D.2.2 Adjuvant treatment of motor symptoms

Stowe (2010)	**Study type** Cochrane Review **Aim/ objective of the study** This meta-analysis aims to assess more reliably the benefits and risks of dopamine agonists, COMTIs and MAOBIs currently used as adjuvant treatment to levodopa in PD patients suffering from motor complications. The three drug classes were compared with the aim of determining whether one class of drug provides better symptomatic control than another **Source of funding** Not reported	**Study dates/duration** Study duration: Ranged from 4 weeks to 2 years with an average length of follow-up being 20 weeks. Majority of studies (36/44, 82%) were of 6 months or less in duration of follow-up. **Sample size** Total (n): 44 trials with a total of 8436 participants. The number of participants randomised in the meta-analysis ranged from 23 to 687 participants.	**Inclusion/ exclusion criteria** Selection criteria (SRs) - Randomised trials comparing an orally administered dopamine agonist, COMTI or MAOBI vs. placebo, both on a background of levodopa therapy, in PD patients experiencing motor complications	**Baseline characteristics** The mean age of the participants in the trials was approximately 63 years, 60% were male and they had had PD for approximately 9 years	**Intervention(s)** Interventions included in SR/MA: - DA vs. placebo n=20: Pramipexole was assessed in 7 trials; bromocriptinein 5, cabergoline in 4, ropinirole in 4 and pergolide in 1 - COMTI vs. placebo n=18: Entacapone was assessed in 11 trials and tolcapone in 7 - MAOBI vs. placebo n=7: Rasagiline was assessed in 3 trials, selegiline in 4 (2 of deprenyl selegiline) and 2 of zydis selegiline	**Types of outcome measures** - Time spent in the "off" state - Levodopa dose - Changes in clinical-rated disability scales, e.g. UPDRS - The incidence of dyskinesia and dystonia - Frequency of AEs, mortality, treatment compliance and withdrawals, and QoL - Health economics
Clarke (2001)	**Study type** Cochrane review **Aim/ objective of the study** To compare the efficacy and safety of adjuvant	**Country/ies where the study was carried out** One published Japanese trial and two unpublished Korean and European randomised controlled	**Inclusion/ exclusion criteria** Selection criteria (SRs): - Randomised trials comparing the efficacy and safety of adjuvant oral ropinirole with bromocriptine - Patients with a clinical diagnosis of idiopathic Parkinson's disease		**Intervention(s)** Interventions included in SR/MA - Ropinirole: maximum dose was 9mg/d in two trials and 24mg/d in one trial	**Types of outcome measures** - Improvement in the time patients spend in the immobile "off" state

	ropinirole vs. bromocriptine in patients with Parkinson's disease, already established on levodopa and suffering from motor complications **Source of funding** Not reported	trials **Study dates/duration** Study duration: Two studies were short term (8 weeks and 16 weeks) and one was medium term (25 weeks) **Sample size** Total (n): 3 trials with a total 484 patients were included with 257 receiving ropinirole and 227 receiving bromocriptine	who had developed long-term motor complications of dyskinesia and/or end-of-dose deterioration - Trial durations of greater than 4 weeks		- Bromocriptine: maximum doses was 17.5mg/d, 22.5mg/d or 39.9mg/d	- Changes in dyskinesia rating scales and the prevalence of dyskinesia - Changes in parkinsonian rating scales - Reduction in L-dopa dose - Number of withdrawals due to lack of efficacy and/or side effects
Clarke (2001)	**Study type** Systematic review Cochrane review **Aim/ objective of the study** To compare the efficacy and safety of adjuvant cabergoline therapy vs. bromocriptine in patients with Parkinson's disease, already established on L-dopa and suffering from	**Study dates/duration** Study duration 4 trials were short term (12 to 15 weeks) and 1 trial had a mean duration of 9 months **Sample size** Total (n): 5 trials with a total of 1071 participants were included	**Inclusion/ exclusion criteria** Selection criteria (SRs) - RCTs of cabergoline vs. bromocriptine in patients with a clinical diagnosis of idiopathic Parkinson's disease and long-term complications of L-dopa therapy - Trial durations of greater than 4 weeks		**Intervention(s)** Interventions included in SR/MA - Cabergoline - maximum dose used in the trials was 4.0 - 6.0mg/d - Cromocriptine: maximum dose ranged between 22.5mg/d in 1 trial and 40mg/d in the other 4 trials	**Types of outcome measures** - Improvement in the time patients spend in the immobile "off" state - Changes in dyskinesia rating scales and the prevalence of dyskinesia

	motor complications **Source of funding** Not reported					- Changes in parkinsonian rating scales - Reduction in L-dopa dose - Number of withdrawals due to lack of efficacy and/or side effects
da Silva-Junior (2005)	**Study type** Randomized, double-blind, placebo-controlled study **Aim/ objective of the study** To evaluate the effect of 3 weeks of amantadine administration on LID in PD patients **Source of funding** The Brazilian National Council for Scientific Research (CNPq) and CAPES	**Country/ies where the study was carried out** Brazil **Study dates/duration** Study duration 3 weeks **Sample size** Total (n): 20 Group 1 (n): Amantadine: 10 Group 2 (n): Placebo: 10	**Inclusion/ exclusion criteria** Inclusion criteria: Individuals who had: a diagnosis of PD, a therapeutic benefit with L-dopa, experienced LID, and never been treated with amantadine. During the study, anti-parkinsonian medication was unchanged. Exclusion criteria: Individuals with: supranuclear gaze palsy, signs of upper motor neuron disease, cerebellar signs, prominent autonomic dysfunction, painful or debilitating disorders, previous history of stroke and cognitive impairment (MMSE <24).	**Baseline characteristics** Mean age (yrs): Amantadine (n=10): 59.1 (SD10.1) Placebo (n=10): 62.1 (SD9.7) Mean disease duration: Amantadine (n=10): 8.6 ± 4.5 yrs Placebo (n=10): 9.4 ± 3.0 yrs Mean UPDRS motor score: Amantadine (n=10): 19.1 ± 9.8	**Intervention(s)** Amantadine: 100mg capsules taken daily for the first week and then twice daily for the next 2 weeks	**Primary outcomes** Change in the CDRS (Clinical Dyskinesia Rating Scale) and UPDRS IVa scores **Secondary outcomes** Change in the UPDRS II and III scores

				Placebo (n=10): 20.2 ± 5.5 Mean UPDRS ADL score: Amantadine (n=10): 17.1 ± 7.2 Placebo (n=10): 18.4 ± 6.1 Mean UPDRS IV score: Amantadine (n=10): 4.1 ± 2.4 Placebo (n=10): 4.8 ± 1.8 Hoehn & Yahr stage: Amantadine (n=10): 2.6 ± 0.5 Placebo (n=10): 2.5 ± 0.4 Mean levodopa dose: Amantadine (n=10): 665 ± 265.1 mg/d Placebo (n=10): 1000 ± 358 mg/d Mean CDRS (hyperkinesia) score:		

				Amantadine (n=10): 8.8 ± 4.7 Placebo (n=10): 9.7 ± 4.2 Mean CDRS (dystonia) score Amantadine (n=10): 3.7 ± 3.0 Placebo (n=10): 4.0 ± 4.0		
Deane (2004)	**Study type** Systematic review Cochrane Review **Aim/ objective of the study** To compare the efficacy and safety of adjuvant COMT inhibitor therapy versus active comparators in patients with Parkinson's disease already established on L-dopa and suffering from motor complications **Source of funding** Orion Pharmaceuticals and Roche Pharmaceuticals	**Country/ies where the study was carried out** - Tolcapone vs. pergolide trial: 3 centres in USA, UK, and Australia - Tolcapone vs. bromocriptine trial: 19 centres in France **Study dates/duration** Study duration - Tolcapone vs. pergolide trial: 12 weeks - Tolcapone vs. bromocriptine trial: 8 weeks **Sample size** Total (n): 2 trials with a total of 349 participants: 1 trial	**Inclusion/ exclusion criteria** Selection criteria (SRs) - RCTs of adjuvant COMT inhibitor therapy versus an active comparator in patients with a clinical diagnosis of idiopathic Parkinson's disease and long-term complications of levodopa therapy - Trial durations of greater than 4 weeks		**Intervention(s)** Interventions included in SR/MA - Tolcapone vs. pergolide: 100 - 200mg tolcapone tid vs. a maximum titrated dose of 5mg/d of pergolide by week 9 (mean final dose: 2.2 mg/d). - Tolcapone vs. bromocriptine: 200 mg tolcapone tid vs. a maximum titrated dose of 30 mg/d of bromocriptine by day 24 (mean final dose 22.4mg/d)	**Types of outcome measures** - Improvement in the time patients spend in the immobile "off" state - Changes in dyskinesia rating scales and the prevalence of dyskinesia - Changes in parkinsonian rating scales - Reduction in L-dopa dose - Number of withdrawals due to lack of efficacy and/or side effects

		with 203 participants examined tolcapone vs. pergolide and the other trial examined tolcapone vs. bromocriptine in 146 participants				
Destee (2009)	**Study type** Randomized, open-label trial **Aim/ objective of the study** To assess the short-term (4 weeks) efficacy and safety of levodopa/DDCI and entacapone therapy vs. convectional levodopa fractionation in patients with symptom re-emergence due to wearing-off and to compare the effect of the initial choice of adding entacapone vs. dose fractionation on the progression of levodopa-associated symptom re-emergence and dyskinesia at 1 year.	**Country/ies where the study was carried out** France **Study dates/duration** Study duration 1 year **Sample size** Total (n): 179 Group 1 (n): Entacapone: 112 Group 2 (n): L-dopa: 67	**Inclusion/ exclusion criteria** Inclusion criteria: - Outpatients aged ≥ 30years, with a clinical diagnosis of idiopathic PD, responsive to L-dopa and treated by stable doses of conventional levodopa, experiencing symptom re-emergence due to wearing-off (with or without dyskinesia) - Other antiparkinsonian therapies such as DAs and selegiline (≤ 10mg/d) were permitted if they had been provided at stable doses for at least 1 month prior to study entry. Exclusion criteria: - Patients with clinically significant psychiatric, systemic or metabolic disorders, clinically significant abnormal laboratory values or a previous history of Neuroleptic Malignant Syndrome and/or rhabdomyolysis - Women of childbearing potential without adequate contraception, pregnant or lactating women - Patients with secondary or atypical parkinsonism -Treatment with	**Baseline characteristics** Mean age (yrs) Entacapone (n=110): 69 ± 9.5 L-dopa (n=66): 71 ± 8.5 Mean disease duration Entacapone (n=110): 6 ± 5.5 yrs L-dopa (n=66): 5 ± 3.4 yrs Mean levodopa dose Entacapone (n=110): 446.1 ± 163.7 mg/d L-dopa (n=66): 425.0 ± 149.4 mg/d Other anti-parkinsonian medication Entacapone (n=110) vs. L-dopa (n=66): DAs (%): 56 vs. 55 Selegiline (%): 9 vs. 8	**Intervention(s)** - Entacapone: 200mg with each L-dopa dose - L-dopa dose fractionation: 1 additional L-dopa dose per day (an increase from 3 to 4 daily doses), with a maximum total daily L-dopa dose increase of 100mg/d	**Primary outcomes** Treatment success based on the investigator's and patient's Clinical Global Impression of Change scores on day 28 compared with baseline **Secondary outcomes** Duration of off time per day, changes in daily L-dopa dosage and therapy strategy at day 28

