hygiene, behavioral and stimulation therapies, compression devices, exercise, and nutritional considerations. • There is insufficient evidence on the effectiveness of any one therapy or the balance of benefits to harm in the treatment of secondary RLS, children, pregnant women, or other special patient groups. • There is insufficient evidence to comment on the use of pharmacological therapy in patients diagnosed with periodic limb movement disorder alone.

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European Federation of Neurological Societies Task Force: **Guidelines on Management of Restless Legs Syndrome and Periodic Limb Movement Disorder in Sleep (2006)**[76]	Primary RLS • Ropinirole is effective in improving RLS scale scores, quality of life, sleep latency and the Periodic Leg Movements in sleep Index/Arousals 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 doses of 0.40 to 0.55 mg daily, and may be effective long-term. • Gabapentin has demonstrated a decrease in RLS scores and improves sleep efficiency and Periodic Leg Movements in sleep Index at doses of 800 to 1,800 mg daily. • Levodopa/benserazide is effective in improving RLS symptoms, quality of sleep, sleep latency, Periodic Leg Movements in sleep Index and quality of life at an average dose of 159/40 mg at bedtime. 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. Periodic limb movement disorder • There is not enough evidence available to determine the effectiveness of non-ergot derivatives or antiseizure medications in periodic limb movement disorder. • Bromocriptine is probably effective in periodic limb movement disorder secondary to narcolepsy. • Clonazepam 0.5 to 2.0 mg per day and levodopa are probably effective in reducing Periodic Leg Movements in sleep Index and Periodic Leg Movements in sleep Arousals. • Triazolam 0.125 mg to 0.500 mg daily is probably effective in improving

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	sleep efficiency but not in the reduction of periodic limb movements during sleep. • Modafinil and propoxyphene are probably ineffective while transdermal estradiol is considered ineffective for the treatment of periodic limb movement disorder. • No specific recommendations can be made in the treatment of periodic limb movement disorder 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)**[77]	Daily RLS • Dopamine agonists are the drugs of choice in most people with daily RLS. Pramipexole and ropinirole are associated with fewer adverse events; 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 treatments. • Nonpharmacological management, such as the discontinuation of medications that may exacerbate RLS (neuroleptic agents, metoclopramide and 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 CR formulation can be administered prior to bedtime for nighttime 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. 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 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.

Conclusions

Pramipexole (Mirapex®), ropinirole (Requip®) and rotigotine transdermal patch (Neupro®) are nonergot-derived dopamine agonists that are Food and Drug Administration (FDA)-approved for the management of the signs and symptoms of idiopathic Parkinson's disease and moderate-to-severe primary restless

legs syndrome (RLS). Both pramipexole and ropinirole are available in extended-release formulations that are only indicated for the treatment of Parkinson's disease.[1-5] Pramipexole and ropinirole immediate-release and ropinirole extended-release are available generically.[6]

The efficacy of these agents in the treatment of Parkinson's disease is well established, although they do not appear to be as effective as levodopa in improving the motor impairments that are characteristic of the condition. Clinical studies have generally demonstrated each of these agents to be significantly more effective compared to placebo with regard to improving the signs and symptoms of both Parkinson's disease and RLS.[16-73] The results of available studies have not reported a difference in clinical efficacy between the immediate- and extended-release formulations of pramipexole and ropinirole.[3,16,17,18] Dopamine agonists are less often associated with the abnormal involuntary movements and "wearing-off" phenomenon that limit long-term levodopa therapy. Therefore, these agents may be considered for initial therapy, especially in younger patients, to delay the use of levodopa and the development of the motor complications associated with its use.[9,10] The dopamine agonist may also be used in combination with levodopa to allow for a decrease in levodopa dose.[21.22,26,27]

The nonergot-derived dopamine agonists are considered the drugs of choice in most patients with daily RLS symptoms.[12-14] The major route of elimination of 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 metabolism by cytochrome P450 1A2. Rotigotine is the only agent within the class that is available as a transdermal patch. Following patch removal, plasma rotigotine levels decline over five to seven hours. The adverse event profiles for these agents are comparable, although pramipexole has shown a higher rate of hallucinations and ropinirole an increased risk of developing somnolence and hypotension.[10] The incidence of adverse events with rotigotine transdermal patch appears to be similar to those occurring with the immediate-release pramipexole and ropinirole formulations.

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