	Source of funding Novartis Pharma AG		MAOB other than selegiline, antipsychotics, or other COMT inhibitors within 2 months prior to study entry and experimental treatment within 1 month prior to study entry			
Deuschl (2007)	**Study type** Randomized, open-label, rater-blinded study **Aim/ objective of the study** To compare the efficacy and tolerability of entacapone and cabergoline in conjunction with L-dopa in the treatment of older PD patients with wearing-off. **Source of funding** Not reported.	**Country/ies where the study was carried out** 27 centres in Germany and 3 centres in Lithuania. **Study dates/duration** Study duration 12 weeks **Sample size** Total (n): 187 Group 1 (n): Entacapone: 82 Group 2 (n): Cabergoline: 79	**Inclusion/ exclusion criteria** Inclusion criteria: ≥60 years with idiopathic PD and wearing off; 3-5 daily doses of L-dopa; at least 60 minutes of daily OFF-tim after the first ON-period in the morning; other anti-parkinsonian treatment had to be stable for 3 weeks prior to randomisation. Exclusion criteria: MMSE ≤26, Beck Depression Scale ≥17, concomitant diseases precluding the proper study conduction, treatment with non-selective MAO inhibitors, treatment with drugs partly metabolised by the COMT enzyme, patients who had already used a COMT inhibitor or a dopamine agonist within 4 weeks prior to the randomisation, or had a history of hypersensitivity to ergot derivatives and ENT. Use of selegiline was allowed, with a maximal daily dosage of 10mg.	**Baseline characteristics** Mean age (yrs) Entacapone (n=82): 69.9 ± 7.4 Cabergoline (n=79): 70.3 ± 6.4 Mean disease duration Entacapone (n=82): 5.7 ± 4.6 yrs Cabergoline (n=79): 5.5 ± 4.3 yrs Hoehn & Yahr stage Stage 2 to 3: Entacapone (n=82): 58 Cabergoline (n=79): 66 Mean levodopa dose Entacapone (n=82): 467 ± 281 mg/d Cabergoline (n=79): 497 ± 273 mg/d Other anti-parkinsonian medication - Entacapone (n=82) vs. Cabergoline (n=79) (n (%)): - Selegiline: 7 (8.5) vs. 7 (5.9) - Amantadine: 20 (24.4) vs. 29 (36.7) - Others: 5 (6.1) vs. 3 (3.8)	**Intervention(s)** - Entacapone: 200mg concomitantly with each of the 3 to 5 daily doses of L-dopa - Cabergoline: Individually titrated with an initial dose of 1mg rising according to requirements to a maximum of 6mg/d over a period of 6 to 8 weeks. - The daily dosage of the study medication was kept constant for the last 4 weeks prior to final assessment.	**Primary outcomes** Change from baseline in the total daily OFF-time after the first daily ON-time. **Secondary outcomes** Change from baseline of total daily ON-time, PDQ-39, and UPDRS parts I-III.
ESS (2007)	**Study type**	**Country/ies where the study was carried**	**Inclusion/ exclusion criteria** Inclusion criteria:	**Baseline characteristics** Mean age (yrs)	**Intervention(s)**	**Primary outcomes**

	Randomised, double-blind, active-controlled trial **Aim/ objective of the study** To examine the efficacy and safety of replacing entacapone with tolcapone in fluctuating PD patients **Source of funding** F. Hoffmann-LA Roche, Basel Switzerland	**out** 32 centres in Finland, France, Germany, Spain, Sweden Switzerland, and the United States **Study dates/duration** Study duration 3 weeks **Sample size** Total (n): 150 Group 1 (n): Entacapone: 75 Group 2 (n): Tolcapone: 75	- Patients with PD diagnosed ≥5 years previously, with significant fluctuations (≥3 hrs/d OFF time) despite best medical therapy, including up to 12 daily doses of L-dopa (maximum total dose 3000 mg/d), and entacapone 200mg with each dose of L-dopa - UPDRS ADL score ≥12 when they were in the OFF state Exclusion criteria: Patients with current or previous liver disease.	- Entacapone (n=75): 63.1 ± 8.1 - Tolcapone (n=75): 65.1 ± 8.9 Mean disease duration - Entacapone (n=75): 11.1 ± 5.2 yrs - Tolcapone (n=75): 12.3 ± 4.8 yrs Mean UPDRS motor score During OFF state: - Entacapone (n=71): 19.9 ± 9.7 - Tolcapone (n=72): 21.2 ± 11.7 Mean UPDRS ADL score During ON state: - Entacapone (n=71): 6.7 ± 4.6 - Tolcapone (n=72): 7.6 ± 5.9 During OFF state: - Entacapone (n=71): 21.8 ± 7.3 - Tolcapone (n=72): 22.0 ± 7.0 Other anti-parkinsonian medication Entacapone (n=75) vs. Tolcapone (n=75) (n (%)): - Previous treatment with Tolcapone: 29 (39%) vs. 28 (37%) - Current treatment with other antiparkinsonian treatments (mostly DAs): 50 (67%) vs. 47 (63%)	- Entacapone: 200mg with each dose of L-dopa - Tolcapone: 100mg three times daily, while maintaining their other antiparkinsonian treatments	The proportion of patients with a mean increase in ON-time (without disabling dyskinesia) of ≥1hr/d from the end of the open optimisation phase to the end of the double-blind phase (3 weeks later), according to patient diaries. **Secondary outcomes** The proportion of patients showing moderate or marked overall improvement in the IGA at the end of the double-blind phase.
Fénelon (2003)	**Study type** Randomised, double-	**Country/ies where the study was carried out**	**Inclusion/ exclusion criteria** Inclusion criteria: - People aged 30-80years; fulfilled	**Baseline characteristics** Mean age (yrs) Entacapone (n=99): 63.5 ±	**Intervention(s)** Entacapone: 200mg	**Primary outcomes** Improvement of ON

	blind, placebo-controlled study **Aim/ objective of the study** To assess the efficacy and tolerability of entacapone in PD patients already treated with a combination of levodopa/DDC inhibitor and a dopamine agonist. **Source of funding** Novartis AG	20 centres in France and 5 in Spain **Study dates/duration** Study duration 3 months **Sample size** Total (n): 162 Group 1 (n): Entacapone: 99 Group 2 (n): Placebo: 63	the UK PD Brain Bank clinical criteria; were responsive to L-dopa therapy; with Hoehn and Yahr stage 2-4 during ON periods; and received 3-10 doses of L-dopa/DCC daily, in combination with a DA. - All DAs were permitted but treatment had to be unchanged for at least 1 month prior to study start - Patients were required to experience wearing-off fluctuations for more than 3 months, with at least 2 hrs of OFF time (excluding early morning akinesia) during the waking day - People must able to complete home diaries, every 30mins, for the 3 days previous to enrolment Exclusion criteria: - People with: severe peak-dose dyskinesia with a score of 2 or above on the UPDRS part IV items 33 and 34; clinically relevant laboratory abnormalities; significant neurological or psychiatric illness including dementia, psychosis, uncontrolled epilepsy, and major depression; or any illness that may have been expected to affect the outcome of the trial such as heart, liver, or renal diseases - People taking controlled-release L-dopa (except for the evening dose); any COMT inhibitor within the previous 30	9.96 Placebo (n=63): 65.0 ± 6.61 Hoehn & Yahr stage Entacapone (n=99): 2.6 ± 0.60 Placebo (n=63): 2.5 ± 0.62 Other anti-parkinsonian medication Entacapone (n=99) vs. Placebo (n=63) (n (%)): - DAs: 95 (96) vs. 62 (98) - Bromocriptine: 46 (46) vs. 30 (48) - Pergolide: 25 (25) vs. 17 (27) - Ropinirole: 22 (22) vs. 9 (14) - Lisuride: 3 (3) vs. 2 (3) - Piribedil: 2 (2) vs. 4 (6) - Apomorphine in addition: 2 (2) vs. 0 (0)	taken with each dose of L-dopa	and OFF time while awake as measured by Patient Diary and UPDRS part IV item 39 **Secondary outcomes** Changes in UPDRS II, III, and IVa scores, Investigator's Global Assessment, the SF-39 Health Survey and changes in L-dopa dosages from baseline

			days; MAOBs except selegiline, provided that it had been prescribed at an unchanged dose for a minimum of 4 weeks prior to entry; neuroleptics; anticholinergics; calcium,-channel blockers; or investigational drugs taken within 30 days prior to enrolment - History of substance abuse - Pregnancy, breast-feeding, or childbearing potential in the absence of effective contraception			
LeWitt (2007)	**Study type** Randomised, double-blind, three-arm study, parallel group trial **Aim/ objective of the study** To assess efficacy and safety with two targeted transdermal doses of rotigotine in subjects with advanced Parkinson disease with ≥2.5hrs of daily "off" time (PREFER trial) **Source of funding**	**Country/ies where the study was carried out** 54 clinical sites in United States and Canada **Study dates/duration** Study duration 29 weeks Study dates 19 December 2001 to 19 April 2004 **Sample size** Total (n): Total: 351 Rotigotine patches 8mg/d: 120 Rotigotine patches	**Inclusion/ exclusion criteria** Inclusion criteria: - Subjects at least 30 years of age and had the diagnosis of idiopathic PD for at least 3 years, with clinical features of bradykinesia plus at least one additional cardinal feature - Hoehn & Yahr stage between II and IV in both the "on" and "off" states and were not demented (MMSE ≥25) - Receiving at least 200mg/d of levodopa administered in at least 2 daily doses and in a regimen stable for at least 28 days prior to baseline - Had inadequate relief of parkinsonism as judged by the treating investigator - Anticholinergics, selegiline, and amantadine were permitted if they had been administered at stable doses for at least 28 days prior to	**Baseline characteristics** Mean age (yrs) Rotigotine patches 8mg/d (n=118): 66.5 ± 10.0 Rotigotine patches 12mg/d (n=111): 64.5 ± 10.4 Placebo (n=120): 66.3 ± 9.6 Mean disease duration Rotigotine patches 8mg/d (n=118): 7.7 ± 4.3 years Rotigotine patches 12mg/d (n=111): 7.8 ± 4.6 years Placebo (n=120): 7.7 ± 4.0 years Mean UPDRS motor score Rotigotine patches 8mg/d (n=118): 27.2 ± 13.9 Rotigotine patches 12mg/d (n=111): 27.5 ± 12.9 Placebo (n=120): 26.7 ± 14.5	**Intervention(s)** Rotigotine: up to either 8mg/d or 12mg/d	**Primary outcomes** Change in the absolute time spent "off" from baseline to final visit (week 25) **Secondary outcomes** The % of subjects achieving ≥30% response in absolute time spent "off" from baseline to final visit (week 25)

	Schwarz Pharma (Monheim, Germany)	12mg/d: 111 Placebo: 120	the baseline visit Exclusion criteria: - A Da or COMT inhibitor was not permitted within 28 days of baseline - Other drugs excluded from use within 28 days of baseline were methylphenidate, amphetamines, monoamine oxidase-type A inhibitors, reserpine, alpha-methyldopa, or neuroleptics - Prior pallidotomy, thalamotomy, deep brain stimulation, or tissue transplant to the brain	Mean UPDRS ADL score Rotigotine patches 8mg/d (n=118): 13.3 ± 6.7 Rotigotine patches 12mg/d (n=111): 13.6 ± 6.6 Placebo (n=120): 13.0 ± 6.9 Mean levodopa dose Rotigotine patches 8mg/d (n=118): 760 ± 601 mg/d Rotigotine patches 12mg/d (n=111): 740 ± 407 mg/d Placebo (n=120): 753 ± 470 mg/d Mean OFF time Rotigotine patches 8mg/d (n=117): 6.7 ± 2.5 hr/d Rotigotine patches 12mg/d (n=111): 6.3 ± 2.6 hr/d Placebo (n=120): 6.4 ± 2.6 hr/d		
Lieberman (1997)	**Study type** Randomised, double-blind trial **Aim/ objective of the study** To evaluate ropinirole as an adjunct to L-dopa in an RCT in PD patients	**Country/ies where the study was carried out** 16 medical centres in the USA **Study dates/duration** Study duration 6 months	**Inclusion/ exclusion criteria** Inclusion criteria: - PD patients who were Hoehn and Yahr stage II - IV in the OFF state and who had evidence of a good response to L-dopa complicated by predictable motor fluctuations with or without dyskinesia - Patients had to have been receiving stable doses of immediate-release or controlled-release Sinemet or a combination of the two for a minimum of 4 weeks before study entry -	**Baseline characteristics** Mean disease duration Ropinirole (n=95): 8.6 ± 4.7 Placebo (n=54): 9.4 ± 6.3 Hoehn & Yahr stage Ropinirole (n=95) vs. Placebo (n=54): - II "off" (%): 41 vs. 39 - III "off" (%): 40.0 vs. 42.6 - IV "off" (%): 19.0 vs. 18.5 Mean levodopa dose Ropinirole (n=95): 759 ± 422 mg/d Placebo (n=54):	**Intervention(s)** Ropinirole: Initial total daily dose of 0.75mg in 3 divided doses and gradually increased in 0.75mg/d increments until a dose of 3.0mg/d was reached over approximately 2 weeks. Thereafter, the daily dose could be increased by 1.5mg each week to a total dose of 9.0mg/d	**Primary outcomes** The number of patients who achieved a 20% or greater decrease in L-dopa dose and a 20% or greater reduction in the % time spent "off" between the baseline and final

	with motor fluctuations **Source of funding** SmithKline Beecham Pharmaceuticals	**Sample size** Total (n): 149 Group 1 (n): Ropinirole: 95 Group 2 (n): Placebo: 54	Anticholinergic, amantadine, or selegiline treatment was permitted if the dose was stable for at least 4 weeks before entry and throughout the study. Other DAs were stopped at least 4 weeks before initiation of the trial Exclusion criteria: - Patients who suffered complex "on-off" phenomena or "yo-yoing", an abrupt and unpredictable loss of efficacy unrelated to the timing of L-dopa administration - Women of childbearing age - Patients with a diastolic BP of more than 110 mm Hg - Patients taking antiarrhythmic medications, vasodilators, calcium channel blockers, beta blockers, or other antihypertensive agents (except diuretics) - Patients with syncopal episodes, psychosis, dementia, or uncompensated heart, lung, liver, kidney, or endocrine disease - Patients with clinically significant medical or laboratory dysfunction	843 ± 517 mg/d	and by 3.0mg/d each week to a maximal dose of 24mg/d. - All patients had to be titrated to a minimum dose of 7.5mg/d.	visits. **Secondary outcomes** Change from baseline to final visit in the % of the waking day in the "off" state as determined by the home diary as well as the proportion of patients rated as improved on the CGI
Mizuno (2003)	**Study type** Randomized, double-blind study **Aim/ objective of the study**	**Country/ies where the study was carried out** 38 sites in Japan **Study dates/duration** Study duration	**Inclusion/ exclusion criteria** Inclusion criteria: - People with diagnosed PD; at least 20 years of age; who exhibited any therapeutically problematic issues based on L-dopa therapy; or in whom the suboptimal dose of L-dopa had been administered due to side	**Baseline characteristics** Mean age (yrs) Pramipexole (n=102): 65.46 ± 9.45 Bromocriptine (n=104): 64.53 ± 7.47 Placebo (n=107): 63.96 ± 8.64 Mean disease duration Pramipexole (n=102): 4.79	**Intervention(s)** - Pramipexole: Up to 4.5mg/d (final mean dose: 3.24 ± 1.33 mg/d) - Bromocriptine: Up to 22.5mg/d (final mean dose: 17.75 ± 5.76 mg/d)	**Primary outcomes** Change from the baseline on the final maintenance of the total score of the ULDRS II and III.

	To determine whether the efficacy of pramipexole (PPX) is significantly inferior to bromocriptine (BR) in patients with advanced PD as an adjunct to Lo-dopa therapy **Source of funding** Nippon Boehringer Ingelheim Co., Ltd., Hyogo, Japan	12 weeks **Sample size** Total (n): - Total: 313 - Pramipexole: 102 - Bromocriptine: 104 - Placebo: 107	effects or therapeutic strategy - Patients had received an individual dosage of L-dopa and were stable for at least 28 days before the initial administration of the study medication Exclusion criteria: - Patients who had received any DAs during the 28 days before the investigator obtained informed consent - Patients with a medical history of hypersensitivity to ergoline derivatives or seizure - Patients suffering from psychiatric symptoms, symptomatic orthostatic hypotension, hypotension in which systolic BP was less than 100 mm Hg, Raynaud's disease, peptic ulcer, or a clinically significant heart, liver, or kidney disease - Treatment with the following drugs during administration of the trial: alpha methyldopa, reserpine, flunarizine, cinnarizine, lisuride, neuroleptics, clebopride, and metoclopramide - Patients who had dementia precluding the signing of the informed consent form - Patients participating in other studies of other investigational drugs within 6 months of baseline	± 4.07 Bromocriptine (n=104): 5.03 ± 3.96 Placebo (n=107): 5.73 ± 7.05 Mean UPDRS motor score Pramipexole (n=102): 27.11 ± 12.53 Bromocriptine (n=104): 27.20 ± 11.78 Placebo (n=107): 27.36 ± 13.53 Mean UPDRS ADL score Pramipexole (n=102): 10.44 ± 6.54 Bromocriptine: (n=104) 10.29 ± 5.28 Placebo (n=107): 10.36 ± 7.09 Hoehn & Yahr stage Mean (SD): - Pramipexole (n=102): 2.66 ± .70 - Bromocriptine (n=104): 2.59 ± 0.74 - Placebo (n=107): 2.64 ± 0.82 Mean levodopa dose Pramipexole (n=102): 404.90 ± 275.17 mg/d Bromocriptine (n=104): 399.88 ± 237.79 mg/d Placebo (n=107): 422.43 ± 330.33 mg/d		**Secondary outcomes** Total score of UPDRS I, IV, and I to III, modified Hoehn and Yahr Staging Scale, CGI, and responder analysis on the changes of UPDRS II and III, and I to IV total scores
Mizuno (2007)	**Study type**	**Country/ies where the study was carried**	**Inclusion/ exclusion criteria** Inclusion criteria:	**Baseline characteristics** Mean age (yrs)	**Intervention(s)**	**Primary outcomes**

	Randomized, double-blind, placebo-controlled study **Aim/ objective of the study** To examine the efficacy of ropinirole as an adjunct therapy to L-dopa in Japanese patients with advanced Parkinson's disease, without such a mandatory reduction in L-dopa dose **Source of funding** GlaxoSmithKline, Japan	**out** 25 medical institutions in Japan **Study dates/duration** Study duration 16 weeks Study dates February 2002 to August 2003 **Sample size** Total (n): 243 Group 1 (n): Ropinirole: 121 Group 2 (n): Placebo: 120	- Patients with PD at 20 years of age or above and at Hoehn and Yahr stages II-IV, with a clear and efficacious response to L-dopa - Patients on stable doses of L-dopa for at least 4 weeks and were experiencing motor fluctuations or were suffering from insufficient therapeutic effect Exclusion criteria: - Patients who had received other DAs in the 4 weeks prior to study start, or who had received other investigational drugs in the 12 weeks prior to the start of study treatment - Patients with a current or previous history of serious cardiac, hepatic, or renal disease, or who had undergone surgery for Parkinson's disease - Patients with symptomatic orthostatic hypotension - Patients who had exhibited serious psychiatric symptoms in the 6 months prior to entry - Women who were pregnant or breast-feeding, or planning to become pregnant	Ropinirole (n=121): 64.9 ± 9.53 Placebo (n=120): 64.7 ± 9.31 Mean disease duration Ropinirole (n=121): 66.4 ± 44.86 months Placebo (n=120): 66.2 ± 49.25 months Mean UPDRS motor score Ropinirole (n=121): 23.8 ± 11.04 Placebo (n=120): 24.9 ± 12.63 Hoehn & Yahr stage Ropinirole (n=121) vs. Placebo (n=120) (n (%)): - II: 41 (33.9) vs 39 (32.5) - III: 74 (61.2) vs. 75 (62.5) - IV: 6 (5) vs. 6 (5)	Ropinirole: 0.25mg 3 times daily (0.75mg/d) and uptitrated to a maximum of 15.0 mg/d (final mean dose: 7.12 ± 2.88 mg/d)	Change in UPDRS III from baseline as assessed by the Japanese version of the UPDRS III **Secondary outcomes** The % of time spent "off", the % of patients showing at least a 20% reduction in time spent "off", the change between baseline and endpoint in the UPDRS II, the % of patients at different H&Y stages, the % of patients classified as "Markedly improved" or "Improved" on the CGI scale and the study continuation rate
Mizuno (2014)	**Study type** Randomised, double-blind, double-dummy, three-arm parallel group placebo- and ropinirole-	**Country/ies where the study was carried out**	**Inclusion/ exclusion criteria** Inclusion criteria: - Patients aged 30-79 years and with a diagnosis of PD according to the UK Brain Bank Criteria, Hoehn & Yahr stage of 2-4, and	**Baseline characteristics** Mean age (yrs) Rotigotine patches (n=164): 64.8 ± 8.8 Ropinirole (n=166): 67.0 ± 7.9 Placebo (n=84): 65.3 ±	**Intervention(s)** - Rotigotine patches: Initial dose of 2mg/d and increased to 16mg/d in weekly increments of	**Primary outcomes** Change in the UPDRS III (ON state) sum score from baseline to

	controlled trial **Aim/ objective of the study** To confirm the superiority of transdermal rotigotine up to 16mg/d over placebo, and non-inferiority to ropinirole, in Japanese Parkinson's disease patients on concomitant levodopa therapy **Source of funding** Otsuka Pharmaceutical Company	62 sites in Japan **Study dates/duration** Study duration 16 treatment weeks + a taper period of up to 4 weeks **Sample size** Total (n): - Total: 414 - Rotigotine patches: 164 - Ropinirole: 166 - Placebo: 84	UPDRS Part III sum score of ≥ 10 at screening (ON state), who were experiencing motor fluctuations or whom L-dopa could not be increased to an optimal level because of side effects or other reasons - L-dopa were taken at a stable dose at least 28 days before starting treatment - L-dopa, selegiline, and entacapone could be used concomitantly, provided there was no change in the dose from 28 days before the first dose of the study drug until the end of the treatment period - Anticholinergics, amantadine, droxidopa and zonisamide could be used concomitantly, provided there was no change in the doses for 14 days before the first dose of the study drug or during the treatment period Exclusion criteria: - Patients with psychiatric symptoms; orthostatic hypotension; a history of epilepsy or convulsion; a history of serious cardiac disease, arrhythmia, or QT prolongation; abnormal liver function; or a history of allergy to topical agents; and female patients who were pregnant or lactating from the trial - Concomitant use of drugs that may affect the symptoms of PD, cause QT	7.9 Mean disease duration Rotigotine patches (n=164): 7.0 ± 4.9 years Ropinirole (n=166): 6.8 ± 7.9 years Placebo (n=84): 7.0 ± 4.2 years Mean UPDRS motor score ON state: - Rotigotine patches (n=164): 25.8 ± 10.6 - Ropinirole (n=166): 25.8 ± 11.0 - Placebo (n=84): 25.6 ± 10.4 Mean UPDRS ADL score Rotigotine patches (n=164): 11.0 ± 6.2 Ropinirole (n=166): 10.6 ± 5.6 Placebo (n=84): 11.1 ± 7.0 Hoehn & Yahr stage Rotigotine patches (n=164): 2.7 ± 0.6 Ropinirole (n=166): 2.8 ± 0.6 Placebo (n=84): 2.8 ± 0.6 Mean levodopa dose Rotigotine patches (n=164): 367.7 ± 151.3 mg/d Ropinirole (n=166): 350.6 ± 125.3 mg/d Placebo (n=84): 370.5 ± 146.6 mg/d Other anti-parkinsonian medication Previous concomitant anti-	2mg/d - Ropinirole: Initial dose of 0.75mg/d and increase to 3mg/d in weekly increments of 0.75mg/d and then increased to 15mg/d in weekly increments of 1.5mg/d	week 16 of the treatment period **Secondary outcomes** Changes from baseline to end of treatment (week 16) for the time spent in OFF, ON, and ON with troublesome dyskinesia and changes from baseline to end of treatment for the score in UPDRS II (ON), UPDRS II (OFF), UPDRS II (average ON and OFF state), sum of UPDRS II (average ON and OFF state) + UPDRS III scores and PD Sleep Scale-2 (PDSS-2)

			prolongation, or interact with ropinirole	PD drugs, rotigotine patches (n=164)vs. ropinirole (n=166) vs. placebo (n=84) (n (%)): - Entacapone: 40(24.4) vs. 54(34.3) vs. 33(39.3) - Anticholinergics: 33(20.1) vs. 32(19.3) vs. 16(19.0) - Amantadine: 39(23.8) vs. 40(24.1) vs. 27(32.1) - Selegiline: 60(36.6) vs. 69(41.6) vs. 35(41.7) - Droxidopa: 12(7.3) vs. 11(6.6) vs. 8(9.5) - Zonisamide: 16(9.8) vs. 13(7.8) vs. 12(14.3)		
Nicholas (2014)	**Study type** Randomized, double-blind, placebo-controlled study **Aim/ objective of the study** To investigate rotigotine dose response of 2, 4, 6, or 8mg/d in patients with advanced PD **Source of funding** UBC Pharma and Teva	**Country/ies where the study was carried out** 77 centres in the US, India, Mexico, Peru, and Chile **Study dates/duration** Study duration 16 weeks **Sample size** Total (n): 514 Group 1 (n): Rotigotine patches:	**Inclusion/ exclusion criteria** Inclusion criteria: - People aged ≥30 years with idiopathic PD of longer than 3 years' duration, presenting with bradykinesia plus at least one of the following: rest tremor, rigidity, or impairment of postural reflexes - Patients within Hoehn and Yahr stage II-IV in both the "on" and "off" states, had an MMSE score of at least 25, and were judged by the treating physician to be inadequately controlled on L-dopa (≥ 200mg/d short-acting or sustained-release, administered in at least 2 daily intakes and at a stable dose ≥28 days prior to baseline) in combination with	**Baseline characteristics** Mean age (yrs) Rotigotine patches 2mg/d (n=101): 65.4 ± 10.5 Rotigotine patches 4mg/d (n=107): 64.6 ± 9.0 Rotigotine patches 6mg/d (n=104): 64.6 ± 10.4 Rotigotine patches 8mg/d (n=94): 63.2 ± 11.6 Placebo (n=108): 64.8 ± 10.2 Mean disease duration Rotigotine patches 2mg/d (n=101): 7.23 ± 3.76 years Rotigotine patches 4mg/d (n=107): 7.51 ± 3.87 years Rotigotine patches 6mg/d (n=104): 7.27 ± 3.94 years	**Intervention(s)** Rotigotine patches: 2, 4, 6, or 8mg/d, titrated over 4 weeks and maintained for 12 weeks	**Primary outcomes** Change from baseline to end of maintenance in absolute time spent "off" **Secondary outcomes** Relative time spent "off", number of "off" periods, absolute time spent "on", motor status of the patient upon awakening ("on"

	Neuroscience	406 Group 2 (n): Placebo: 108	benserazide or carbidopa, with an average "off" time of ≥2.5h/d - Permitted PD drugs included anticholinergics, MAOBs, N-Methyl-D-aspartate antagonists, and entacapone that were at stable doses for ≥28 days prior to baseline Exclusion criteria: - Prohibited medications included dopamine receptor agonists (during the study or within 28days prior to baseline), dopamine-releasing or modulating substances, MAOA inhibitors, tolcapone, budipine and dopamine receptor antagonists	Rotigotine patches 8mg/d (n=94): 7.79 ± 3.92 years Placebo (n=108): 7.49 ± 4.75 years Mean UPDRS motor score Rotigotine patches 2mg/d (n=98): 25.3 ± 12.4* Rotigotine patches 4mg/d (n=100): 23.1 ± 11.3*** Rotigotine patches 6mg/d (n=99): 24.7 ± 13.1** Rotigotine patches 8mg/d (n=94): 23.9 ± 9.8 Placebo (n=105): 26.1 ± 12.5 Mean UPDRS ADL score Rotigotine patches 2mg/d (n=99): 12.1 ± 6.4 Rotigotine patches 4mg/d (n=102): 11.8 ± 6.0* Rotigotine patches 6mg/d (n=99): 12.6 ± 6.4** Rotigotine patches 8mg/d (n=92): 11.7 ± 6.2** Placebo (n=105): 12.8 ± 6.4 Hoehn & Yahr stage Stage 2 vs. 3 vs. 4 during ON state (n): - Rotigotine patches 2mg/d (n=101): 61 vs. 37 vs. 3 - Rotigotine patches 4mg/d (n=107): 73 vs. 32 vs. 2 - Rotigotine patches 6mg/d (n=104): 63 vs. 38 vs. 3 - Rotigotine patches 8mg/d (n=94): 65		with or without troublesome dyskinesias or "off", UPDRS II, III, and IV

				vs. 27 vs. 1 - Placebo (n=108): 70 vs. 29 vs. 9 Stage 2 vs. 3 vs. 4 during OFF state (n): - Rotigotine patches 2mg/d (n=101): 25 vs. 58 vs. 18 - Rotigotine patches 4mg/d (n=107): 29 vs. 67 vs. 11 - Rotigotine patches 6mg/d (n=104): 25 vs. 57 vs. 22 - Rotigotine patches 8mg/d (n=94): 24 vs. 54 vs. 16 - Placebo (n=108): 27 vs. 60 vs. 21 Mean levodopa dose Rotigotine patches 2mg/d (n=101): 643.3 ± 344.5 mg/d Rotigotine patches 4mg/d (n=107): 627.7 ± 359.4 mg/d Rotigotine patches 6mg/d (n=104): 619.0 ± 376.4 mg/d Rotigotine patches 8mg/d (n=94): 643.0 ± 365.8 mg/d Placebo (n=108): 642.8 ± 420.3 mg/d		
Nomoto (2014)	**Study type** Randomized, double-blind, placebo-controlled trial **Aim/ objective of the study**	**Country/ies where the study was carried out** 38 centres in Japan **Study dates/duration** Study duration 15 weeks	**Inclusion/ exclusion criteria** Inclusion criteria: - Patients with advanced PD, aged 30-79 years, and with Hoehn and Yahr stage II-IV and a UPDRS III sum score of ≥10 ('on" state) - Patients had to have received a stable L-dose for ≥28 days before study start and had to show problematic motor complications -	**Baseline characteristics** Mean age (yrs) Rotigotine patches (n=86): 67.0 ± 6.8 Placebo (n=86): 66.8 ± 8.3 Mean disease duration Rotigotine patches (n=86): 7.5 ± 6.0 years Placebo (n=86): 5.4 ± 3.0 years Mean UPDRS motor score	**Intervention(s)** Rotigotine patches: Initial dose 2mg/d then increased with a weekly increment of 2mg/d to a maximum of 16mg/d during the dose-titration period	**Primary outcomes** The absolute change in UPDRS III from baseline to end of treatment **Secondary outcomes**

	To investigate the efficacy and safety of rotigotine transdermal patches delivering up to 16mg of rotigotine per day in combination with L-dopa in patients with advanced-stage PD **Source of funding** Otsuka Pharmaceutical Co., Ltd., Japan	Study dates August 2006 and September 2006 **Sample size** Total (n): 214 Group 1 (n): Rotigotine patches: 87 Group 2 (n): Placebo: 87	Anti-PD agents such as L-dopa, selegiline, amantadine, and anticholinergics were permitted if the patient were on a stable dose for ≥28 days before baseline and throughout study *Subjects were considered to have been on the optimal L-dopa treatment when they were enrolled in the study, even though the dose of L-dopa was low in many of them Exclusion criteria: Patients with previous surgery for PD; psychiatric symptoms; orthostatic hypotension; a history of epilepsy or convulsion; clinically relevant hepatic, renal or cardiac disorders; a prolonged QTc interval; a history of skin sensitivity to adhesives or other transdermal medications; or if they were pregnant, nursing, or a women of child-bearing potential	Rotigotine patches (n=86): 28.1 ± 12.2 Placebo (n=86): 26.2 ± 10.4 Mean UPDRS ADL score Rotigotine patches (n=86): 11.8 ± 6.1 Placebo (n=86): 10.3 ± 4.6 Hoehn & Yahr stage Rotigotine patches (n=86) vs Placebo (n=86) (n (%): - 2: 11 (12.8) vs. 22 (25.6) - 2.5: 22 (25.6) vs. 20 (23.3) - 3: 45 (52.3) vs. 38 (44.2) - 4: 8 (9.3) vs. 6 (7.0) Mean levodopa dose Rotigotine patches (n=86): 348.8 ±170.3 mg/d Placebo (n=86): 329.1 ±132.5 mg/d Other anti-parkinsonian medication Rotigotine patches (n=86) vs. Placebo (n=86) (n (%)): - Anticholinergics: 19 (22.1) vs 11 (12.8) - Amantadine: 36 (41.9) vs. 31 (36.0) - Selegiline: 42 (48.8) vs. 41 (47.7)		The absolute changes in off-time, UPDRS II (average ON and OFF state) sum score, UPDRS II (ON state) sum score, UPDRS II (OFF state) sum score, and the Hoehn and Yahr scale
Ondo (2007)	**Study type** Randomised, double-blind, placebo-controlled, parallel-design trial	**Country/ies where the study was carried out** United States	**Inclusion/ exclusion criteria** Inclusion criteria: - Patients older than 30 years with a confirmed diagnosis of idiopathic PD and had a documented response to L-dopa - Patients with symptom deterioration at the end	**Baseline characteristics** Mean age (yrs) Selegiline ODT (n=98): 68.4 ± 9.0 Placebo (n=50): 66.3 ± 10.6 Mean disease duration Selegiline ODT (n=98): 7.2	**Intervention(s)** Selegiline ODT: Initially a dose of 1.25 mg once daily. At week 6, this dose was increased to 2.5mg once daily (2 x	**Primary outcomes** The reduction in total daily off as determined by an average of the % of off time reported at

	Aim/ objective of the study Not reported **Source of funding** Not reported	**Study dates/duration** Study duration 12 weeks **Sample size** Total (n): 180 Group 1 (n): Selegiline Orally Disintegrated Tablet (ODT): 98 Group 2 (n): Placebo: 50	of the L-dopa dosing interval with predictable mild-to-moderate motor fluctuations and at least 3 hrs of off time daily - Anticholinergics and DAs were permitted but required stable dosing throughout the study Exclusion criteria: - If patients had taken selegiline during the preceding 3 months, were known to be hypersensitive to selegiline, or were taking a COMT inhibitor, another MAO inhibitor, an opioid analgesic, or a selective serotonin reuptake inhibitor - Patients with severe depression, psychosis, or impaired cognitive function (MMSE <24	± 5.5 years Placebo (n=50): 6.2 ± 4.5 years Mean OFF time Selegiline ODT (n=98): 6.7 ± 2.3 hr/d Placebo (n=50): 6.8 ± 2.2 hr/d	1.5mg tablets) and was maintained for the remainder of the study	weeks 10 and 12 **Secondary outcomes** Reductions in hours off, changes from baseline in the Motor (off and on) and UPDRS II, and changes in scores on the CGI-I scales
Pahwa (2007)	**Study type** Randomised, double-blind, parallel-group, placebo-controlled study **Aim/ objective of the study** To evaluate the efficacy of ropinirole 24-h prolonged release (ropinirole 24-hour) as an adjunct to L-dopa in patients with Parkinson's disease and motor	**Country/ies where the study was carried out** EASE-PD Adjunct Study: 67 centres in Belgium, the Czech Republic, France, Hungary, Italy, Poland, Spain, and the United States **Study dates/duration** Study duration	**Inclusion/ exclusion criteria** Inclusion criteria: - People at least 30 years of age with a diagnosis of idiopathic PD and a modified Hoehn & Yahr stage of II 0 IV with suboptimal control with L-dopa therapy - A stable dose of L-dopa for at least 4 weeks prior to screening and a minimum of 3 hrs in the "off" state - Selegiline, amantadine, anticholinergics, and COMT inhibitors were permitted provided the dose was stable for at least 4 weeks prior to screening Exclusion criteria: - Neuroleptics and antiemetics -	**Baseline characteristics** Mean age (yrs) Ropinirole 24-hour (n=201): 66.3 ± 9.2 Placebo (n=190): 66.0 ± 9.7 Mean disease duration Ropinirole 24-hour (n=201): 8.6 ± 4.8 years; n=200 Placebo (n=190): 8.6 ± 5.2 years; n=188 Mean UPDRS motor score Ropinirole 24-hour (n=201): 29.8 ± 12.9; n=197 Placebo (n=190): 30.7 ± 14.4; n=188 Mean UPDRS ADL score	**Intervention(s)** Ropinirole 24-hour: Initial dose of 2mg once daily with gradual increments up to a maximum of 24mg/d. Minimum titrated dose was 6mg/d (mean final dose 18.8mg/d).	**Primary outcomes** Reduction in hours of daily "off" time **Secondary outcomes** Change in hours and % of daily "on" time and "on" time without troublesome dyskinesia, UPDRS II and III, Beck Depression Inventory-II, PDQ-

	fluctuations **Source of funding** GlaxoSmithKline and Skye Pharma	2 years **Sample size** Total (n): 393 Group 1 (n): Ropinirole 24-hour: 202 Group 2 (n): Placebo: 191	Patients with incapacitating peak dose or biphasic dyskinesia - Any dopamine agonist use within 4 weeks of screening; significant or uncontrolled psychiatric, neurologic, or other medical disorders; clinically significant laboratory abnormalities at screening; a recent history of severe dizziness or fainting due to postural hypotension; clinical dementia precluding assessment; a recent history or current evidence of drug abuse or alcoholism; or withdrawal, introduction, or dose change of hormone replacement therapy or any drug known to substantially inhibit or induce cytochrome P450 1A2	Ropinirole 24-hour (n=201): 13.9 ± 6.2; n=199 Placebo (n=190): 14.2 ± 6.8; n=189 Hoehn & Yahr stage Ropinirole 24-hour (n=201): 2.7 ± 0.5; n=201 Placebo (n=190): 2.7 ± 0.6; n=190 Mean levodopa dose Ropinirole 24-hour (n=201): 824 ± 424.4 mg/d; n=199 Placebo (n=190): 776 ± 357.3 mg/d; n=190 Mean OFF time Ropinirole 24-hour (n=201): 7.0 ± 2.8 hr/d Placebo (n=190): 7.0 ± 2.6 hr/d		39 subscales of mobility, ADL, emotional well-being, stigma and communication, and PD Sleep Scale
Pahwa (2015)	**Study type** Randomised, double-blind, placebo-controlled, parallel-group study **Aim/ objective of the study** To investigate the safety, efficacy and tolerability of three dose levels of ADS-5102 (amantadine ER capsule formulation)	**Country/ies where the study was carried out** EASED Study: 31 sites in the United States **Study dates/duration** Study duration 8 weeks Study dates July 2011 to April 2013	**Inclusion/ exclusion criteria** Inclusion criteria: - People aged between 30 and 85 years with a diagnosis of PD based on the UK PD Society Brain Bank Clinical Diagnostic Criteria, score of at least 2 on part IV, item 4.2 at screening and on day 1 (baseline) and at least two half-hour periods between 9am and 4pm documented as ON time with troublesome dyskinesia on each 2 consecutive days just before day 1 - All anti-PD drugs, including L-dopa preparations, were	**Baseline characteristics** Mean age (yrs) Placebo (n=22): 65.5 ± 10.2 260mg ADS-5102 (n=20): 67.5 ± 8.6 340mg ADS-5102 (n=21): 64.7 ± 10.0 420mg ADS-5102 (n=20): 66.4 ± 9.4 Mean disease duration Placebo (n=22): 10.7 ± 7.1 years 260mg ADS-5102 (n=20): 8.9 ± 3.4 years 340mg ADS-5102 (n=21): 9.3 ± 4.9 years 420mg ADS-5102 (n=20): 9.0 ±	**Intervention(s)** Amantadine ER: 260mg, 340mg or 420mg	**Primary outcomes** The change from baseline to week 8 in Unified Dyskinesia Rating Scale total score for 340mg ADS-5102 vs. placebo **Secondary outcomes** Change in Unified

	dosed once daily at bedtime for the treatment of LID in PD patients **Source of funding** Adamas Pharmaceuticals, Inc.	**Sample size** Total (n): Total: 83 Group 1 (n): Amantadine ER overall: 61 Group 2 (n): Placebo: 22	unchanged for at least 30 days prior to screening and throughout study - L-dopa preparations had to be administered at least 3 times daily Exclusion criteria: - History of dyskinesia that was exclusively diphasic, off state, myoclonic, dystonic, or akathetic without peak dose dyskinesia, neurosurgical intervention related to PD, atypical parkinsonism, levodopa or dopamine agonist-induced psychosis, MMSE score of less than 24 during screening, estimated glomerular filtration rate less than 50mL/min/1.73m2, use of amantadine within 30days before screening, documented inability to tolerate or lack of dyskinesia response to prior amantadine treatment, current treatment with apomorphine or dopamine receptor blocking agents, clinically significant electrocardiogram abnormalities, use of rimantadine or history of hypersensitivity or allergic reaction to amantadine, rimantadine, or memantine	3.5 years Mean UPDRS motor score Movement Disorder Society-UDRS: - Placebo (n=22): 11.7 ± 3.1 - 260mg ADS-5102 (n=20): 10.7 ± 2.6 - 340mg ADS-5102 (n=21): 11.7 ± 2.8 - 420mg ADS-5102 (n=20): 10.8 ± 3.0 Hoehn & Yahr stage Placebo (n=22): 2.5 ± 0.7 260mg ADS-5102 (n=20): 2.5 ± 0.9 340mg ADS-5102 (n=21): 2.5 ± 0.6 420mg ADS-5102 (n=20): 2.4 ± 0.8 Mean levodopa dose Placebo (n=22): 801.1 ± 431.9 mg/d 260mg ADS-5102 (n=20): 714 ± 449.3 mg/d 340mg ADS-5102 (n=21): 694.0 ± 278.4 mg/d 420mg ADS-5102 (n=20): 862.5 ± 585.9 mg/d Mean OFF time PD home diary: - Placebo (n=22): 3.2 ± 2.7 hr/d - 260mg ADS-5102 (n=20): 2.7 ± 2.6 hr/d - 340mg ADS-5102 (n=21): 4.1 ± 2.7 hr/d - 420mg ADS-5102 (n=20): 2.2 ± 1.6 hr/d		Dyskinesia Rating Scale for 260mg and 420mg of ADS-5102, Fatigue Severity Scale, Movement Disorder Society Unified Parkinson's Disease Rating Scale, patient diary, Clinician's Global Impression of Change, and PDQ-39

Poewe (2007)	**Study type** Double-blind, double-dummy, randomised controlled trial **Aim/ objective of the study** To assess the efficacy of adjunct treatment with rotigotine in comparison with placebo and with pramipexole in levodopa-treated patients with advanced Parkinson's disease and wearing-off type motor fluctuations **Source of funding** Schwarz Pharma (Monheim, Germany)	**Country/ies where the study was carried out** 77 centres in Europe, South Africa, Australia, and New Zealand **Study dates/duration** Study duration Up to 29 weeks **Sample size** Total (n): Total: 506 - Pramipexole: 201 - Rotigotine patches: 204 - Placebo: 101	**Inclusion/ exclusion criteria** Inclusion criteria: - Patients ≥30 years with diagnosed idiopathic Parkinson's disease as defined by the UK Brain Bank criteria for >3 years, and had to be on stable treatment with L-dopa and stable doses of any concomitant anti-PD drugs for at least 4 weeks before enrolment. - Patients with motor fluctuations of the wearing-off type with an average of at least 2.5h per day spent in the "off" state - Hoehn & Yahr stage II - IV Exclusion criteria: - If more than 2 of the 6 screening diaries were invalid of if patients had received concomitant treatment with any dopamine agonist during the 4 weeks before starting the 6 screening diary recordings - Suspicion of atypical parkinsonism - Previous surgery for PD - MMSE score <25 - Concurrent hallucination or psychosis - History of myocardial infarction over past 12 months - QTc interval >450ms (men) or >470 ms (women) - History of skin hypersensitivity to adhesives or other transdermals - Intake of investigational drug within 4 weeks before pre-treatment visit - Concomitant treatment with DAs,	**Baseline characteristics** Mean age (yrs) Pramipexole (n=200): 63.2 ± 9.7 Rotigotine patches (n=201): 64.3 ± 9.0 Placebo (n=100): 65.0 ± 10.0 Mean disease duration Pramipexole (n=200): 8.4 ± 4.7 years Rotigotine patches (n=201): 8.9 ± 4.4 years Placebo (n=100): 8.5 ± 5.0 years Mean UPDRS motor score Pramipexole (n=200): 26.4 ± 11.6 Rotigotine patches (n=201): 26.3 ± 11.4 Placebo (n=100): 26.8 ± 11.4 Mean UPDRS ADL score Pramipexole (n=200): 12.1 ± 6.0 Rotigotine patches (n=201): 12.3 ± 5.8 Placebo (n=100): 12.8 ± 6.2 Mean UPDRS IV score Pramipexole (n=200): 5.6 ± 2.9 Rotigotine patches (n=201): 5.6 ± 2.5 Placebo (n=100): 5.6 ± 2.8 Mean levodopa dose Pramipexole (n=200): 813 ± 459 mg/d Rotigotine patches (n=201): 795 ± 380 mg/d Placebo	**Intervention(s)** - Rotigotine patches: Initial dose of 4mg/d with weekly increments of 2mg/d up to an optimum response or a maximum dose of 16mg/d - Pramipexole: Initial dose of 0.375mg/d followed by weekly increments of 0.75mg/d up to a maximum dose of 4.5mg/d in three divided doses for an optimum response	**Primary outcomes** - Absolute change in total hours "off" from baseline to end of study and responder rate **Secondary outcomes** - Changes from baseline to end of maintenance of the absolute time spent on without troublesome dyskinesias, number of off periods, motor status after morning wake-up (on with or without troublesome dyskinesias or off) and UPDRS Ii and III scores during ON periods

			monoamine oxidase A inhibitors, dopamine-releasing drugs, tolcapone, neuroleptics, cimetidine, ranitidine, diltiazem, triamterene, verapamil, quinidine, or quinine	(n=100): 814 ± 398 mg/d		
PSG (2007)	**Study type** Multicenter, parallel-group, double-blind, randomized, placebo-controlled trial **Aim/ objective of the study** To evaluate the safety, tolerability, and efficacy of adjunctive pramipexole in PD patients of African, Asian or Hispanic heritage stably treated with L-dopa **Source of funding** Pharmacia Corporation (Peapack, NJ) and The National Parkinson Foundation Center of Excellence and the National Institute of	**Country/ies where the study was carried out** 17 Parkinson Study Group sites in the United States and Puerto Rico **Study dates/duration** Study duration 10 weeks Study dates January 1997 to October 1998 **Sample size** Total (n): 144 Group 1 (n): Pramipexole: 109 Group 2 (n): Placebo: 35	**Inclusion/ exclusion criteria** Inclusion criteria: - Subjects self-identified as being African, Hispanic, or Asian heritage of age 30 years or older, had idiopathic PD, were treated with a stable dose of L-dopa for at least 1 month prior to randomisation and were Hoehn and Yahr stages 2-4 Exclusion criteria: - Subjects who had atypical parkinsonian syndromes; MMSE <22 or history of psychosis; active epilepsy; clinically significant hepatic or renal disease; clinically significant coronary artery disease, bradycardia, or congestive heart failure; myocardial infarction within 6 months of randomisation; symptomatic orthostatic hypotension; active neoplastic disease; use of dopamine agonist medications in the prior 2 months (pramipexole use prior 3 months); use of instable dose of CNS active therapies 60 days prior to randomisation; or positive hep B	**Baseline characteristics** Mean age (yrs) Pramipexole (n=109): 64.8 ± 10.6 Placebo (n=35): 65.4 ± 10.3 Mean disease duration Pramipexole (n=109): 72.6 ± 60.8 months Placebo (n=35): 69.8 ± 52.7 months Mean UPDRS motor score Pramipexole (n=109): 31.6 ± 14.3 Placebo (n=35): 31.9 ± 11.5 Mean UPDRS ADL score Pramipexole (n=109): 14.7 ± 6.9 Placebo (n=35): 15.5 ± 6.4 Hoehn & Yahr stage Pramipexole (n=109): 2.5 ± 0.54 Placebo (n=35): 2.4 ± 0.47 Mean levodopa dose Pramipexole (n=109): 278.9 ± 211.6 mg/d Placebo (n=35): 272.9 ± 204.1 mg/d	**Intervention(s)** Pramipexole: 0.375mg/d to a maximum tolerated dose (≤4.5mg/d) over a 6-week period, achieving optimum levels (0.375, 1.5, 3.0 or 4.5 mg/d) in the 4-week maintenance period	**Primary outcomes** Change in the sum of the UPDRS II and III from baseline to week 10 **Secondary outcomes** Changes in the individual UPDRS part II and III scores, the modified Hoehn and Yahr stage, PDQALIF, and the Schwab and England Daily Living score

	Health for Clinical Research Center grant at the University of Rochester		screen			
Rektorova (2003)	**Study type** Prospective randomised, open-label trial **Source of funding** Not reported	**Study dates/duration** Study duration 8 months **Sample size** Total (n): 41 Group 1 (n): Pramipexole: 22 Group 2 (n): Pergolide: 19	**Inclusion/ exclusion criteria** Inclusion criteria: - People with advanced idiopathic PD according to the Parkinson's disease Society Brain Back criteria, fluctuations and/or dyskinesias and mild or moderate depression - Patients treated with a stable dose of L-dopa for at least 4 weeks prior to inclusion in the study Exclusion criteria: - Hypersensitivity to the preparations under study - Renal or cardiovascular failure, recent myocardial infarction, narrow-angle glaucoma, psychotic disorders in patient's medical history, active ulcer of gastrointestinal tract, hypotension, vascular disease - Pregnancy, lactation, planned pregnancy - Treatment with neuroleptics - Presence of dementia (MMSE score ≤24 - Severe depression - Current treatment with dopamine receptor agonists - Inclusion in another clinical study	**Baseline characteristics** Mean age (yrs) Pramipexole (n=22): 59.7 ± 7.7 Pergolide (n=19): 63.5 ± 7.5 Hoehn & Yahr stage Pramipexole (n=22): 2.7 ± 0.8 Pergolide (n=19): 3.0 ± 1.0	**Intervention(s)** Pramipexole: 1.5 - 4.5mg/d Pergolide: 1.5 - 4.5mg/d	**Primary outcomes** Effects on depression, treatment complications, and changes in motor symptoms of PD and activities of daily living **Secondary outcomes** The occurrence of AEs and reduction in the total daily dose of L-dopa
Schapira (2011)	**Study type** Randomised, double-	**Country/ies where the study was carried out**	**Inclusion/ exclusion criteria** Inclusion criteria: - Subjects ≥30 years old and had	**Baseline characteristics** Mean age (yrs) Placebo (n=178): 60.9 ±	**Intervention(s)** - Pramipexole ER: 0.375,	**Primary outcomes** Changes in UPDRS

	blind, parallel trial **Aim/ objective of the study** To determine the efficacy, safety, and tolerability of pramipexole ER in patients experiencing motor fluctuations with L-dopa for advanced PD **Source of funding** Boehringer Ingelheim	76 centres in Austria, Czech Republic, Hungary, India, Italy, Philippines, Poland, Russia, Slovakia, South Korea, Spain, Sweden, Ukraine, and the UK **Study dates/duration** Study duration 18 weeks + subsets of patients continued to take the double-blind study drug for 33 weeks, permitting descriptive assessments of whether the 18-week change was maintained Study dates May 2007 to November 2008 **Sample size** Total (n): - Total: 517 - Pramipexole ER: 164 - Pramipexole IR: 175 - Placebo: 178	idiopathic PD at Hoehn & Yahr stage 2-4 during ON time, were diagnosed ≥2 years before entry, and were being treated with L-dopa at an optimised dose unchanged during at least the 4 weeks before baseline - Subjects with motor fluctuations (≥2 cumulative hrs of daily OFF time during waking hours, on 2 consecutive days) - Patients were not permitted any dopamine agonists within the prior 4 weeks - Continuing use of other anti-PD drugs was allowed, provided the dose was unchanged during the prior 4 weeks and throughout study Exclusion criteria: - MMSE score <24, atypical parkinsonian syndromes, any history of deep brain stimulation, psychiatric or non-PD medical disorders capable of impeding trial participation, clinically significant hypotension or electrocardiographic abnormalities, or creatinine clearance <50 mL/min	9.7 Pramipexole ER (n=164): 61.6 ± 9.7 Pramipexole IR (n=175): 62.0 ± 10.3 Mean disease duration Placebo (n=178): 5.9 ± 3.8 years Pramipexole ER (n=164): 6.4 ± 4.0 years Pramipexole IR (n=175): 6.6 ± 4.4 years Mean UPDRS motor score During ON state: - Placebo (n=178): 27.7 ± 13.6 - Pramipexole ER (n=164): 29.0 ± 12.9 - Pramipexole IR (n=175): 28.3 ± 13.3 Mean UPDRS ADL score Placebo (n=178): 11.9 ± 6.1 Pramipexole ER (n=164):12.7 ± 6.5 Pramipexole IR (n=175): 12.3 ± 5.7 Mean UPDRS IV score Placebo (n=178): 5.1 ± 2.5 Pramipexole ER (n=164): 5.1 ± 2.5 Pramipexole IR (n=175): 5.1 ± 2.7 Hoehn & Yahr stage Placebo (n=178) vs. Pramipexole ER (n=164) vs. Pramipexole IR (n=175) (%): - ON state 2-3: 97.2 vs. 98.2 vs. 96.6 - ON state 4-5: 2.8 vs. 1.8 vs. 3.4 - OFF state 2-3: 86	0.75, 1.5, 2.25, 3.0, 3.75, or 4.5 mg once daily (over a 7-week flexible titration period) - Pramipexole IR: 0.125, 0.25, 0.50, 0.75, 1.0, 1.25, or 1.5mg 3 times daily (over a 7-week flexible titration period)	II + III score at 18 weeks, with further assessments at 33 weeks in a subset of patients **Secondary outcomes** Change in diary-determined daily on- and off-time, responder rates on the CGI-I and PGI-I scales, responder rate for PGI-I assessment of early morning off symptoms, UPDRS II + III responder rate, UPDRS I, II, III, IC scores and PDQ-39

				vs. 88.4 vs. 79.4 - OFF state 4-5: 14 vs. 11.6 vs. 20 Other anti-parkinsonian medication Placebo (n=178) vs. Pramipexole ER (n=164) vs. Pramipexole IR (n=175) (%): - Amantadine: 28.7vs. 23.8 vs. 26.9 - MAOBs: 18 vs. 14.6 vs. 15.4 - Anticholinergics: 16.9 vs. 14 vs. 14.3 - Entacapone: 7.3 vs. 6.7 vs. 9.7		
Tolosa (2014)	**Study type** Multicentre, parallel-group, double-blind, and randomised phase IV study **Aim/ objective of the study** To compare the efficacy and safety of levodopa/carbidopa/entacapone (LCE) with levodopa/carbidopa (LC) on Parkinson's disease patients with mild or only minimally disabling motor	**Country/ies where the study was carried out** 27 centres in Spain **Study dates/duration** Study duration 3 months Study dates October 2006 to march 2008 **Sample size** Total (n): 95 Group 1 (n): Levodopa/Carbidopa/E	**Inclusion/ exclusion criteria** Inclusion criteria: - Patients aged 30-80 years with a previous diagnosis of idiopathic PD according to the UK Parkinson's Disease Society Brain Bank criteria - On stable levodopa treatment for at least 1 month prior to study entry - Required to acknowledge experiencing wearing-off diagnosed by the QUICK questionnaire, impaired ADLs, according to the UPDRS II and either absent or mild dyskinesia - Women in fertile age should be negative with a urine pregnancy test before baseline visit Exclusion criteria: - Patients previously or currently	**Baseline characteristics** Mean age (yrs) LCE (n=46): 66.4 ± 8.2 LC (n=49): 66.5 ± 9.0 Mean disease duration LCE (n=46): 4.7 ± 4.0 years LC (n=49): 4.4 ± 3.8 years Mean UPDRS motor score LCE (n=46): 17.8 ± 6.5 LC (n=49):18.6 ± 5.5 Mean UPDRS ADL score LCE (n=46): 11.3 ± 2.0 LC (n=49): 11.6 ± 2.0 Mean UPDRS IV score LCE (n=46): 2.9 ± 1.8 LC (n=49): 2.7 ± 1.7 Hoehn & Yahr stage LCE (n=46) vs. LC (n=49) (n (%)): - 1: 0 (0) vs. 1 (2) -	**Intervention(s)** - Levodopa/Carbidopa/Entacapone: 100/25/200mg (Stalevo 100) or LCE 150/37.5/200mg (Stalevo 150) per day - Levodopa/Carbidopa: 100/25mg per day	**Primary outcomes** To assess the efficacy of LCE compared to LC on ADLs using UPDRS II **Secondary outcomes** Changes in UPDRS I, III, and IV scores, QUICK and PDQ-39, and patient and investigator clinical global impression (CGI) from baseline

	complications **Source of funding** Nippon Boehringer Ingelheim	ntacapone: 46 Group 2 (n): Levodopa/Carbidopa: 49	treated with entacapone; symptoms, signs or history of atypical or secondary Parkinsonism; hallucinations or psychiatric disorders related to dopaminergic treatments; major depression; current treatment with neuroleptics, rotigotine or monoaminooxidase inhibitors (with the exception of 10mg of selegiline/day or 1 mg of rasagiline per day) during the 60 days prior to screening visit; history of neuroleptic malignant syndrome and/or nontraumatic rhabdomyolysis	1.5: 2 (4.4) vs. 1 (2) - 2: 23 (51.1) vs. 24 (49) - 2.5: 13 (28.9) vs. 12 (24.5) - 3: 7 (15.6) vs. 10 (20.4) - 4: 0 (0) vs. 1 (2) Mean levodopa dose Equivalent dose (levodopa with decarboxylase inhibitor, mg/d): - LCE (n=46): 390 ± 100.9 - LC (n=49): 410.2 ± 96.8 Other anti-parkinsonian medication Equivalent dose (dopamine agonists, mg/d): LCE (n=46): 293 ± 172.2 LC (n=49): 318.9 ± 215.5		
Watts (2010)	**Study type** Multicenter, randomised, double-blind, parallel-group, L-dopa controlled, flexible-dose study **Aim/ objective of the study** To determine if the addition of once-daily ropinirole 24-hour prolonged-release in PD patients not optimally controlled with levodopa	**Country/ies where the study was carried out** 52 centres in the United States **Study dates/duration** Study duration Up to 104 weeks (26 months) **Sample size** Total (n): Ropinirole 24-h	**Inclusion/ exclusion criteria** Inclusion criteria: - Patients aged between 30-70 years with a diagnosis of idiopathic PD and Hoehn and Yahr stage of - I-III in the medication "on" state - Had received a stable dose of L-dopa for at least 4 weeks and not longer than 3 years, a maximum dose of 600mg/d and suboptimal symptom control including mild wearing off and simple motor fluctuations - The use of selegiline, amantadine, anticholinergics, and COMTI were permitted, provided the dose was stable for at least 4 weeks but they could not be	**Baseline characteristics** Mean age (yrs) Ropinirole prolonged-release (n=104): 61.4 ± 7.0 L-dopa (n=104): 62.1 ± 7.2 Mean disease duration Ropinirole prolonged-release (n=100): 2.7 ± 21 years L-dopa (n=102): 2.7 ± 2.4 years Mean UPDRS ADL score Ropinirole prolonged-release (n=102): 8.6 ± 4.8 L-dopa (n=104): 8.2 ± 5.7 Mean UPDRS IV score Ropinirole prolonged-release (n=102): 19.6 ±	**Intervention(s)** - Ropinirole prolonged-release: Initial dose of 2mg/d and then uprated to a maximum of 24mg/d - L-dopa: Initial dose of 50mg/d (in addition to baseline L-dopa dose) up to a maximum dose of 1000mg/d	**Primary outcomes** Time to onset of dyskinesia **Secondary outcomes** Change from baseline in the averaged medication "on" and "off" UPDRS ADL scores, UPDRS motor scores, ESS, PDSS, PDQ-39 and

	after up to 3 years of therapy with less than 600 mg/d delays the onset of dyskinesia compared with increasing doses of levodopa **Source of funding** GlaxoSmithKline Research and Development	prolonged release: 105 Group 2 (n): Carbidopa-levodopa: 104	initiated during the study Exclusion criteria: - A clinical history of dyskinesia, clinically relevant laboratory abnormalities, recent history of severe symptomatic postural hypotension, MMSE<26, significant uncontrolled medical conditions, or an active malignancy other than basal cell carcinoma. - Any patient with a recent history or current evidence of drug abuse or alcoholism - Any patient with introduction or dose change of hormone replacement therapy or any drug known to substantially inhibit or induce cytochrome P450-1A2 within 7 days of enrolment	10.5 L-dopa (n=104): 19.4 ± 12.4 Hoehn & Yahr stage Ropinirole prolonged-release (n=104): 2.0 ± 0.7 L-dopa (n=104): 1.9 ± 0.7 Mean levodopa dose Ropinirole prolonged-release (n=102): 369 ± 168 mg/d L-dopa (n=102): 364 ± 212 mg/d		PPRS scales
Zhang (2013)	**Study type** Randomized, double-blind, placebo-controlled, parallel-group, multi-centre trial **Aim/ objective of the study** To investigate the safety and efficacy of rasagiline as adjunctive therapy to levodopa treatment in	**Country/ies where the study was carried out** 9 centres across China **Study dates/duration** Study duration 12 weeks **Sample size** Total (n): 244 Group 1 (n):	**Inclusion/ exclusion criteria** Inclusion criteria: - Patients aged between 30 and 75 years; diagnosed as idiopathic PD based on the presence of at least 2 of the cardinal signs; if resting tremor was not present, subjects must have unilateral onset of symptoms; duration of disease <10 years; experienced motor fluctuations with a modified Hoehn and Yahr score of < stage 5 when assessed in the "off" state; had received levodopa therapy(the dose no more than 800mg/d) for at least 2 weeks prior to the	**Baseline characteristics** Mean age (yrs) Rasagiline (n=119): 61.64 ± 8.53 Placebo (n=125): 61.56 ± 9.50 Mean disease duration Rasagiline (n=119): 5.57 ± 2.13 years Placebo (n=125): 5.4 ± 2.24 years Mean UPDRS motor score Rasagiline (n=119): 20.30 ± 6.13 Placebo (n=125): 20.67 ± 6.83 Mean UPDRS ADL score Rasagiline (n=119): 15.35 ± 5.31 Placebo (n=125):	**Intervention(s)** Rasagiline: 1mg/d	**Primary outcomes** Changes in "on" and "off" time while awake between baseline and week 12, which were recorded using patient daily score cards **Secondary outcomes** Changes in "on" and

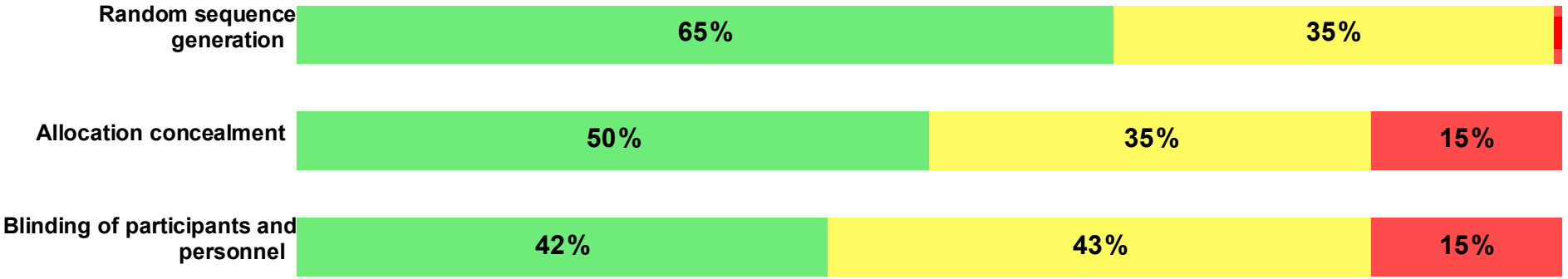
	Chinese PD patients **Source of funding** Chongqing Pharmaceutical Research Institute Co., Ltd.	Rasagiline: 119 Group 2 (n): Placebo: 125	screening visit - Required washout periods were 60 days for selegiline and 35 days for fluoxetine and fluvoxamine Exclusion criteria: - Parkinson's syndrome or Parkinson's plus syndrome; significant cognitive dysfunction or psychiatric problems compromising the ability to complete the study or give informed consent; surgery history of PD or stereotactic brain surgery; any severe illness, such as heart, liver, renal diseases or malignant tumour; significant laboratory parameter abnormalities, such as liver or renal dysfunction; a history of rasagiline or rasagiline invalidity; depression receiving fluoxetine or fluvoxamine antidepressant therapy; participation in other medicine trials within the previous 3 months - Patients with excessive drinking, drug abuse, pregnancy, breastfeeding, closed angle glaucoma, dysphagia, nasal feeding or consciousness disorders	16.30 ± 5.59 Other anti-parkinsonian medication Treated with other anti-PD agents (n (%)): - Rasagiline (n=119): 18 (15.1) - Placebo (n=125): 17 (13.6)		"off" time, as well as UPDRS Total, I, II, and III scores at weeks 4. 8. and 12 from baseline

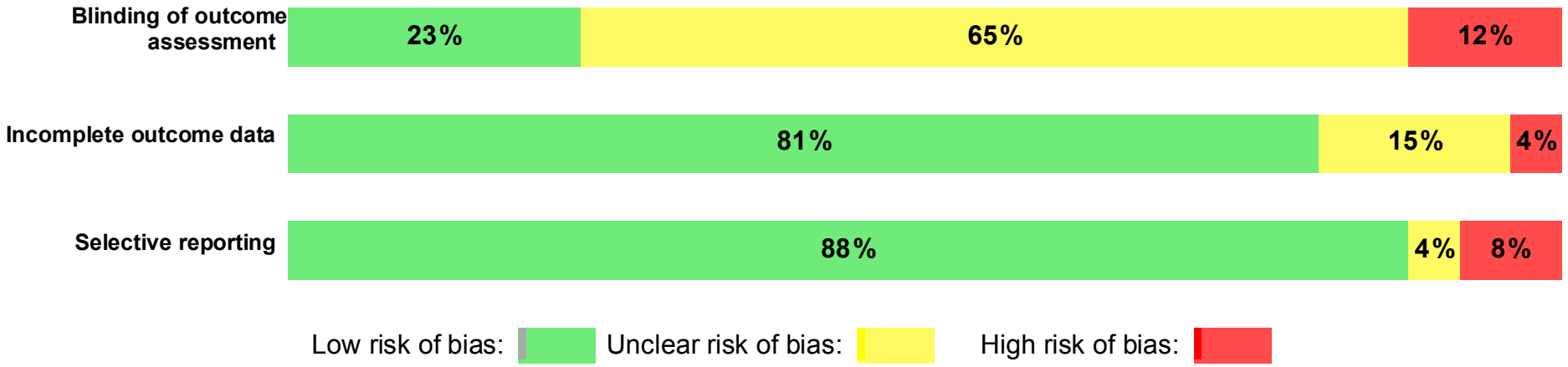
Risk of Bias

Short Title	Random sequence generation	Allocation concealment	Blinding of participants and personnel	Blinding of outcome assessment	Incomplete outcome data	Selective reporting

Stowe (2010)	+	+	+	+	+	+
Clarke (2001)	+	+	+	+	+	+
Clarke (2001)	+	+	+	+	+	+
da Silva-Junior (2005)	?	?	?	?	+	+
Deane (2004)	?	-	-	-	?	?
Destee (2009)	?	-	-	-	+	+
Deuschl (2007)	?	-	-	+	+	+
Entacapone (2007)	+	?	?	?	+	+
Fénelon (2003)	?	?	?	?	+	+
LeWitt (2007)	+	+	+	+	+	+
Lieberman (1997)	+	+	?	?	+	+
Mizuno (2003)	+	+	+	?	+	+
Mizuno (2007)	?	?	?	?	?	+
Mizuno (2014)	?	?	?	?	+	+
Nicholas (2014)	+	?	?	?	+	+

Nomoto (2014)	?	?	?	?	+	+
Ondo (2007)	+	?	?	?	?	+
Pahwa (2007)	+	+	+	?	+	+
Pahwa (2015)	+	+	+	?	+	+
Poewe (2007)	+	+	+	?	+	+
PSG (2007)	+	+	?	?	+	-
Rektorova (2003)	?	-	-	-	?	+
Schapira (2011)	+	?	+	?	+	+
Tolosa (2014)	+	+	?	+	+	+
Watts (2010)	+	+	+	?	-	-
Zhang (2013)	+	+	+	?	+	+




Blinding of outcome assessment
23%
65%
12%
Incomplete outcome data
81%
15%
4%
Selective reporting
88%
4%
8%
Low risk of bias:
Unclear risk of bias:
High risk of bias: