D.1 Information needs of people with Parkinson’s disease and their families and carers

D.1.1 Impulse control behaviours

Bibliographic reference	**Phu,A.L., Xu,Z., Brakoulias,V., Mahant,N., Fung,V.S., Moore,G.D., Martin,A., Starcevic,V., Krause,M., 20140821, Effect of impulse control disorders on disability and quality of life in Parkinson's disease patients, Journal of Clinical Neuroscience, 21, 63-66, 2014**
Full citation	Phu,A.L., Xu,Z., Brakoulias,V., Mahant,N., Fung,V.S., Moore,G.D., Martin,A., Starcevic,V., Krause,M., 20140821, Effect of impulse control disorders on disability and quality of life in Parkinson's disease patients, Journal of Clinical Neuroscience, 21, 63-66, 2014
Country/ies where the study was carried out	Australia
Study type	Cohort study
Aim of the study	To examine the effect of impulse control disorder on quality of life in Parkinson’s disease patients.
Study dates	Study carried out between Jan 2009 and March 2011. received Oct 2012 accepted Feb 2013 published 2014
Source of funding	Parkinson's Australia and the Nepean Research fund
Sample size	N = 100
Inclusion criteria	Idiopathic PD according to Queen square brain bank criteria
Exclusion criteria	Those with active psychotic symptoms or severe cognitive impairment or other reasons which preclude an interview i.e. language barriers
Details	All patients interviewed by an experienced psychiatrist using expanded structured clinical interview from DSM-IV for obsessive compulsive disorder related spectrum disorders (OCSD) Corresponding diagnoses based on DSM IV criteria and on research criteria where DSM does not provide diagnostic criteria Mini international neuropsychiatric interview used to assess presence and severity of suicidality PD symptoms assessed by UPDRS III and UPDRS ADL MMSE and MOCA used for cognitive testing LEDD calculated for levodopa and DA's QoL measured using PDQ39
Interventions	N/A
Results	N ICD = 15, N no ICD = 85

Bibliographic reference	**Phu,A.L., Xu,Z., Brakoulias,V., Mahant,N., Fung,V.S., Moore,G.D., Martin,A., Starcevic,V., Krause,M., 20140821, Effect of impulse control disorders on disability and quality of life in Parkinson's disease patients, Journal of Clinical Neuroscience, 21, 63-66, 2014**
	mean age ICD = 64.6 (7.7), no = 67.6 (9.2) ICD male = 80%, no = 67% PD duration ICD = 0.0 (5.4), no = 7.2 (6.3) ICD and PDQ39 scores ICD mean total PDQ39 = 59 (SD = 29) (95%CI: 45 to 73) , no ICD = 41 (SD=27) (95%CI: 36 to 47) - MD = 18 (2.24 to 33.76) ADL ADL significantly reduced in patients suffering from ICRD compared to those without ICRD - regression coefficient = 3.0 (1.4) p=0.04 Major depressive disorder and ICD Incidence of MDD in ICD was 4/15 (27%) in ICD patients compared to 9/85 (11%) of patients without an ICD. (Odds ratio calculated using RevMan: OR =3.07, 95%CI: 0.86 to 11.69)
Overall Risk of Bias	NICE cohort study checklist: 1. Method of allocation to treatment groups was unrelated to potential confounding factors: N/A - no treatment 2. Attempts were made within the design or analysis to balance the comparison groups for potential confounders? NA; patients allocated on basis of ICD or not, no intentional allocation 3. Groups were comparable at baseline, including all major confounding and prognostic factors? yes, baseline characteristics similar 4. Based on above, was selection bias present? If so, direction of effect? No selection bias present 5. Comparison groups received same care apart from interventions studied? Yes, all assessment procedures the same for all participants 6. Participants receiving care were kept blind to treatment allocation? NA 7. Individuals administering care were kept blind to treatment allocation? NA 8. Based on above, was performance bias present? If so, direction of effect? NO - not applicable 9. All groups followed for equal length of time? No longitudinal follow up 10. How many pts did not complete follow-up? No longitudinal follow up11. Groups were comparable for treatment completion? No treatment 12. Groups were comparable with respect to availability of outcome data? Yes 13. Based on above, was attrition bias present? If so, direction of effect? No 14. Study had appropriate length of follow up? No longitudinal follow up 15. Study used precise definition of outcome? Yes. Well-validated measures used. 16. Valid and reliable method was used to determine outcome? Yes. Well-validated measures used 17. Investigators kept blind to participant's exposure to intervention? No intervention 18. Investigators kept blind to other important confounding factors? NA 19. Based on above, detection bias present? If so, direction of effect? NO No serious bias present

Bibliographic reference	**Phu,A.L., Xu,Z., Brakoulias,V., Mahant,N., Fung,V.S., Moore,G.D., Martin,A., Starcevic,V., Krause,M., 20140821, Effect of impulse control disorders on disability and quality of life in Parkinson's disease patients, Journal of Clinical Neuroscience, 21, 63-66, 2014**
Other information	None

Bibliographic reference	**Mestre,T.A., Teodoro,T., Reginold,W., Graf,J., Kasten,M., Sale,J., Zurowski,M., Miyasaki,J., Ferreira,J.J., Marras,C., Reluctance to start medication for Parkinson's disease: A mutual misunderstanding by patients and physicians, Parkinsonism and Related Disorders.20 (6) (pp 608-612), 2014.Date of Publication: June 2014., 608-612, 2014**
Full citation	Mestre,T.A., Teodoro,T., Reginold,W., Graf,J., Kasten,M., Sale,J., Zurowski,M., Miyasaki,J., Ferreira,J.J., Marras,C., Reluctance to start medication for Parkinson's disease: A mutual misunderstanding by patients and physicians, Parkinsonism and Related Disorders.20 (6) (pp 608-612), 2014.Date of Publication: June 2014., 608-612, 2014
Country/ies where the study was carried out	Portugal, Canada, and Germany
Study type	Cross-sectional observational study
Aim of the study	To study reluctance to start medication for PD motor symptoms, namely its prevalence, underlying reasons, drug-specificity, and associated delay in the start of PD medication
Study dates	Not reported
Source of funding	Not reported
Sample size	469 participants (201 PD patients, 268 physicians)
Inclusion criteria	Clinical diagnosis of PD by a movement disorders specialist Recommendation to start anti-PD drugs in the preceding 5 years
Exclusion criteria	Patients with cognitive impairment reported in clinical records
Details	Patients were interviewed with a structured questionnaire conducted by a study investigator other than the caring physician. The questionnaire included questions using a five-point Likert scale to estimate the degree of reluctance to start medication for PD and individual anti-PD drug classes. Reasons for the delay of starting anti-PD drugs were also asked. Open questions were included to determine the causes for reluctance to start medication. Demographic and PD-related information were abstracted from medical records. Physicians were sent an electronic survey that included various multiple-choice questions covering the same topics included in the patient questionnaire. A list of reasons for reluctance to start medication was provided and physicians were asked to order the reasons listed from the most to the least common, in the patient's point of view.
Interventions	N/A

Bibliographic reference	Mestre,T.A., Teodoro,T., Reginold,W., Graf,J., Kasten,M., Sale,J., Zurowski,M., Miyasaki,J., Ferreira,J.J., Marras,C., Reluctance to start medication for Parkinson's disease: A mutual misunderstanding by patients and physicians, Parkinsonism and Related Disorders.20 (6) (pp 608-612), 2014.Date of Publication: June 2014., 608-612, 2014
Results	Causes for reluctance to start medication: Patients - 62 participants expressed their reasons for reluctance out of the 82 who reported some degree of reluctance. The most common reason for reluctance to start medication was the fear of side effects (n=35; 55.6%), followed by non-acceptance of diagnosis (n=23, 36.5%). Other frequently reported reasons were a general dislike for medications (n=17, 27%) and scepticism regarding the efficacy of medication (n=10, 15.9%). Treatment-induced dyskinesia (n=5), sleep problems (n=4) and impulse control disorders (n=3) were the most commonly reported specific adverse effects of concern. Physicians - The patient's fear that antiparkinsonian medication would have a temporally limited benefit (n=92/267, 34.5%) was judged to be the most common cause for reluctance to start medication (p=0.0065). A dislike of chronic medication (n=67/236, 28.4%) was judged to be the second most common reason (p<0.0001). Non-acceptance of the diagnosis (n=24/236, 10.1%) was rarely selected for higher levels of reluctance.
Overall Risk of Bias	1. Method of allocation to treatment groups was unrelated to potential confounding factors: N/A - no treatment 2. Attempts were made within the design or analysis to balance the comparison groups for potential confounders? NA - no intentional allocation 3. Groups were comparable at baseline, including all major confounding and prognostic factors? No, participants were only comparable in terms of age and sex. 4. Based on above, was selection bias present? If so, direction of effect? Unclear. 5. Comparison groups received same care apart from interventions studied? Unsure. 6. Participants receiving care were kept blind to treatment allocation? NA 7. Individuals administering care were kept blind to treatment allocation? NA 8. Based on above, was performance bias present? If so, direction of effect? NA 9. All groups followed for equal length of time? No longitudinal follow up 10. How many pts did not complete follow-up? No longitudinal follow up 11. Groups were comparable for treatment completion? No treatment 12. Groups were comparable with respect to availability of outcome data? Yes 13. Based on above, was attrition bias present? If so, direction of effect? NA 14. Study had appropriate length of follow up? No longitudinal follow up 15. Study used precise definition of outcome? Yes. 16. Valid and reliable method was used to determine outcome? Unclear.17. Investigators kept blind to participant's exposure to intervention? No intervention 18. Investigators kept blind to other important confounding factors? NA 19. Based on above, detection bias present? If so, direction of effect? Unclear Likely high risk of bias.
Other information	None

D.1.2 Women of childbearing age

Study details	Participants	Methods	Results	Comments

Study details	Participants	Methods	Results	Comments
Full citation Golbe,L.I., 19870731, Parkinson's disease and pregnancy, Neurology, 37, 1245-1249, 1987 Ref Id 306405 Country/ies where the study was carried out USA Study type Qualitative semi-structured interview Aim of the study To study the interactions between PD and pregnancy Study dates received August 4	Sample size N=18 women Inclusion criteria females diagnosed with PD before the age of 40 who had become pregnant after onset of PD symptoms ; no other criteria listed Exclusion criteria Not listed	Details Suitable cases ascertained through 1) announcements in newsletters of United PD foundation and American PD association; 2) follow-up inquiries of people who responded to an unrelated questionnaire in the UPDF newsletter; 3) referrals from colleagues patients questioned by telephone regarding accuracy of diagnosis of PD; medications take at time of conception and during pregnancy labour and delivery complications of pregnancy, labour, and delivery subsequent health of the child nature and degree of PD symptoms before, during, and after pregnancy side-effects of anti PD drugs before, during, and after pregnancy symptomatic course of PD since the pregnancy Interventions NA	Results 18 women met diagnostic criteria, of whom 24 pregnancies were reported after onset of PD symptoms mean age at time of conception 34.6 +- 6.1 years pregnancy occurred a mean of 4.1 (4.2) years after diagnosis of PD 4 elective abortions in 3 women one, age 41, performed because trisomy 21 revealed Other 3 performed because patient feared consequences of the PD/pregnancy combination for herself and child no obstetric or neurologic complications reported prior to the abortions obstetric complications 3 women each had 1 spontaneous miscarriage medications taken during these pregnancies were amantadine and benztropine, amantadine and levodopa (w/o carbidopa), and benztropine and diphenhydramine. the 2 miscarriages reported at 4thmonth were not associated with gross foetal abnormalities women had had previous uneventful pregnancies (2 and 3, respectively) maternal ages at time of miscarriage 31, 38, 42; mean 37 (5.6) mean maternal age for successful pregnancies was 33.1 (6.0) disease duration at time of conception similar	Overall Risk of Bias 1. Is a qualitative approach appropriate? Yes - interview appropriate for this study 2. Is the study clear in what it seeks to do? Yes - clearly seeks to understand pregnancy experience in women with a diagnosis of PD 3. How defensible /rigorous is the design and methodology-methodology reasonably rigorous. Serious of question about pregnancy experience and complications as well as PD symptoms and medication asked of each women 4. How well was the data collection carried out? Methodology of data collection unclear. Not clear how many women were approached and excluded, and if so, why/ 5. Is the role of the researcher clearly described? Role of researcher not described 6. Is the context clearly described? Context not described; some women describing pregnancy of up to 35 years ago, other only 1 month ago. Context of PD and treatment experience potentially very different over this span of time 7. Were methods reliable?

Study details	Participants	Methods	Results	Comments
1986, accepted Oct 13 1986, , published 1987 Source of funding Not listed			in successful pregnancy 4.2 (4.5) years and miscarriage group 3.0 (2.6) years all 4 pregnancies (in 4 diff women) during which amantadine was received were associated with complications: 2 miscarriages first trimester vaginal bleeding proteinuria and hypertension, diagnosed with preeclampsia in 3rd pregnancy. In same patient first pregnancy in which only on levodopa/carbidopa taken was uneventful 4/16 pregnancies in which amantadine not taken were associated with complications no reports of premature labour or delivery one C-section because of inadequate progression of labour All children, mean age 7 years (range 1 month to 32 years) apparently healthy neurological complications minor exacerbation of PD symptoms or appearance of new symptom during pregnancy was reported in 11/ pregnancies in all 11, reported rate of progression during pregnancy was greater than during the months before or after pregnancy in only one of these did symptoms improve after delivery one women reported increase of duration of action of levodopa/carbidopa no subject reported a significant functional change in disability the one women who had dopa-induced chorea noted transient worsening of that	Methods not clearly written, difficult to assess reliability 8. Is data analysis sufficiently rigorous? Data analysis is not sufficiently rigorous. Statistical analyses not reported. 9. Is the data 'rich' i.e. how well are contexts described, has diversity of perspective been explored, how well was detail and depth demonstrated, are responses compared and contrasted across groups/sites? Depth of detail and 'richness' of data lacking. Many areas which are not well explained. 10. Is the analysis reliable? Analysis not described in detail; therefore, not reliable. Some women were retrospectively recalling experience up to 35 years prior, high potential for bias. 11. Are the findings convincing? Findings are in keeping with case studies and general consensus opinion 12. Are findings relevant to aims of the study? Yes 13. Conclusions? May be some association between amantadine and obstetric outcomes. Levodopa/carbidopa does not appear to induce any obstetric complications. Symptoms of PD may worsen as a complication of

Study details	Participants	Methods	Results	Comments
			symptom during pregnancy depression reported de novo during pregnancy in one case and resolved after delivery another 4 pregnancies (in 3 women) were followed by postpartum depression not requiring drug treatment only one women (who also reported depression during pregnancy) reported nausea and vomiting after the first trimester	pregnancy. Does not appear to be any association between birth defects and PD 14. How clear and coherent is reporting of ethics? Ethics not reported Overall assessment: Serious risk of bias Other information Authors state no obvious pathophysiologic common denominator among the amantadine-associated pregnancy complications. No definite statement can be made as to any causal relationship between amantadine and obstetric complications, however these anecdotal evidences may provide some informative value - further research in this area warranted overall incidence of miscarriage, 3 of 20 (15%) lies within the normal range of between 10- 20% for the general population study revealed no major ill effect of the major anti-PD drug levodopa/carbidopa on the 6 pregnancies during which it was taken - but numbers too small to support claim levodopa safe during pregnancy

D.2 Pharmacological management of motor symptoms

D.2.1 First-line treatment of motor symptoms

<table>
<tr><th>Bibliographic reference</th><th>Stern,M.B., Marek KL FAU - Friedman,Joseph, Friedman,J.FAU, Hauser RA FAU - LeWitt,Peter, LeWitt PA FAU - Tarsy,Daniel, Tarsy,D.FAU, Olanow,C.W., Double-blind, randomised, controlled trial of Rasagiline as monotherapy in early Parkinson's disease patients, Movement Disorders., 19, 916-923, 2004</th></tr>
<tr><td>Country/ies where the study was carried out</td><td>US</td></tr>
<tr><td>Study type</td><td>Double-blind randomised, placebo-controlled, parallel-group, dose-ranging study</td></tr>
<tr><td>Aim of the study</td><td>To evaluate the safety and tolerability of orally administered rasagiline, and to make a preliminary assessment of its efficacy, when administered as once-daily onotherapy in patients with early PD and who were not receiving L-dopa.</td></tr>
<tr><td>Study dates</td><td>Study date: Not reported
Study duration: 10 weeks</td></tr>
<tr><td>Source of funding</td><td>Teva Pharmaceuticals</td></tr>
<tr><td>Sample size</td><td>In total: n= 56; Rasagiline 1mg: n=15; Rasagiline 2mg: n=14; Rasagiline 4mg: n=14; Placebo: n=13</td></tr>
<tr><td>Inclusion criteria</td><td>• Between 40 to 75 years of age
• A diagnosis of idiopathic PD
• Hoehn and Yahr disease severity if less than stage III
• Required washout periods were 60 days for selegiline and 14 days for other antiparkinsonian medications, serotine reuptake inhibitors (except fluoxetine, which required 35 days), tricyclic antidepressants, opiates, and sympathomimetic agents.</td></tr>
<tr><td>Exclusion criteria</td><td>• Patients with a history of intolerance to selegiline.
• The presence of clinically significant medical or psychiatric problems, moderate or severe hypertension, or significant cognitive dysfunction compromising the patient's ability to give informed consent or to complete the study.</td></tr>
<tr><td>Details</td><td>Baseline characteristics:
<table>
<tr><td rowspan="2">Characteristics</td><td colspan="3">Selegiline group</td><td></td></tr>
<tr><td>1mg/day (n=15)</td><td>2mg/day (n=14)</td><td>4mg/day (n=14)</td><td>Placebo (n=13)</td></tr>
<tr><td>Age (yr)</td><td>59.3(8.6)</td><td>60.3(7.2)</td><td>62.0(9.7)</td><td>64.8(9.4)</td></tr>
<tr><td>Disease duration (yr)</td><td>1.3(2.6)</td><td>0.4(0.8)</td><td>0.3(0.5)</td><td>0.8(1.0)</td></tr>
</table></td></tr>
</table>

<table>
<tr><th>Bibliographic reference</th><th>Stern,M.B., Marek KL FAU - Friedman,Joseph, Friedman,J.FAU, Hauser RA FAU - LeWitt,Peter, LeWitt PA FAU - Tarsy,Daniel, Tarsy,D.FAU, Olanow,C.W., Double-blind, randomised, controlled trial of Rasagiline as monotherapy in early Parkinson's disease patients, Movement Disorders., 19, 916-923, 2004</th></tr>
<tr><td></td><td>
<table>
<tr><td>UPDRS total</td><td>18.2(6.5)</td><td>21.0(5.2)</td><td>20.2(7.4)</td><td>17.7(7.9)</td></tr>
<tr><td>UPDRS motor</td><td>9.4(3.9)</td><td>11.3(3.0)</td><td>11.6(3.8)</td><td>10.8(4.8)</td></tr>
<tr><td>UPDRS ADL</td><td>7.7(3.6)</td><td>8.4(2.8)</td><td>7.3(3.3)</td><td>6.6(3.6)</td></tr>
<tr><td>Hoehn & Yahr stage</td><td>1.5(0.4)</td><td>1.6(0.4)</td><td>1.6(0.4)</td><td>1.5(0.4)</td></tr>
</table>
</td></tr>
<tr><td>Interventions</td><td>Group 1: Rasagiline 1 mg once daily for 10 weeks;
Group 2: Rasagiline 1 mg once daily for 1 week, then rasagiline 2 mg once daily for 9 weeks;
Group 3: Rasagiline 1 mg once daily for 1 week, then rasagiline 2 mg once daily for 2 weeks, followed by rasagiline 4 mg once daily for 7 weeks.</td></tr>
<tr><td>Primary outcomes</td><td>To evaluate the safety and tolerability of rasagiline as monotherapy at doses of 1, 2, or 4 mg administered once daily over a 10 week treatment period in patients with early PD and who were not receiving L-dopa.</td></tr>
<tr><td>Secondary outcomes</td><td>A preliminary assessment of the efficacy of rasagiline monotherapy as assessment of its plasma pharmacokinetics.</td></tr>
<tr><td>Results</td><td>At week 10, the mean (±SE) change from baseline in total UPDRS score was -1.8(±1.3) in the rasagiline 1mg group (9.9% improvement from baseline), -3.6(±1.7) in the rasagiline 2mg group (17% improvement), -3.6(±1.2) in the rasagiline 4mg group (17.8% improvement), and -0.5(±0.8) in those receiving placebo (2.8% improvement).

Incidence of the most common adverse events in rasagiline-treated patients and of adverse events commonly associated with dopaminergic medications:
<table>
<tr><td colspan="3">% of patients reporting adverse event (P vs. placebo)</td></tr>
<tr><td>Adverse event</td><td>Rasagiline-treated patients</td><td>Placebo-treated patients</td></tr>
<tr><td>Pain</td><td>30%[0.48]</td><td>15%</td></tr>
<tr><td>Headache</td><td>26%[0.73]</td><td>31%</td></tr>
<tr><td>Dizziness</td><td>23%[0.71]</td><td>15%</td></tr>
<tr><td>Infection</td><td>12%[0.19]</td><td>31%</td></tr>
</table>
</td></tr>
</table>

Bibliographic reference	Stern,M.B., Marek KL FAU - Friedman,Joseph, Friedman,J.FAU, Hauser RA FAU - LeWitt,Peter, LeWitt PA FAU - Tarsy,Daniel, Tarsy,D.FAU, Olanow,C.W., Double-blind, randomised, controlled trial of Rasagiline as monotherapy in early Parkinson's disease patients, Movement Disorders., 19, 916-923, 2004

Diarrhoea	12%[0.37]	23%
Insomnia	12%[0.58]	0%
Paraesthesia	12%[0.58]	0%
Nausea	7%[1.00]	8%
Somnolence	5%[1.00]	0%
Nausea & vomiting	2%[1.00]	0%
Oedema	2%[1.00]	0%
Hallucinations	2%[1.00]	0%

Overall Risk of Bias

1. Has an appropriate method of randomisation been used? Yes
2. Was there adequate concealment of allocation? Yes
3. Were the groups comparable at baseline for all major confounding/prognostic factors? Unclear
4. Did the comparison groups receive the same care apart from interventions studied? Yes
5. Were participants receiving care kept blind to treatment allocation? Yes
6. Were the individuals administering care kept blind to treatment allocation? Yes
7. Were groups comparable with respect to availability of outcome data and for how many participants were no outcome data available? Yes
8. Did the study have an appropriate length of follow up? Yes
9. Did the study use a precise definition of outcome? Yes
10. Was a valid and reliable method used to determine that outcome? Yes
11. Were investigators kept blind to participant’s exposure to the intervention? Unclear
12. Were investigators kept blind to other important confounding and prognostic factors? Unclear

<table>
<tr><th>Bibliographic reference</th><th>Giladi,N., Boroojerdi,B.FAU, Korczyn AD FAU - Burn,David, Burn DJ FAU - Clarke,Carl, Clarke CE FAU - Schapira,Anthony, Schapira,A.H., Rotigotine transdermal patch in early Parkinson's disease: a randomised, double-blind, controlled study versus placebo and ropinirole, Movement Disorders., 22, 2398-2404, 2007</th></tr>
<tr><td>Country/ies where the study was carried out</td><td>Not reported</td></tr>
<tr><td>Study type</td><td>Multicentre, multinational, randomised, double-blind, double-dummy, placebo- and ropinirole-controlled study</td></tr>
<tr><td>Aim of the study</td><td>To investigate the efficacy and safety of the rotigotine transdermal patch in the early stages of PD.</td></tr>
<tr><td>Study dates</td><td>Study dates: Not reported.
Study duration: 41 weeks.</td></tr>
<tr><td>Source of funding</td><td>Not reported.</td></tr>
<tr><td>Sample size</td><td>In total: n= 561; Ropinirole n= 228; Rotigotine n=215; Placebo n= 118</td></tr>
<tr><td>Inclusion criteria</td><td>• 30 years or older with a diagnosis of PD based on the UK Brain Bank Criteria
• Hoehn & Yahr clinical stage of 3 or less
• UPDRS III score of at least 10
• Patients were permitted to take selegiline, amantadine, or anticholinergic agents or other CNS active drugs if maintained at stable dosages for 28 days before baseline and throughout the trial.</td></tr>
<tr><td>Exclusion criteria</td><td>• MMSE score <25
• Clinically significant psychiatric or cognitive condition
• Inability to apply and remove the patches appropriately
• A history of skin sensitivity of adhesives or other transdermal medications
• Administration of a dopamine agonist or levodopa within 28 days of the baseline visit or had ever taken levodopa for longer than 6 months
• Clinically relevant hepatic, renal, or cardiac dysfunction
• An average QTc interval of ≥450 ms for men and ≥470 ms for women in three repeated electrocardiograms performed at baseline; symptomatic orthostatic hypotension; recent exposure to monoamine oxidase A inhibitors and neuroleptics.</td></tr>
<tr><td>Details</td><td>Baseline characteristics:
<table>
<tr><td>Characteristics</td><td>Placebo (n=118)</td><td>Rotigotine (n=215)</td><td>Ropinirole (n=228)</td></tr>
<tr><td>Mean age, yr</td><td>60.4</td><td>61.1</td><td>61.6</td></tr>
<tr><td>Mean years since diagnosis</td><td>1.2</td><td>1.4</td><td>1.3</td></tr>
</table></td></tr>
</table>

Bibliographic reference	Giladi,N., Boroojerdi,B.FAU, Korczyn AD FAU - Burn,David, Burn DJ FAU - Clarke,Carl, Clarke CE FAU - Schapira,Anthony, Schapira,A.H., Rotigotine transdermal patch in early Parkinson's disease: a randomised, double-blind, controlled study versus placebo and ropinirole, Movement Disorders., 22, 2398-2404, 2007
	Hoehn & Yahr stage, %:
	1 | 25 | 24 | 27
	2 | 59 | 62 | 53
	3 | 15 | 13 | 21
	Mean UPDRS score:
	ADL (Part II) | 8.7 | 9.3 | 9.1
	Motor (Part III) | 22.6 | 23.8 | 23.2
Interventions	• Transdermal rotigotine began active treatment at 2mg/24hrs with weekly increments of 2mg/24hrs. The maximum permitted dose was 8mg/24hrs. Titration period was up to 4 weeks and there was a minimum dose-maintenance phase of 33 weeks. • Ropinirole began active treatment at 0.25mg tid with weekly increments of 0.25mg tid. The maximum permitted dose was 24mg/day. Titration period was up to 13 weeks and there was a minimum dose-maintenance phase of 24 weeks.
Primary outcomes	The proportion of patients with a minimum of 20% decrease in the combined UPDRS Part II and Part III scores.
Secondary outcomes	• Absolute change in UPDRS II + III scores from baseline visit to the end of the double-blind maintenance period • Changes in the UPDRS II and III subscale scores • Demonstration of noninferiority to ropinirole
Results	The mean decrease from baseline in UPDRS subtotal score to the end of treatment was -7.2 (SD±9.9) for patients receiving rotigotine compared with -2.2(SD±10.2) for patients receiving placebo (P<0.0001). A mean decrease of -11.0(SD±10.5) were observed for ropinirole (P<0.0001). The mean UPDRS Part II and III scores improved from baseline to end of treatment by 2.1 and 5.2, respectively, for patients receiving rotigotine and by 0.1 and 2.1 for patients receiving placebo. The difference between rotigotine transdermal patch and ropinirole for the primary efficacy parameters did not show noninferiority. Most common treatment-emergent adverse events (in%) during the overall treatment period (≥5% in any group):

Bibliographic reference	Giladi,N., Boroojerdi,B.FAU, Korczyn AD FAU - Burn,David, Burn DJ FAU - Clarke,Carl, Clarke CE FAU - Schapira,Anthony, Schapira,A.H., Rotigotine transdermal patch in early Parkinson's disease: a randomised, double-blind, controlled study versus placebo and ropinirole, Movement Disorders., 22, 2398-2404, 2007

Adverse events	Placebo (n=118)	Rotigotine (n=215)	Ropinirole (n=228)
Application-site reaction	11	38	7
Dizziness	10	14	17
Headache	8	10	9
Nausea	16	29	36
Vomiting	3	12	11
Abdominal pain	5	4	7
Constipation	4	7	9
Dyspepsia	2	3	6
Diarrhoea	4	4	6
Arthralgia	2	5	3
Back pain	8	7	5
Somnolence	20	23	28
Insomnia	5	6	6

Overall Risk of Bias

1. Has an appropriate method of randomisation been used? Yes
2. Was there adequate concealment of allocation? Unclear
3. Were the groups comparable at baseline for all major confounding/prognostic factors? Yes
4. Did the comparison groups receive the same care apart from interventions studied? Unclear
5. Were participants receiving care kept blind to treatment allocation? Yes
6. Were the individuals administering care kept blind to treatment allocation? Yes
7. Were groups comparable with respect to availability of outcome data and for how many participants were no outcome data available? Unclear
8. Did the study have an appropriate length of follow up? Yes

Bibliographic reference	Giladi,N., Boroojerdi,B.FAU, Korczyn AD FAU - Burn,David, Burn DJ FAU - Clarke,Carl, Clarke CE FAU - Schapira,Anthony, Schapira,A.H., Rotigotine transdermal patch in early Parkinson's disease: a randomised, double-blind, controlled study versus placebo and ropinirole, Movement Disorders., 22, 2398-2404, 2007
	9. Did the study use a precise definition of outcome? Yes 10. Was a valid and reliable method used to determine that outcome? Yes 11. Were investigators kept blind to participant's exposure to the intervention? Unclear 12. Were investigators kept blind to other important confounding and prognostic factors? Unclear

Bibliographic reference	Mally,J., Kovacs AB,F.A.U., Stone,T.W., Delayed development of symptomatic improvement by (--)-deprenyl in Parkinson's disease, J Neurol Sci., 134, 143-145, 1995
Country/ies where the study was carried out	Not reported
Study type	Randomised, double-blind trial.
Aim of the study	To examine the effects of deprenyl (Selegiline) alone in order to be sure of distinguishing improvements due to this drug from any slowly developing changes due to L-dopa.
Study dates	Study dates: Not reported. Study duration: 6 weeks.
Source of funding	Not reported.
Sample size	In total: n=20; Selegiline: n=10; Placebo: n=10
Inclusion criteria	No other disease was evident and the patients were never on levodopa therapy.
Exclusion criteria	Not reported.
Details	Baseline characteristics:

Characteristics	Selegiline n=10	Placebo n=10
Age (yrs)	57±2.8	68±2.4
Duration of disease (yrs)	1.5±0.27	2.6±0.58
Hoehn-Yahr (n)	Stage 1: 2 Stage 2: 5 Stage 3: 3	Stage 1: 2 Stage 2: 4 Stage 3: 4

<table>
<tr><th>Bibliographic reference</th><td>Mally,J., Kovacs AB,F.A.U., Stone,T.W., Delayed development of symptomatic improvement by (--)-deprenyl in Parkinson's disease, J Neurol Sci., 134, 143-145, 1995</td></tr>
<tr><td></td><td>Patients were scored on 3 different occasions before the commencement of treatment and then weekly for the next 6 weeks of drug administration.</td></tr>
<tr><td>Interventions</td><td>Selegiline: 10mg/day for 6 weeks.</td></tr>
<tr><td>Primary outcomes</td><td>Severity of symptoms as measured by UPDRS (Total, Mental, Daily activities, Motor), the North Western self-rating scale and a simple graded clinical test.</td></tr>
<tr><td>Secondary outcomes</td><td>N/A</td></tr>
<tr><td>Results</td><td>
<table>
<tr><td></td><td></td><td>Baseline</td><td>wk1</td><td>wk2</td><td>wk3</td><td>wk4</td><td>wk5</td><td>wk6</td></tr>
<tr><td>UPDRS Daily activities</td><td>Placebo n=10</td><td>9.2±1.5</td><td>9.2±1.6</td><td>9.6±1.7</td><td>9.8±1.6</td><td>9.8±1.6</td><td>10.0±1.7</td><td>10.1±1.7</td></tr>
<tr><td></td><td>Selegiline n=10</td><td>9.1±1.5</td><td>8.9±1.6</td><td>8.4±1.4</td><td>6.0±0.9</td><td>5.8±0.5</td><td>5.3±0.3</td><td>5.3±0.3</td></tr>
<tr><td>UPDRS Motor</td><td>Placebo n=10</td><td>15.2±1.6</td><td>15.2±1.6</td><td>15.3±1.6</td><td>15.5±1.7</td><td>16.0±1.8</td><td>16.3±1.8</td><td>16.4±1.7</td></tr>
<tr><td></td><td>Selegiline n=10</td><td>15.7±2.2</td><td>15.6±2.1</td><td>12.4±1.5</td><td>11.0±1.0</td><td>9.1±1.0</td><td>8.2±0.9</td><td>8.2±0.9</td></tr>
</table>
Data are given as mean ± SE.
</td></tr>
<tr><td>Overall Risk of Bias</td><td>
1. Has an appropriate method of randomisation been used? Unclear
2. Was there adequate concealment of allocation? Unclear
3. Were the groups comparable at baseline for all major confounding/prognostic factors? Yes
4. Did the comparison groups receive the same care apart from interventions studied? Unclear
5. Were participants receiving care kept blind to treatment allocation? Unclear*
6. Were the individuals administering care kept blind to treatment allocation? Unclear*
7. Were groups comparable with respect to availability of outcome data and for how many participants were no outcome data available? Yes
8. Did the study have an appropriate length of follow up? No (6 weeks)
9. Did the study use a precise definition of outcome? Yes
10. Was a valid and reliable method used to determine that outcome? Yes
11. Were investigators kept blind to participant’s exposure to the intervention? Unclear*
12. Were investigators kept blind to other important confounding and prognostic factors? Unclear*
</td></tr>
</table>

Bibliographic reference	Mally,J., Kovacs AB,F.A.U., Stone,T.W., Delayed development of symptomatic improvement by (--)-deprenyl in Parkinson's disease, J Neurol Sci., 134, 143-145, 1995
	*Level of blinding unclear - no details beyond description of study as "randomised, double-blind trial". Overall there is likely to be a high risk of bias.

Bibliographic reference	Adler,C.H., Sethi KD,F.A.U., Hauser RA,F.A.U., Davis TL,F.A.U., Hammerstad JP,F.A.U., Bertoni,J.FAU, Taylor RL FAU - Sanchez-Ramos,, Sanchez-Ramos,J.FAU, O'Brien,C.F., Ropinirole for the treatment of early Parkinson's disease. The Ropinirole Study Group, Neurology, 49, 393-399, 1997
Country/ies where the study was carried out	US
Study type	Prospective, randomised, multi-centre (25 sites), double-blind, placebo-controlled study
Aim of the study	To assess the efficacy and safety of ropinirole in patients with early PD.
Study dates	Study dates: Not reported Study duration: 6 months
Source of funding	SmithKline Beecham Pharmaceuticals
Sample size	In total: n=241; Ropinirole: n=116; Placebo: n=125
Inclusion criteria	• Hoehn & Yahr stages I to III • Motor symptoms of sufficient severity to warrant the introduction of dopaminergic therapy but had not received L-dopa or any dopaminergic agonist for more than 6 weeks prior to study entry. Patients entering the trial on selegiline were required to remain on stable dose of selegiline for 4 weeks prior to study entry and for the duration of the study. All other antiparkinsonian therapies, except selegiline, must be discontinued at least 4 weeks prior to study entry.
Exclusion criteria	• Treatment with vasodilators, antiarrhythmic, digoxin, calcium channel blockers, angiotensin-converting enzyme inhibitors, or other antihypertensive agents (excluding diuretics) • Previous treatment with ropinirole • History of severe dizziness or fainting • Diastolic blood pressure ≥110 mm hg • Recent history of alcoholism or drug dependence
Details	Baseline characteristics (patients were stratified by concomitant use of selegiline):

Bibliographic reference	**Adler,C.H., Sethi KD,F.A.U., Hauser RA,F.A.U., Davis TL,F.A.U., Hammerstad JP,F.A.U., Bertoni,J.FAU, Taylor RL FAU - Sanchez-Ramos,, Sanchez-Ramos,J.FAU, O'Brien,C.F., Ropinirole for the treatment of early Parkinson's disease. The Ropinirole Study Group, Neurology, 49, 393-399, 1997**
	<table><tr><td></td><td colspan="2">Ropinirole</td><td colspan="2">Placebo</td></tr><tr><td>Characteristics</td><td>Nonselegiline n=58 n (%)</td><td>Selegiline n=58 n (%)</td><td>Nonselegiline n=64 n (%)</td><td>Selegiline n=61 n (%)</td></tr><tr><td>Mean age (years) (SD)</td><td>64.9(9.8)</td><td>59.1(10.6)</td><td>65.9(10.3)</td><td>61.6(10.6)</td></tr><tr><td>Mean duration of disease (months) (SD)</td><td>18.8(19.7)</td><td>30.4(19.7)</td><td>18.2(17.8)</td><td>27.5(19.8)</td></tr><tr><td colspan="5">Hoehn & Yahr stage:</td></tr><tr><td>I & I.5</td><td>14(24.1)</td><td>18(31)</td><td>19(29.7)</td><td>18(29.5)</td></tr><tr><td>II & II.5</td><td>35(60.4)</td><td>35(60.3)</td><td>35(54.7)</td><td>38(62.3)</td></tr><tr><td>III</td><td>9(15.5)</td><td>5(8.6)</td><td>10(15.6)</td><td>5(8.2)</td></tr><tr><td>Mean UPDRS III (SD)</td><td>19.1(8.2)</td><td>16.7(9.2)</td><td>17.6(7.7)</td><td>17.7(8.6)</td></tr></table>
Interventions	Ropinirole: Starting dose of 0.25 mg tid, which was titrated upward at weekly intervals until an optimal therapeutic response was achieved (minimum dose was 1.5 mg tid and maximum dose was 8 mg tid). Patients were maintained at their optimal dose level for the remainder or the study.
Primary outcomes	• UPDRS III • Adverse events
Secondary outcomes	Number (%) of patients with: • ≥30% reduction in the UPDRS III (responders) • scores of 1 (very much improved) or 2 (much improved) on the CGI global improvement item • no sufficient symptomatic benefit, thereby requiring the initiation of L-dopa therapy
Results	The mean ± SD UPDRS motor examination score in all ropinirole-treated patients improved from 17.9 ± 8.8 at baseline to 13.4 ± 9.5 at endpoint. There was a statistically significant improvement of 24% in the UPDRS motor examination score in the ropinirole treated arm compared with placebo (P<0.001). The placebo group experienced a 3% worsening in the UPDRS motor examination score (17.7 ±9.5 at baseline to 17.9 ±10.5 at endpoint).

Bibliographic reference	Adler,C.H., Sethi KD,F.A.U., Hauser RA,F.A.U., Davis TL,F.A.U., Hammerstad JP,F.A.U., Bertoni,J.FAU, Taylor RL FAU - Sanchez-Ramos,, Sanchez-Ramos,J.FAU, O'Brien,C.F., Ropinirole for the treatment of early Parkinson's disease. The Ropinirole Study Group, Neurology, 49, 393-399, 1997

Results were similar in the patients receiving selegiline compared with patients not receiving selegiline.

Adverse experiences occurring in ≥10% patients and withdrawals due to those adverse experiences:

	Incidence n (%)		Withdrawal n (%)	
Adverse event	Ropinirole n=116	Placebo n=125	Ropinirole n=116	Placebo n=125
Nausea	61(52.6)	27(21.6)	8(6.9)	2(1.6)
Dizziness	42(36.2)	23(18.4)	5(4.3)	2(1.2)
Somnolence	42(36.2)	6(4.8)	2(1.7)	0(0)
Headache	20(17.2)	19(15.2)	1(0.9)	3(2.4)
Upper respiratory tract infection	17(14.7)	18(14.4)	0(0)	0(0)
Insomnia	13(11.2)	13(10.4)	0(0)	1(0.8)
Constipation	12(10.3)	8(6.4)	0(0)	0(0)
Syncope	12(10.3)	2(1.6)	1(0.9)	0(0)

Overall Risk of Bias

1. Has an appropriate method of randomisation been used? Yes
2. Was there adequate concealment of allocation? Unclear
3. Were the groups comparable at baseline for all major confounding/prognostic factors? Yes
4. Did the comparison groups receive the same care apart from interventions studied? Unclear
5. Were participants receiving care kept blind to treatment allocation? Yes
6. Were the individuals administering care kept blind to treatment allocation? Unclear
7. Were groups comparable with respect to availability of outcome data and for how many participants were no outcome data available? Yes
8. Did the study have an appropriate length of follow up? Yes
9. Did the study use a precise definition of outcome? Yes

Bibliographic reference	**Adler,C.H., Sethi KD,F.A.U., Hauser RA,F.A.U., Davis TL,F.A.U., Hammerstad JP,F.A.U., Bertoni,J.FAU, Taylor RL FAU - Sanchez-Ramos,, Sanchez-Ramos,J.FAU, O'Brien,C.F., Ropinirole for the treatment of early Parkinson's disease. The Ropinirole Study Group, Neurology, 49, 393-399, 1997**
	10. Was a valid and reliable method used to determine that outcome? Yes 11. Were investigators kept blind to participant's exposure to the intervention? Unclear 12. Were investigators kept blind to other important confounding and prognostic factors? Unclear

Bibliographic reference	**Hubble,J.P., Koller WC,F.A.U., Cutler NR,F.A.U., Sramek JJ,F.A.U., Friedman,J.FAU, Goetz,C.FAU, Ranhosky,A.FAU, Korts,D.FAU, Elvin,A., Pramipexole in patients with early Parkinson's disease, Clin Neuropharmacol., 18, 338-347, 1995**
Country/ies where the study was carried out	US
Study type	Four-centre randomised, parallel-group trial
Aim of the study	To evaluate the safety and efficacy of pramipexole on the motor disabilities of subjects with early PD who were not receiving levodopa treatment.
Study dates	Study dates: Not reported Study duration: 9 weeks
Source of funding	Boehringer Ingelheim Pharmaceuticals
Sample size	In total: n=55; Pramipexole n=28; Placebo n=27
Inclusion criteria	• 21 years of age or older • Had a diagnosis of early idiopathic PD (stages I-III by the Modified Hoehn and Yahr scale) • Treatment with anticholinergic agent was permitted, but no other antiparkinsonian medications were taken.
Exclusion criteria	Patients with evidence of atypical parkinsonian syndromes, clinically significant cardiac, vascular, or cerebrovascular disease, or other unstable medical condition
Details	There were no significant differences in demographic measures between the pramipexole and the placebo groups.

Characteristics	Pramipexole n=28	Placebo n=27	Total n=55
Mean age (yrs) SD	63.5(12.3)	63(8.8)	63.3(10.6)
Mean duration of disease (yrs) SD	2.1(2.5)	2.4(2.4)	2.3(2.5)

Bibliographic reference	**Hubble,J.P., Koller WC,F.A.U., Cutler NR,F.A.U., Sramek JJ,F.A.U., Friedman,J.FAU, Goetz,C.FAU, Ranhosky,A.FAU, Korts,D.FAU, Elvin,A., Pramipexole in patients with early Parkinson's disease, Clin Neuropharmacol., 18, 338-347, 1995**
	<table><tr><td>Mean UPDRS II</td><td>10.94</td><td>10.46 (n=25)</td><td>-</td></tr><tr><td>Mean UPDRS III</td><td>26.47</td><td>27.43 (n=25)</td><td>-</td></tr></table> All subjects received selegiline (10 mg/d) but were not treated with levodopa.
Interventions	Intervention: Selegiline 5mg bid + Pramipexole with a starting dose of 0.10mg three times daily, this was uptitrated over 6 weeks to either the maximum tolerated dose level or a maximum of 1.5mg three times daily (ascending dose schedule: 0.25, 0.5, 0.75, 1.0, 1.25 or 1.5mg three times daily). The maintenance dose interval of the trial lasted 3 weeks and was followed by a dose reduction phase during which the daily dosage was decreased by one dose level each day. Placebo: Selegiline 5mg bid
Primary outcomes	• Mean change in score UPDRS II and III comparing baseline with final maintenance visit • Adverse events
Secondary outcomes	Mean change in score from baseline to the average score of the 3 week maintenance period for UPDRS II and III
Results	Change in mean UPDRS II from baseline to maintenance average: Pramipexole (n=28): -4.84 Placebo (n=23): -2.29 Change in mean UPDRS III from baseline to maintenance average: Pramipexole (n=28): -11.96 Placebo (n=23): -8.15 Common treatment-related adverse events: <table><tr><td></td><td>No. of subjects (%)</td><td></td></tr><tr><td>Adverse events</td><td>Pramipexole n=28</td><td>Placebo n=27</td></tr><tr><td>Total with any adverse event</td><td>28 (100%)</td><td>27 (100%)</td></tr><tr><td>Asymptomatic orthostatic HTN</td><td>28 (100%)</td><td>27 (100%)</td></tr></table>

Bibliographic reference	**Hubble,J.P., Koller WC,F.A.U., Cutler NR,F.A.U., Sramek JJ,F.A.U., Friedman,J.FAU, Goetz,C.FAU, Ranhosky,A.FAU, Korts,D.FAU, Elvin,A., Pramipexole in patients with early Parkinson's disease, Clin Neuropharmacol., 18, 338-347, 1995**

Symptomatic orthostatic HTN	7 (25%)	5 (18.5%)
Dry mouth	3 (10.7%)	0
Dizziness	12 (42.9%)	8 (29.6%)
Headache	9 (32.1%)	6 (22.2%)
Nausea	6 (21.4%)	4 (14.8%)
Insomnia	6 (21.4%)	3 (11.1%)
Hallucination	4 (14.3%)	0
Vision abnormal	3 (10.7%)	0

Overall Risk of Bias

1. Has an appropriate method of randomisation been used? Yes
2. Was there adequate concealment of allocation? Unclear
3. Were the groups comparable at baseline for all major confounding/prognostic factors? Yes
4. Did the comparison groups receive the same care apart from interventions studied? Yes
5. Were participants receiving care kept blind to treatment allocation? Yes
6. Were the individuals administering care kept blind to treatment allocation? Unclear
7. Were groups comparable with respect to availability of outcome data and for how many participants were no outcome data available? Unclear
8. Did the study have an appropriate length of follow up? Yes
9. Did the study use a precise definition of outcome? Yes
10. Was a valid and reliable method used to determine that outcome? Yes
11. Were investigators kept blind to participant’s exposure to the intervention? Unclear
12. Were investigators kept blind to other important confounding and prognostic factors? Unclear

Bibliographic reference	**Viallet,Francois., Pitel,S., Lancrenon,Sylvie, Blin,Olivier, Evaluation of the safety and tolerability of rasagiline in the treatment of the early stages of Parkinson’s disease, Current Medical Research and Opinion, 29, 23-31, 2013**

<table>
<tr><th>Bibliographic reference</th><th>Viallet,Francois., Pitel,S., Lancrenon,Sylvie, Blin,Olivier, Evaluation of the safety and tolerability of rasagiline in the treatment of the early stages of Parkinson’s disease, Current Medical Research and Opinion, 29, 23-31, 2013</th></tr>
<tr><td>Country/ies where the study was carried out</td><td>France</td></tr>
<tr><td>Study type</td><td>Phase IV, multi-centre, randomised, double-blind study</td></tr>
<tr><td>Aim of the study</td><td>To assess the safety and tolerability of rasagiline compared with the dopaminergic agonist pramipexole in the treatment of early PD.</td></tr>
<tr><td>Study dates</td><td>Study dates: Not reported
Study duration: 15 weeks</td></tr>
<tr><td>Source of funding</td><td>Qualissima, who received a grant from Lundbeck</td></tr>
<tr><td>Sample size</td><td>In total: n=109; Rasagiline: n=53; Pramipexole: n=56</td></tr>
<tr><td>Inclusion criteria</td><td>• Patients must have never received anti-Parkinson treatment or had received levodopa for less than 12 weeks at a dose less than 200mg; patients discontinued all anti-Parkinson treatment other than the study drugs as part of the study protocol
• Patients on dopamine agonist other than pramipexole were also eligible for inclusion, on the condition that the patient was still in the titration phase at the time of inclusion, or that treatment was given for less than 6 weeks and had not been given for 2 weeks prior the time of inclusion.</td></tr>
<tr><td>Exclusion criteria</td><td>• Breastfeeding women
• Women of a childbearing age without sterilization or a reliable birth control method
• Patients with liver disease
• Patients with a concomitant disease considered to be significant by the investigator
• Patients treated with cerebral stimulation and patients with skin lesions not assessed by a dermatologist
• Patients treated with fluoxetine during the 5 weeks preceding inclusion
• Patients treated with fluvoxamine, pethidine, selegiline or any other MAOB-I during the 2 weeks preceding inclusion
• Patients likely to receive dextromethorphan or a sympathomimetic drug during the trial</td></tr>
<tr><td>Details</td><td>The two treatment groups were similar at baseline with regard to demographic variables, with the exception of pain/cramp, which was significantly higher in the pramipexole group (p=0.027).

<table><tr><td>Characteristic</td><td>Rasagiline n=53</td><td>Pramipexole n=56</td></tr><tr><td>Age (yrs)</td><td>63.2±7.3</td><td>62.1±6.2</td></tr></table></td></tr>
</table>

<table>
<tr><th>Bibliographic reference</th><th>Viallet,Francois., Pitel,S., Lancrenon,Sylvie, Blin,Olivier, Evaluation of the safety and tolerability of rasagiline in the treatment of the early stages of Parkinson’s disease, Current Medical Research and Opinion, 29, 23-31, 2013</th></tr>
<tr><td></td><td>
<table>
<tr><td>Time since diagnosis (months)</td><td>2.5±3.8</td><td>4.3±7.3</td></tr>
<tr><td>EQ-5D original score</td><td>0.75±0.15</td><td>0.67±0.25</td></tr>
<tr><td>EQ-VAS score</td><td>67.48±16.07</td><td>63.74±18.76</td></tr>
<tr><td>PDQ-8</td><td>5.45±3.67</td><td>6.99±5.23</td></tr>
<tr><td>Tremor</td><td>7(13.2%)</td><td>13(23.2%)</td></tr>
<tr><td>Akinetic hypertonicity</td><td>12(22.6%</td><td>15(26.8%)</td></tr>
</table>
</td></tr>
<tr><td>Interventions</td><td>Rasagiline: 1mg once daily (plus placebo twice daily)
Pramipexole: three times daily, titrated from 0.375mg/day in week 1, 0.75mg/day in week 2 to a maximum dose of 1.5mg/day in week 3</td></tr>
<tr><td>Primary outcomes</td><td>Adverse events</td></tr>
<tr><td>Secondary outcomes</td><td>• The percentage of patients with sleep disorders
• The Epworth Sleepiness Scale
• Clinical Global Impression of Improvement scale
• Patient Global Impression of Improvement scale
• PDQ-8 scale
• EQ-5D
• EQ-VAS</td></tr>
<tr><td>Results</td><td>Adverse events reported by the physician in >5% of patients in either treatment group:
<table>
<tr><td>Adverse event</td><td>Rasagiline n=53</td><td>Pramipexole n=56</td></tr>
<tr><td>Total patients with an AE</td><td>36 (67.9%)</td><td>43 (76%)</td></tr>
<tr><td>Central nervous system</td><td>4 (7.5%)</td><td>6 (10.7%)</td></tr>
<tr><td>Malaise, syncope</td><td>2 (3.8%)</td><td>6 (10.7%)</td></tr>
<tr><td>Nervous system</td><td>11 (20.8%)</td><td>13 (23.2%)</td></tr>
</table>
</td></tr>
</table>

Bibliographic reference	Viallet,Francois., Pitel,S., Lancrenon,Sylvie, Blin,Olivier, Evaluation of the safety and tolerability of rasagiline in the treatment of the early stages of Parkinson’s disease, Current Medical Research and Opinion, 29, 23-31, 2013		
	Headache	3 (5.7%)	5 (8.9%)
	Tingling	4 (7.5%)	2 (3.6%)
	Dizziness	3 (5.7%)	5 (8.9%)
	Gastrointestinal system	15 (28.3%)	27 (48.2%)
	Gastralgia	4 (7.5%)	5 (8.9%)
	Constipation	2 (3.8%)	4 (7.1%)
	Nausea, vomiting	5 (9.4%)	16 (28.6%)
	Musculo-skeletal system	12 (22.6%)	14 (25%)
	Joint pain, join disease	7 (13.2%)	12 (21.4%)
	Muscle cramps	5 (9.4%)	2 (3.6%)
	Cardiovascular system	4 (7.5%)	6 (10.7%)
	Orthostatic hypotension	1 (1.9%)	3 (5.4%)
	General disorders	11 (20.8%)	11 (19.6%)
	Weight loss	3 (5.7%)	0
	Weight gain	2 (3.8%)	4 (7.1%)
	Weakness	6 (11.3%)	7 (12.5%)
	Psychiatric disorder	18 (34%)	31 (55.4%)
	Anxiety, irritability, emotionality	4 (7.5%)	4 (7.1%)
	Mood swings	5 (9.4%)	4 (7.1%)
	Hallucinations	0	3 (5.4%)
	Sleep disorders, daytime sleepiness	9 (17%)	20 (35.7%)

Bibliographic reference	Viallet,Francois., Pitel,S., Lancrenon,Sylvie, Blin,Olivier, Evaluation of the safety and tolerability of rasagiline in the treatment of the early stages of Parkinson's disease, Current Medical Research and Opinion, 29, 23-31, 2013
	<table><tr><td>Respiratory Tract</td><td>5 (9.4%)</td><td>5 (8.9%)</td></tr><tr><td>Respiratory infection</td><td>4 (7.5%)</td><td>5 (8.9%)</td></tr><tr><td>Skin, hair and nails</td><td>8 (15.1%)</td><td>2 (3.6%)</td></tr><tr><td>Itching</td><td>3 (5.7%)</td><td>0</td></tr><tr><td>Rash</td><td>5 (9.4%)</td><td>0</td></tr></table>All values reported as n (%). Patients could have more than one type of AE. There were no significant differences in quality of life outcomes between the treatments.
Overall Risk of Bias	1. Has an appropriate method of randomisation been used? Yes 2. Was there adequate concealment of allocation? Yes 3. Were the groups comparable at baseline for all major confounding/prognostic factors? No 4. Did the comparison groups receive the same care apart from interventions studied? Unclear 5. Were participants receiving care kept blind to treatment allocation? Yes 6. Were the individuals administering care kept blind to treatment allocation? Yes 7. Were groups comparable with respect to availability of outcome data and for how many participants were no outcome data available? Yes 8. Did the study have an appropriate length of follow up? Yes 9. Did the study use a precise definition of outcome? Yes 10. Was a valid and reliable method used to determine that outcome? Yes 11. Were investigators kept blind to participant's exposure to the intervention? Yes 12. Were investigators kept blind to other important confounding and prognostic factors? Unclear

Bibliographic reference	Olanow,C.Warren, Rascol,Olivier, Hauser,Robert, Feigin,Paul D., Jankovic,Joseph, Lang,Anthony, Langston,William, Melamed,Eldad, Poewe,Werner, Stocchi,Fabrizio, Tolosa,Eduardo, A Double-Blind, Delayed-Start Trial of Rasagiline in Parkinson's Disease, New England Journal of Medicine, 361, 1268-1278, 2009
Country/ies where the study was carried out	14 countries (not reported)

<table>
<tr><th>Bibliographic reference</th><td>Olanow,C.Warren, Rascol,Olivier, Hauser,Robert, Feigin,Paul D., Jankovic,Joseph, Lang,Anthony, Langston,William, Melamed,Eldad, Poewe,Werner, Stocchi,Fabrizio, Tolosa,Eduardo, A Double-Blind, Delayed-Start Trial of Rasagiline in Parkinson's Disease, New England Journal of Medicine, 361, 1268-1278, 2009</td></tr>
<tr><td>Study type</td><td>Double-blind, placebo-controlled, multicentre trial that used a delayed-start design.</td></tr>
<tr><td>Aim of the study</td><td>To examine the potential disease-modifying effects of rasagiline in Parkinson's disease.</td></tr>
<tr><td>Study dates</td><td>Study dates: Not reported.
Study duration: 72 weeks (18 months); 36 weeks per phase (2 phases in total).</td></tr>
<tr><td>Source of funding</td><td>Teva Pharmaceutical Industries</td></tr>
<tr><td>Sample size</td><td>In total: n=1176; Rasagiline 1mg/d n=288, Rasagiline 2mg/d n=293; Placebo n=595 (two placebo groups were combined for analysis).</td></tr>
<tr><td>Inclusion criteria</td><td>• Men and women between 30 and 80 years of age who were not currently receiving treatment for PD.
• The presence of at least two of the three cardinal features of the disease (resting tremor, bradykinesia, or rigidity); if resting tremor was not present, subjects had to have unilateral onset of symptoms.</td></tr>
<tr><td>Exclusion criteria</td><td>• Subjects who had previously received any antiparkinsonian medication for more than 3 weeks or who had received rasagiline or selegiline (at any dose) or coenzyme Q10 (at more than 300mg per day) within the previous 120 days.
• Disease duration of more than 18 months since diagnosis.
• A Hoehn and Yahr stage of 3 or higher and atypical or secondary Parkinsonism.</td></tr>
<tr><td>Details</td><td>The study was performed in 2 phases. In phase 1, subjects were randomly assigned to one of four study groups: rasagiline at a dose of either 1 mg or 2 mg per day (the early-start groups) or corresponding placebo. In phase 2, subjects in the early-start groups continued to receive their assigned treatment while subject in the placebo groups switched to rasagiline at a dose of 1 mg or 2 mg per day (the delayed-start groups). No concomitant anti-parkinsonian medication was permitted.

Baseline characteristics:
<table>
<tr><td rowspan="2">Characteristics</td><td colspan="2">Rasagiline 1 mg/d</td><td colspan="2">Rasagiline 2 mg/d</td></tr>
<tr><td>Placebo n=300</td><td>Treatment n=288</td><td>Placebo n=295</td><td>Treatment n=293</td></tr>
<tr><td>Age (yr)</td><td>61.9±9.7</td><td>62.4±9.7</td><td>62.4±9.7</td><td>62.3±9.6</td></tr>
<tr><td>Time since diagnosis (mo)</td><td>4.3±4.6</td><td>4.6±4.7</td><td>4.6±4.6</td><td>4.6±4.6</td></tr>
<tr><td>UPDRS Total (range, 0-176)</td><td>20.2±8.8</td><td>20.6±8.4</td><td>19.9±8.1</td><td>20.8±8.8</td></tr>
</table></td></tr>
</table>

Bibliographic reference	**Olanow,C.Warren, Rascol,Olivier, Hauser,Robert, Feigin,Paul D., Jankovic,Joseph, Lang,Anthony, Langston,William, Melamed,Eldad, Poewe,Werner, Stocchi,Fabrizio, Tolosa,Eduardo, A Double-Blind, Delayed-Start Trial of Rasagiline in Parkinson's Disease, New England Journal of Medicine, 361, 1268-1278, 2009**
	UPDRS Motor (range, 0-108) | 14.0±6.5 | 14.5±6.3 | 13.8±6.1 | 14.6±6.5 UPDRS ADL (range, 0-52) | 5.3±3.1 | 5.1±2.8 | 5.1±2.9 | 5.4±3.1 Hoehn and Yahr stage (range, 1-5) | 1.51±0.5 | 1.53±0.5 | 1.46±0.5 | 1.52±0.5 Visits and measurements were performed at baseline and at weeks 4, 12, 24, 36, 42, 48, 54, 60, 66, and 72. Only available data of interest from Phase 1 (rasagiline vs. placebo) is extracted for analysis.
Interventions	Rasagiline: 1mg or 2mg per day.
Primary outcomes	The change in total UPDRS points per week between the rasagiline groups (1mg pr 2 mg per day).
Secondary outcomes	• The change in total UPDRS score between baseline and week 72 in the early-start and delayed-start rasagiline groups (1mg or 2 mg per day). • Adverse events
Results	Study discontinuation after Phase 1: 1 mg placebo (n=300) - In total n=30 withdrew: 11 withdrew consent, 7 had AE, 10 needed other treatment for PD, 2 had other reason. 1 mg rasagiline (n=288) - In total 15 withdrew: 3 withdrew consent, 9 had AE, 2 needed other treatment for PD, 1 had other reason. 2 mg placebo (n=295) - In total 20 withdrew: 6 withdrew consent, 10 had AE, 2 needed other treatment for PD, 2 had other reason. 2 mg rasagiline (n=293) - In total 20 withdrew: 3 withdrew consent, 11 had AE, 2 needed other treatment for PD, 4 had other reason. Event | Placebo* | Rasagiline 1 mg/d (no./total no. (%) | Rasagiline 2 mg/d In >5% of subjects in any group, placebo phase Headache | 37/595 (6.2) | 14/288 (4.9) | 15/293 (5.1) Back pain | 32/595 (5.4) | 14/288 (4.9) | 15/293 (5.1)

Bibliographic reference	Olanow,C.Warren, Rascol,Olivier, Hauser,Robert, Feigin,Paul D., Jankovic,Joseph, Lang,Anthony, Langston,William, Melamed,Eldad, Poewe,Werner, Stocchi,Fabrizio, Tolosa,Eduardo, A Double-Blind, Delayed-Start Trial of Rasagiline in Parkinson's Disease, New England Journal of Medicine, 361, 1268-1278, 2009			
	Depression	36/595 (6.1)	10/288 (3.5)	10/293 (3.4)
	Nasopharyngitis	32/595 (5.4)	12/288 (4.2)	11/293 (3.8)
	Anxiety	34/595 (5.7)	10/288 (3.5)	9/293 (3.1)
	Fatigue	17/595 (2.9)	17/288 (5.9)	10/293 (3.4)
	Related to dopaminergic therapy, placebo phase			
	Nausea or vomiting	23/595 (3.9)	12/288 (4.2)	8/293 (2.7)
	Hypertension	23/595 (3.9)	5/288 (1.7)	7/293 (2.4)
	Somnolence	9/595 (1.5)	2/288 (0.7)	4/293 (1.4)
	Orthostatic hypotension	5/595 (0.8)	2/288 (0.7)	1/293 (0.3)
	Hallucination	1/595 (0.2)	0/288	1/293 (0.3)
	Hypersexuality	0/595	0/288	1/293 (0.3)
Overall Risk of Bias	1. Has an appropriate method of randomisation been used? Yes 2. Was there adequate concealment of allocation? Unclear 3. Were the groups comparable at baseline for all major confounding/prognostic factors? Yes 4. Did the comparison groups receive the same care apart from interventions studied? Unclear 5. Were participants receiving care kept blind to treatment allocation? Unclear* 6. Were the individuals administering care kept blind to treatment allocation? Unclear* 7. Were groups comparable with respect to availability of outcome data and for how many participants were no outcome data available? Yes but <10% dropout rate and no ITT analysis for efficacy outcomes 8. Did the study have an appropriate length of follow up? Yes (9 months) 9. Did the study use a precise definition of outcome? Yes 10. Was a valid and reliable method used to determine that outcome? Yes 11. Were investigators kept blind to participant's exposure to the intervention? Unclear* 12. Were investigators kept blind to other important confounding and prognostic factors? Unclear*			

Bibliographic reference	Olanow,C.Warren, Rascol,Olivier, Hauser,Robert, Feigin,Paul D., Jankovic,Joseph, Lang,Anthony, Langston,William, Melamed,Eldad, Poewe,Werner, Stocchi,Fabrizio, Tolosa,Eduardo, A Double-Blind, Delayed-Start Trial of Rasagiline in Parkinson's Disease, New England Journal of Medicine, 361, 1268-1278, 2009
	*Level of blinding unclear - no details beyond description of study as "randomised, double-blind, placebo-controlled trial". Overall there is likely high risk of bias.

Bibliographic reference	Fahn,S., The Parkinson Study Group, Does levodopa slow or hasten the rate of progression of Parkinson's disease?, Journal of Neurology, 252, 37-42, 2005
Country/ies where the study was carried out	US and Canada
Study type	A multi-centre, parallel-group, double-blind, dosage-ranging randomised, controlled clinical trial.
Aim of the study	To determine whether levodopa treatment affects the rate of progression of PD.
Study dates	Study dates: Not reported. Study duration: 40 weeks, withdrawal of treatment for 2 weeks.
Source of funding	Grants from the National Institute of Neurological Disorders and Stroke, the Department of Defence, and the General Clinical Research Centre of the National Centre for Research Resources, National Institutes of Health. Tablets were provided by Teva Pharmaceuticals (Israel).
Sample size	In total n=361 37.5/150 mg/d carbidopa-levodopa n=92 75/300 mg/d carbidopa-levodopa n=88 150/600 mg/d carbidopa-levodopa n=91 Placebo n=90
Inclusion criteria	• Subjects 30 years of age or older. • Had received a diagnosis of PD within the past 2 years. • Had a rating on modified Hoehn and Yahr scale of less than stage 3 and were not likely to require therapy for symptoms of the disease within 9 months after enrolment in the study.
Exclusion criteria	• Subjects who were receiving antiparkinsonian medication. • Had been exposed to levodopa or to any dopamine agonist for more than 14 days. • Had an identifiable cause of Parkinsonism, or had a tremor in any limb that was given a score of 3 or more on UPDRS,

<table>
<tr><th>Bibliographic reference</th><th>Fahn,S., The Parkinson Study Group, Does levodopa slow or hasten the rate of progression of Parkinson's disease?, Journal of Neurology, 252, 37-42, 2005</th></tr>
<tr><td></td><td>freezing of gait, loss of postural reflexes, major depression or dementia.</td></tr>
<tr><td>Details</td><td>The demographic and clinical characteristics of the subjects in the treatment groups were similar at baseline*:
<table>
<tr><td>Characteristics</td><td>Placebo</td><td>Carbidopa/Levodopa 37.5/ 150 mg/d</td><td>Carbidopa/Levodopa 75/300 mg/d</td><td>Carbidopa/Levodopa 150/600 mg/d</td></tr>
<tr><td>Age (yr)</td><td>64.9±10.3</td><td>64.5±10.6</td><td>63.8±12.1</td><td>65.2±10.7</td></tr>
<tr><td>Duration of disease (mo)</td><td>5.3±5.6</td><td>5.7±6.1</td><td>7.6±7.5</td><td>6.0±6.1</td></tr>
<tr><td>UPDRS Total</td><td>27.7±12</td><td>27.2±12.6</td><td>27.5±11.6</td><td>29.4±13.9</td></tr>
<tr><td>UPDRS Mental</td><td>1.4±1.5</td><td>1.3±1.5</td><td>1.3±1.4</td><td>1.4±1.6</td></tr>
<tr><td>UPDRS ADL</td><td>7.5±3.6</td><td>7.5±4.4</td><td>7.3±3.7</td><td>7.6±4.0</td></tr>
<tr><td>UPDRS Motor</td><td>18.8±8.9</td><td>18.6±9.1</td><td>18.9±8.8</td><td>20.5±10.8</td></tr>
<tr><td>Hoehn-Yahr</td><td>1.8±0.5</td><td>1.9±0.6</td><td>1.8±0.5</td><td>1.9±0.6</td></tr>
</table>
*Plus-minus values are means ± SD.</td></tr>
<tr><td>Interventions</td><td>Carbidopa-levodopa: 37.5/150 mg/d, 75/300 mg/d, or 150/600 mg/d.
The daily dose was built up gradually over a 9-week period. After 40 weeks of treatment, the patients underwent a 3-day taper of their medications, followed by a 2-week washout period during which they received no treatment for their PD.</td></tr>
<tr><td>Primary outcomes</td><td>Change in the total UPDRS score between baseline and after the washout period at week 42.</td></tr>
<tr><td>Secondary outcomes</td><td>• Changes in the scores on the UPDRS ADL, Motor, and Mental components between baseline and week 42.
• Adverse events and dropouts.</td></tr>
<tr><td>Results</td><td>Dopaminergic AEs:
<table>
<tr><td>Adverse events</td><td>Placebo (n=90)</td><td>Levodopa 150 mg/d (n=92)</td><td>Levodopa 300 mg/d (n=88)</td><td>Levodopa 600 mg/d (n=91)</td></tr>
<tr><td>Dyskinesia</td><td>3(3.3)</td><td>3(3.3)</td><td>2(2.3)</td><td>15(16.5)</td></tr>
<tr><td>Dystonia</td><td>19(21.1)</td><td>19(20.1)</td><td>14(15.9)</td><td>12(13.2)</td></tr>
<tr><td>Freezing</td><td>13(14.4)</td><td>9(9.8)</td><td>6(6.8)</td><td>5(5.5)</td></tr>
</table></td></tr>
</table>

On-off	3(3.3)	1(1.1)	0(0.0)	3(3.3)
Wearing-off	12(13.3)	15(16.3)	16(18.2)	27(29.7)

Data shown are the number of subjects (with percentages in parentheses) affected with each adverse event.

Study discontinuation:
Placebo (n=90) - 20 did not complete trial:
13 worsening symptoms, 3 AEs, 2 withdrew, 1 lost to follow-up, 1 other.
150 mg/d Carbidopa-Levodopa (n=92) - 14 did not complete trial:
5 worsening symptoms, 2 AEs, 2 withdrew, 3 lost to follow-up, 2 other.
300 mg/d Carbidopa-Levodopa (n=88) - 6 did not complete trial:
1 worsening symptoms, 2 AEs, 2 withdrew, 1 other.
600 mg/d Carbidopa-Levodopa (n=91) - 10 did not complete trial:
2 worsening symptoms, 1 AEs, 3 withdrew, 2 lost to follow-up, 2 other.

Changes in the scores on the UPDRS between baseline and week 42*:

Characteristics	Placebo (n=70)	Levodopa 150 mg/d (n=78)	Levodopa 300 mg/d (n=82)	Levodopa 600 mg/d (n=81)
Evaluation by primary rater				
UPDRS Total	27.7±12	27.2±12.6	27.5±11.6	29.4±13.9
UPDRS Mental	1.4±1.5	1.3±1.5	1.3±1.4	1.4±1.6
UPDRS ADL	7.5±3.6	7.5±4.4	7.3±3.7	7.6±4.0
UPDRS Motor	18.8±8.9	18.6±9.1	18.9±8.8	20.5±10.8
Evaluation by treating investigator				
UPDRS Total	9.0±10.4	4.0±8.2	4.0±8.4	1.0±9.9
UPDRS Mental	0.5±1.3	-0.1±1.4	0.1±1.4	0.1±1.6

Bibliographic reference	**Fahn,S., The Parkinson Study Group, Does levodopa slow or hasten the rate of progression of Parkinson's disease?, Journal of Neurology, 252, 37-42, 2005**
	<table><tr><td>UPDRS ADL</td><td>2.5±4.0</td><td>0.8±3.1</td><td>1.0±2.8</td><td>0.3±3.5</td></tr><tr><td>UPDRS Motor</td><td>6.0±7.6</td><td>3.2±6.4</td><td>3.0±6.4</td><td>0.6±7.7</td></tr></table> *Plus–minus values are means ±SD. On the UPDRS, higher scores indicate greater severity of impairment. Negative numbers indicate improvement as compared with the baseline value. The total score on the UPDRS showed a significant trend toward the reduction of symptoms with higher doses of levodopa in the evaluations by both the primary raters and the treating investigators. The post hoc analysis showed that the effects of all three doses of levodopa differed significantly from the effect of the placebo. Scores on the UPDRS showed that treatment effects were significant for activities of daily living (ADL) and the motor component but not for the mental component.
Overall Risk of Bias	1. Has an appropriate method of randomisation been used? Unclear 2. Was there adequate concealment of allocation? Unclear 3. Were the groups comparable at baseline for all major confounding/prognostic factors? Yes 4. Did the comparison groups receive the same care apart from interventions studied? Unclear 5. Were participants receiving care kept blind to treatment allocation? Unclear* 6. Were the individuals administering care kept blind to treatment allocation? Unclear* 7. Were groups comparable with respect to availability of outcome data and for how many participants were no outcome data available? No >10% dropout rate and no ITT analysis for efficacy outcomes 8. Did the study have an appropriate length of follow up? Yes (10 months) 9. Did the study use a precise definition of outcome? Yes 10. Was a valid and reliable method used to determine that outcome? Yes 11. Were investigators kept blind to participant's exposure to the intervention? Unclear* 12. Were investigators kept blind to other important confounding and prognostic factors? Unclear* *Level of blinding unclear - no details beyond description of study as "randomised, double-blind, placebo-controlled trial". Overall there is likely high risk of bias.

Bibliographic reference	**Thomas,A., Bonanni,L.FAU, Di Iorio,A.FAU, Varanese S FAU - Anzellotti,Francesca, Anzellotti,F.FAU, D'Andreagiovanni,A.FAU, Stocchi,F.FAU, Onofrj,M., End-of-dose deterioration in non ergolinic dopamine agonist monotherapy of Parkinson's disease, Journal of Neurology, 253, 1633-1639, 2006**

<table>
<tr><th>Bibliographic reference</th><th>Thomas,A., Bonanni,L.FAU, Di Iorio,A.FAU, Varanese S FAU - Anzellotti,Francesca, Anzellotti,F.FAU, D'Andreagiovanni,A.FAU, Stocchi,F.FAU, Onofrj,M., End-of-dose deterioration in non ergolinic dopamine agonist monotherapy of Parkinson's disease, Journal of Neurology, 253, 1633-1639, 2006</th></tr>
<tr><td>Country/ies where the study was carried out</td><td>Italy</td></tr>
<tr><td>Study type</td><td>Prospective, randomised trial</td></tr>
<tr><td>Aim of the study</td><td>To assess, in a blind protocol, the appearance of end of dose motor deterioration and eventually to understand whether WO patients had different characteristics from non-fluctuating patients (i.e. age or motor score at onset, progression of motor deterioration, need for higher drug doses).</td></tr>
<tr><td>Study dates</td><td>Study dates: Not reported.
Study duration: 24 months</td></tr>
<tr><td>Source of funding</td><td>Not reported.</td></tr>
<tr><td>Sample size</td><td>In total n=60; Ropinirole n=30 and Pramipexole n=30.</td></tr>
<tr><td>Inclusion criteria</td><td>• Patients with idiopathic PD according to the UK Brain Bank criteria.
• Patients with "de novo" PD (had never received any antiparkinsonian treatment)
• Patients were in Hoehn and Yahr stages I-II.</td></tr>
<tr><td>Exclusion criteria</td><td>Not reported.</td></tr>
<tr><td>Details</td><td>Demographic, at admission, of patients completing the study:
<table>
<tr><td>Characteristic</td><td>Total</td><td>Ropinirole (n=27)</td><td>Pramipexole (n=25)</td></tr>
<tr><td>Mean age ± SD (yr)</td><td>56.2±2.0</td><td>55.3±2.0</td><td>57.1±2.0</td></tr>
<tr><td>Hoehn/Yahr stage ± SD</td><td>1.5±0.6</td><td>1.4±0.6</td><td>1.6±0.6</td></tr>
<tr><td>UPDRS baseline ± SD</td><td>16.3±4.6</td><td>16.7±4.6</td><td>15.8±4.7</td></tr>
</table></td></tr>
<tr><td>Interventions</td><td>Ropinirole: start dose from 3-5 mg per day to 15 mg per day during the first 3 months.
Pramipexole: start dose from 0.7 mg per day to 2.1 mg per day during the first 3 months.

In the following year, daily doses could be further increased (maximum recommended dose: ropinirole to 24 mg and pramipexole to 4.2 mg) according to patients' needs.</td></tr>
<tr><td>Primary outcomes</td><td>Self-reported "wearing-off" periods confirmed by a 30% worsening in the UPDRS score during the 5 hours after a DA dose. The primary end point was therefore checked twice (subjective reports and objective observations).</td></tr>
</table>

Bibliographic reference	**Thomas,A., Bonanni,L.FAU, Di Iorio,A.FAU, Varanese S FAU - Anzellotti,Francesca, Anzellotti,F.FAU, D'Andreagiovanni,A.FAU, Stocchi,F.FAU, Onofrj,M., End-of-dose deterioration in non ergolinic dopamine agonist monotherapy of Parkinson's disease, Journal of Neurology, 253, 1633-1639, 2006**
Secondary outcomes	• Difference between fluctuating and non-fluctuating patients (WO vs. no-WO) in UPDRS scores and Hoehn and Yahr stages at the onset of the study. • Change of UPDRS scores over time and at the end of the study.
Results	Study end-point was reached in 18-21 months. UPDRS motor scores through the study:

		Baseline	3 months	12 months	Last assessment before end of study	End of study
Ropinirole						
17 patients	No WO*	15.3±4.1	7.7±3.1	10.2±2.8	10.8±2.5	12.5±3.0
10 patients	WO**	19.1±4.5	8.9±1.3	11.7±1.8	12.0±2.7	12.7±2.7
Pramipexole						
17 patients	No WO*	14.9±4.8	6.4±3.3	10.4±2.5	11.2±2.9	11.9±2.4
10 patients	WO**	17.8±4.0	7.8±2.4	11.5±1.9	11.7±2.0	12.0±2.1

*No WO=Patients unaffected by motor fluctuation during the 24-months study

Trial discontinuation due to adverse events:
Ropinirole n=3
Pramipexole n=5
In total 6 patients dropped out during the titration period because of gastrointestinal side effects and 2 patients dropped off because of excessive day time somnolence.

Of the 27 patients of the ropinirole group: 3 patients at 14 months, 1 patient at 15 and 3 patients at 16-17 moths reported transient worsening of motor symptoms, but the subjective self-assessment of worsening was not confirmed by UPDRS motor subscale scores, being lower than the 30% cut-off.
**WO="wearing-off" patients

Bibliographic reference	**Thomas,A., Bonanni,L.FAU, Di Iorio,A.FAU, Varanese S FAU - Anzellotti,Francesca, Anzellotti,F.FAU, D'Andreagiovanni,A.FAU, Stocchi,F.FAU, Onofrj,M., End-of-dose deterioration in non ergolinic dopamine agonist monotherapy of Parkinson's disease, Journal of Neurology, 253, 1633-1639, 2006**
Overall Risk of Bias	1. Has an appropriate method of randomisation been used? Yes 2. Was there adequate concealment of allocation? Unclear 3. Were the groups comparable at baseline for all major confounding/prognostic factors? Yes 4. Did the comparison groups receive the same care apart from interventions studied? Unclear 5. Were participants receiving care kept blind to treatment allocation? Unclear* 6. Were the individuals administering care kept blind to treatment allocation? No 7. Were groups comparable with respect to availability of outcome data and for how many participants were no outcome data available? Yes but >10% dropout rate and no ITT analysis 8. Did the study have an appropriate length of follow up? Yes (2 years) 9. Did the study use a precise definition of outcome? Yes 10. Was a valid and reliable method used to determine that outcome? Yes 11. Were investigators kept blind to participant's exposure to the intervention? Unclear* 12. Were investigators kept blind to other important confounding and prognostic factors? Unclear* *Level of blinding unclear - no details beyond description of study as "randomised, double-blind, placebo-controlled trial". Overall there is likely high risk of bias.

Bibliographic reference	**Palhågen,S., Heinonen EH,F.A.U., Hagglund,J.FAU, Kaugesaar,T.FAU, Kontants,H.FAU, Maki-Ikola,O.FAU, Palm,R.FAU, Turunen,J., Selegiline delays the onset of disability in de novo parkinsonian patients. Swedish Parkinson Study Group, Neurology, 51, 520-525, 1998**
Country/ies where the study was carried out	Sweden
Study type	Randomised, placebo-controlled, double-blind, parallel trial.
Aim of the study	To investigate the effect of selegiline first as monotherapy and then in combination with levodopa in the early phase of PD.
Study dates	Study dates: Not reported. Study duration: Until levodopa therapy became necessary.
Source of funding	Not reported

Bibliographic reference	**Palhågen,S., Heinonen EH,F.A.U., Hagglund,J.FAU, Kaugesaar,T.FAU, Kontants,H.FAU, Maki-Ikola,O.FAU, Palm,R.FAU, Turunen,J., Selegiline delays the onset of disability in de novo parkinsonian patients. Swedish Parkinson Study Group, Neurology, 51, 520-525, 1998**
Sample size	In total n=157; Selegiline n=81; Placebo n=76.
Inclusion criteria	Patients with previously untreated idiopathic PD.
Exclusion criteria	Patients with: • Secondary parkinsonism • Unstable pulmonary, hepatic, renal or gastrointestinal disease • Major psychiatric disorders • Severe infections, • Duodenal or gastric ulcer • Evidence of severe heart disease • Malignant disease (except for basal cell carcinoma of the skin or treated in situ carcinoma of uterine cervix) • Narrow-angle glaucoma • Age more than 75 years (at inclusion) • Known allergy to selegiline or quinine (included in the placebo tablets) • Women who were pregnant or who were breast-feeding • Patients who abused drugs or alcohol • Patients who could not be followed at the intervals determined by the study protocol.
Details	Patients were assigned randomly to receive either selegiline 10 mg or matching placebo given in the morning. This regimen continued until the patient reached a level of clinical disability sufficient to warrant the initiation of levodopa therapy. At this time, the experimental treatments were withdrawn for 8 weeks, and investigators and patients were kept unaware of the treatment assignments. Thereafter, levodopa therapy was started and the study drug reinstituted. The study continued in a double-blind manner for 7 years or until the patient needed additional dopaminergic therapy. There were no statistically significant differences in the demographic data of the patients and the duration and severity of the disease between the groups. However, the mean UPDRS total score at inclusion as well as the subscores of UPDRS, the VAS tremor and the VAS motor dysfunction subscales were slightly worse in the selegiline group than the placebo group at baseline. Parameter measured | Selegiline group* | Placebo group*

Bibliographic reference	**Palhågen,S., Heinonen EH,F.A.U., Hagglund,J.FAU, Kaugesaar,T.FAU, Kontants,H.FAU, Maki-Ikola,O.FAU, Palm,R.FAU, Turunen,J., Selegiline delays the onset of disability in de novo parkinsonian patients. Swedish Parkinson Study Group, Neurology, 51, 520-525, 1998**
	<table><tr><td>Age (y)</td><td>63.3±9.1</td><td>64.2±6.6</td></tr><tr><td>Duration of PD before the study (y)</td><td>1.9±1.6</td><td>1.9±1.3</td></tr><tr><td>UPDRS motor</td><td>16.7±8.8</td><td>14.2±8.6</td></tr><tr><td>Schwab and England ADL</td><td>89.1±6.2</td><td>89.6±6.4</td></tr><tr><td>Hoehn and Yahr stage (%)</td><td>Stage 1: 45(55.6) Stage 2: 34(42.0) Stage 3: 2(2.4)</td><td>Stage 1: 49(64.5) Stage 2: 24(31.6) Stage 3: 3(3.9)</td></tr></table> *Mean ± SD values are given.
Interventions	Selegiline: 10mg given in the morning.
Primary outcomes	The time until the initiation of levodopa therapy became necessary, as judged by parkinsonian disability, ADL or employability.
Secondary outcomes	Assessment of progression of clinical disability using the following scales: • UPDRS • Schwab and England Activities of Daily Living • Hoehn and Yahr staging • Tremor and motor dysfunction assessed by the Visual Analogue Scale (VAS) • MMSE • Hamilton Depression Scale
Results	<table><tr><td rowspan="2">UPDRS</td><td colspan="2">6-Month interval (mean±SD)</td><td colspan="2">12-Month interval (mean±SD)</td></tr><tr><td>Selegiline n=57</td><td>Placebo n=39</td><td>Selegiline n=37</td><td>Placebo n=24</td></tr><tr><td>ADL</td><td>0.0±2.1</td><td>0.9±2.4</td><td>0.5±2.4</td><td>0.8±2.3</td></tr><tr><td>Motor</td><td>-1.5±4.7</td><td>2.5±4.4</td><td>0.7±6.1</td><td>2.6±6.8</td></tr></table> The median time from inclusion until the start of washout (i.e. time to the need for addition of levodopa into the treatment regimen) was 12.7 months (quartile deviation, 9.1 months) in the selegiline group and 8.6 months (quartile deviation, 8.0 months) in the placebo group.

Bibliographic reference	**Palhågen,S., Heinonen EH,F.A.U., Hagglund,J.FAU, Kaugesaar,T.FAU, Kontants,H.FAU, Maki-Ikola,O.FAU, Palm,R.FAU, Turunen,J., Selegiline delays the onset of disability in de novo parkinsonian patients. Swedish Parkinson Study Group, Neurology, 51, 520-525, 1998**
	In total 16 patients (9 in the selegiline group and 7 in the placebo group) discontinued the trial prematurely. The reasons for this were the following: 6 patients did not want to continue to study; one was lost to follow-up; 5 patients discontinued due to AEs (prostate cancer, leukaemia/lymphoma, psychiatric AEs, laboratory abnormality, broken femur, and deterioration of parkinsonian syndrome with an urgent need for levodopa therapy); and 4 patients due to protocol violation.
Overall Risk of Bias	1. Has an appropriate method of randomisation been used? Unclear 2. Was there adequate concealment of allocation? Unclear 3. Were the groups comparable at baseline for all major confounding/prognostic factors? No, treatment group had slightly worse scores in UPDRS Total and Motor subscale + VAS tremor and motor dysfunction subscales 4. Did the comparison groups receive the same care apart from interventions studied? Unclear 5. Were participants receiving care kept blind to treatment allocation? Unclear* 6. Were the individuals administering care kept blind to treatment allocation? Unclear* 7. Were groups comparable with respect to availability of outcome data and for how many participants were no outcome data available? No >10% dropout rate and no ITT analysis 8. Did the study have an appropriate length of follow up? Yes (12 months) 9. Did the study use a precise definition of outcome? Yes 10. Was a valid and reliable method used to determine that outcome? Yes 11. Were investigators kept blind to participant's exposure to the intervention? Unclear* 12. Were investigators kept blind to other important confounding and prognostic factors? Unclear* *Level of blinding unclear - no details beyond description of study as "randomised, double-blind, placebo-controlled trial". Overall there is likely high risk of bias.

Bibliographic reference	**Schapira,Anthony HV, McDermott,Michael P., Barone,Paolo, Comella,Cynthia L., Albrecht,Stefan, Hsu,Helen H., Massey,Daniel H., Mizuno,Yoshikuni, Poewe,Werner, Rascol,Olivier, Marek,Kenneth, Pramipexole in patients with early Parkinson's disease (PROUD): a randomised delayed-start trial, Lancet Neurology, 12, 747-755, 2013**
Country/ies where the study was carried out	Austria, Finland, France, Germany, Italy, Japan, Spain, Sweden, the UK and the USA.
Study type	Randomised, double-blind, placebo-controlled, delayed-start trial.

Bibliographic reference	**Schapira,Anthony HV, McDermott,Michael P., Barone,Paolo, Comella,Cynthia L., Albrecht,Stefan, Hsu,Helen H., Massey,Daniel H., Mizuno,Yoshikuni, Poewe,Werner, Rascol,Olivier, Marek,Kenneth, Pramipexole in patients with early Parkinson's disease (PROUD): a randomised delayed-start trial, Lancet Neurology, 12, 747-755, 2013**
Aim of the study	To identify whether early versus delayed pramipexole initiation has clinical and neuroimaging benefits in patients with PD.
Study dates	Study dates: Not reported. Study duration: 15 months (6-9 months for period 1, pramipexole vs. placebo).
Source of funding	Boehringer Ingelheim GmbH.
Sample size	In total n=535; Pramipexole n=261, Placebo n=274.
Inclusion criteria	• Patients between 30-79 years of age. • Had idiopathic PD characterised by bradykinesia plus at least two further PD signs (resting tremor, rigidity, or asymmetry). • Were at modified Hoehn and Yahr stage 1 or 2. • Were diagnosed within the preceding 2 years and were judged unlikely to need symptomatic treatment for at least the next 6 months, preferably 9 months.
Exclusion criteria	• Patients who were currently using PD drugs. • Had used antipsychotic drugs within the preceding 6 months, or had any clinically significant abnormalities unrelated to PD in physical findings or laboratory values. • Patients with medical or psychiatric disorders capable of interfering with study participation or the interpretation of study data and those with any history of psychosis, dementia, or major or seasonal depression.
Details	The month 9 visit (which could be conducted as much as 3 months earlier) marked the transition from study period 1 (double-blind pramipexole vs. placebo) to period 2 (double-blind early vs. delayed pramipexole). Any patients needing additional PD treatment discontinued the study. Only available data of interest from period 1 (pramipexole vs. placebo) is extracted.
Interventions	Pramipexole: up-titrated over 4 weeks from 0.125 mg three times a day to 0.25 mg three times a day, and finally 0.5mg three times a day.
Primary outcomes	15-month change from baseline in total score on the UPDRS, as assessed by an independent rater (period 2 full-analysis set).
Secondary outcomes	• Total score on the UPDRS assessed at 3, 6, 9, and 15 months by a study investigator. • CGI-I and CGI-S applied at 15 months by the independent raters. • AEs.
Results	Study discontinuation during period 1: Pramipexole (n=261) - 40 discontinued:

Bibliographic reference	**Schapira,Anthony HV, McDermott,Michael P., Barone,Paolo, Comella,Cynthia L., Albrecht,Stefan, Hsu,Helen H., Massey,Daniel H., Mizuno,Yoshikuni, Poewe,Werner, Rascol,Olivier, Marek,Kenneth, Pramipexole in patients with early Parkinson's disease (PROUD): a randomised delayed-start trial, Lancet Neurology, 12, 747-755, 2013**

25 AEs (including 1 with worsened PD), 4 inadequate efficacy, 5 non-compliance, 5 withdrew consent, 1 other.

Placebo (n=274) - 60 discontinued:

26 AEs (including 15 worsened PD), 12 inadequate efficacy, 3 non-compliance, 16 withdrew consent, 2 lost to follow-up, 1 other.

Adverse events during period 1:

AEs	Pramipexole (n=261)	Placebo (n=274)
Any AEs	194(74%)	196(72%)
Severe AEs	34(13%)	23(8%)
Serious AEs	17(7%)	18(7%)
Study-drug-related AEs	113(43%)	72(26%)
AEs leading to discontinuation	25(10%)	26(9%)
Nausea*	54(21%)	21(8%)
Dizziness*	29(11%)	24(9%)
Somnolence*	28(11%)	9(3%)
Fatigue*	26(10%)	21(8%)
Headache*	17(7%)	23(8%)
Insomnia*	17(7%)	8(3%)
Peripheral oedema*	17(7%)	4(1%)
Constipation*	16(6%)	20(7%)
Nasopharyngitis*	16(6%)	15(5%)
Back pain*	14(5%)	13(5%)

Bibliographic reference	Schapira,Anthony HV, McDermott,Michael P., Barone,Paolo, Comella,Cynthia L., Albrecht,Stefan, Hsu,Helen H., Massey,Daniel H., Mizuno,Yoshikuni, Poewe,Werner, Rascol,Olivier, Marek,Kenneth, Pramipexole in patients with early Parkinson's disease (PROUD): a randomised delayed-start trial, Lancet Neurology, 12, 747-755, 2013

Depression*	13(5%)	12(4%)
Hallucination*	13(5%)	3(1%)
Diarrhoea*	8(3%)	15(5%)

*Event types reported in ≥5% of patients in either group.

Adjusted mean changes (SE) on UPDRS ADL and UPDRS Motor at 9 months (as measured by study investigator):

UPDRS	Early Pramipexole* n=210 or 211***	Delayed Pramipexole (Placebo)** n=200
ADL	0.4(0.2)	1.5(0.2)
Motor	-0.6(0.5)	2.7(0.5)

*Includes 45 patients who entered period 2 before 9 months.
**Includes 65 patients who entered period 2 before 9 months.
***Depending on time point.

Changes on quality of life scales and BDI (data are median change (IQR) or mean change (SE) at 9 months:

	Early Pramipexole* n=208-211***	Delayed Pramipexole (Placebo)** n=197-200***
PDQ-39 total score	-0.5(-3.6 to 2.0)	1.4(-2.2 to 5.0)
EQ-5D total score	0.0(-0.03 to 0.09)	0.0(-0.14 to 0.0)
EQVAS	0.0(-5.5 to 5.0)	-0.5(-10.0 to 5.0)
BDI, adjusted for baseline and country	-1.1(0.3)	0.3(0.3)

*Includes 45 patients who entered period 2 before 9 months.
**Includes 65 patients who entered period 2 before 9 months.
***Depending on time point.

Bibliographic reference	**Schapira,Anthony HV, McDermott,Michael P., Barone,Paolo, Comella,Cynthia L., Albrecht,Stefan, Hsu,Helen H., Massey,Daniel H., Mizuno,Yoshikuni, Poewe,Werner, Rascol,Olivier, Marek,Kenneth, Pramipexole in patients with early Parkinson's disease (PROUD): a randomised delayed-start trial, Lancet Neurology, 12, 747-755, 2013**
Overall Risk of Bias	1. Has an appropriate method of randomisation been used? Yes 2. Was there adequate concealment of allocation? Yes 3. Were the groups comparable at baseline for all major confounding/prognostic factors? Yes 4. Did the comparison groups receive the same care apart from interventions studied? Unclear 5. Were participants receiving care kept blind to treatment allocation? Yes 6. Were the individuals administering care kept blind to treatment allocation? Yes 7. Were groups comparable with respect to availability of outcome data and for how many participants were no outcome data available? No (apart from AEs), approximately 20% and 30% in treatment and placebo group, respectively, moved into phase 2 of the study prematurely, which involved a delayed pramipexole dosing in the placebo group + no ITT analysis. 8. Did the study have an appropriate length of follow up? Yes (9 months) 9. Did the study use a precise definition of outcome? Yes 10. Was a valid and reliable method used to determine that outcome? Yes 11. Were investigators kept blind to participant's exposure to the intervention? Yes 12. Were investigators kept blind to other important confounding and prognostic factors? Unclear* *Level of blinding unclear - no details beyond description of study as "randomised, double-blind, placebo-controlled trial". Overall there is likely low risk of bias.

Bibliographic reference	**Barone, P., Santangelo, G., Morgante, L., Onofrj, M., Meco, G., Abbruzzese, G., Bonuccelli, U., Cossu, G., Pezzoli, G., Stanzione, P., Lopiano, L., Antonini, A., Tinazzi, M., A randomised clinical trial to evaluate the effects of rasagiline on depressive symptoms in non-demented Parkinson's disease patients, 22, 1184-1191, 2015**
Country/ies where the study was carried out	Italy
Study type	Randomised, double-blind, placebo-controlled trial
Aim of the study	To evaluate the effects of rasagiline on depressive symptoms and cognition in non-demented PD patients with depressive symptoms.
Study dates	Study dates: 5 March 2010 to 2 July 2012

<table>
<tr><th>Bibliographic reference</th><th>Barone, P., Santangelo, G., Morgante, L., Onofrj, M., Meco, G., Abbruzzese, G., Bonuccelli, U., Cossu, G., Pezzoli, G., Stanzione, P., Lopiano, L., Antonini, A., Tinazzi, M., A randomised clinical trial to evaluate the effects of rasagiline on depressive symptoms in non-demented Parkinson's disease patients, 22, 1184-1191, 2015</th></tr>
<tr><td></td><td>Study duration: 12 weeks</td></tr>
<tr><td>Source of funding</td><td>Lundbeck Italia SpA</td></tr>
<tr><td>Sample size</td><td>In total: n=123; Rasagiline: n=58; Placebo: n=65</td></tr>
<tr><td>Inclusion criteria</td><td>• A diagnosis of PD (at least 2 of 3 cardinal signs - resting tremor, bradykinesia, rigidity - and no other known or suspected cause of parkinsonism)
• Age ≥40 and <80 years
• Hoehn and Yahr stage ≥1 and ≤3 (on treatment)
• A beck Depression Inventory score ≥15
• Should have been under stable (4 weeks prior to baseline) dopaminergic treatment.
• All stable doses of dopamine receptor agonists, levodopa/carbidopa, levodopa/benserazide and COMT inhibitors were permitted.</td></tr>
<tr><td>Exclusion criteria</td><td>• Patients with motor fluctuations (the presence of which may be associated with mood)
• Previous deep brain stimulation surgery
• MMSE <26
• A diagnosis of current or a history of major depressive episode according to the Diagnostic and Statistical Manual of Mental Disorders, 4th Edition, Text Revision (DSM-IV-TR) criteria within 1 year before recruitment into the study
• The presence of psychotic symptoms
• Treatment with antidepressants, antipsychotics, cholinesterase inhibitors, memantine, amantadine, anticholinergics, and the hypnotics zaleplon, zolpidem, zopiclone and antihistamines were not allowed and must have been discontinued at least 4 weeks prior to study initiation
• Patients currently or previously treated with selegiline (<90 days prior to randomisation) were also excluded</td></tr>
<tr><td>Details</td><td>Patient demographics and baseline PD characteristics were well matched, with no significant difference between groups:
<table>
<tr><td>Characteristics</td><td>Rasagiline n=58</td><td>Placebo n=65</td></tr>
<tr><td>Age (yrs), mean±SD</td><td>66.0±4.33</td><td>66.1±4.49</td></tr>
<tr><td>Duration of PD (yrs), mean ±SD</td><td>3.7±3.17</td><td>4.8±3.78</td></tr>
</table></td></tr>
</table>

Bibliographic reference	**Barone, P., Santangelo, G., Morgante, L., Onofrj, M., Meco, G., Abbruzzese, G., Bonuccelli, U., Cossu, G., Pezzoli, G., Stanzione, P., Lopiano, L., Antonini, A., Tinazzi, M., A randomised clinical trial to evaluate the effects of rasagiline on depressive symptoms in non-demented Parkinson's disease patients, 22, 1184-1191, 2015**
	Hoehn & Yahr staging, n (%) I: 9(15.5%) / 9(13.8%) I.5: 12(20.7%) / 11(16.9%) II: 29(50%) / 34(52.3%) II.5: 5(8.6%) / 6(9.2%) III: 3(5.2%) / 5(7.7%)
Interventions	Rasagiline: 1 mg daily
Primary outcomes	The change from baseline to week 12 in cognitive function as assessed by the Beck Depression Inventory total score
Secondary outcomes	• Change from baseline to week 12 in cognitive function as assessed by a comprehensive neuropsychological battery • PDQ-39 scores • Apathy Scale scores • UPDRS subscores
Results	Treatment with rasagiline significantly improved UPDRS II scores versus placebo at week 12 (marginal means difference ± SE: rasagiline -1.37±0.35 vs. placebo 0.06±0.32. P=0.003). There was no significant effect of treatment on UPDRS III subscores (rasagiline -0.88±0.56 vs. placebo 0.42±0.51, P=0.090). There was no significant effect of treatment on PDQ-39 total scores (rasagiline -6.28±2.24 vs. placebo -0.73±2.06, P=0.074. However, a post hoc analysis of PDQ-39 domains found significant differences favouring rasagiline in PDQ-mobility scores (P=0.007) and PDQ-cognition scores (P=0.026). A total of 15 vs. 17 patients (rasagiline vs. placebo group, respectively) reported at least one treatment-emergent adverse event (TEAE); most TEAEs were mild or moderate. No TEAE was reported more than two times in either group. Two patients in the rasagiline group (radius fracture; melanocytic nevus) and one in the placebo group (polyneuropathy in malignant disease and respiratory disorder) reported a serious TEAE. Four patients in the rasagiline group withdrew due to a TEAE (aggravated dyskinesia, vertigo, left trunk flexion due to PD, nausea) vs. none in the placebo group.
Overall Risk of Bias	1. Has an appropriate method of randomisation been used? Yes

Bibliographic reference	Barone, P., Santangelo, G., Morgante, L., Onofrj, M., Meco, G., Abbruzzese, G., Bonuccelli, U., Cossu, G., Pezzoli, G., Stanzione, P., Lopiano, L., Antonini, A., Tinazzi, M., A randomised clinical trial to evaluate the effects of rasagiline on depressive symptoms in non-demented Parkinson's disease patients, 22, 1184-1191, 2015
	2. Was there adequate concealment of allocation? Yes 3. Were the groups comparable at baseline for all major confounding/prognostic factors? No 4. Did the comparison groups receive the same care apart from interventions studied? Yes 5. Were participants receiving care kept blind to treatment allocation? Yes 6. Were the individuals administering care kept blind to treatment allocation? Yes 7. Were groups comparable with respect to availability of outcome data and for how many participants were no outcome data available? Unclear 8. Did the study have an appropriate length of follow up? Yes 9. Did the study use a precise definition of outcome? Yes 10. Was a valid and reliable method used to determine that outcome? Yes 11. Were investigators kept blind to participant's exposure to the intervention? Yes 12. Were investigators kept blind to other important confounding and prognostic factors? Unclear

Bibliographic reference	Jankovic, Joseph, Watts, Ray L., Martin, Wayne, Boroojerdi, Babak, Transdermal rotigotine: double-blind, placebo-controlled trial in Parkinson disease, 64, 676-82, 2007
Country/ies where the study was carried out	US and Canada
Study type	Randomised, double-blind, multicentre, placebo-controlled study
Aim of the study	To assess the response to the rotigotine transdermal system in patients with early Parkinson disease.
Study dates	Study dates: Not reported Study duration: 24 weeks
Source of funding	Schwarz Pharma Ltd
Sample size	In total: n=277; Rotigotine: n= 181; Placebo: n=96
Inclusion criteria	• 30 years or older with an established diagnosis of idiopathic PD of 5 years' duration or less • With at least 2 of the following cardinal signs, without any other known or suspected causes of parkinsonism: bradykinesia, resting tremor, rigidity and postural instability • UPDRS motor score of at least 10

<table>
<tr><th>Bibliographic reference</th><th>Jankovic, Joseph, Watts, Ray L., Martin, Wayne, Boroojerdi, Babak, Transdermal rotigotine: double-blind, placebo-controlled trial in Parkinson disease, 64, 676-82, 2007</th></tr>
<tr><td></td><td>• Hoehn and Yahr stage of III or less
• MMSE score of 25 or higher
• Patients previously receiving an anticholinergic agent, monoamine oxidase-B inhibitor, or N-methyl-D-aspartate antagonist must have had a stable dose for at least 28 days before study baseline and were required to maintain that dose for the duration of the trial.</td></tr>
<tr><td>Exclusion criteria</td><td>• Patients who had:
• Previous or concurrent therapy with a dopamine agonist or with carbidopa or levodopa within 28 days of the baseline visit
• Carbidopa or levodopa therapy for more than 6 months since diagnosis
• Atypical parkinsonism
• Surgical intervention for PD
• Clinically relevant hepatic, renal, or cardiac dysfunction
• A diagnosis of epilepsy
• A history of seizures as an adult, or stroke or a transient ischemic attack within the last year
• pronounced skin hypersensitivity to adhesive or other transdermal patches or recent unresolved contact dermatitis
• Known intolerance or hypersensitivity to the antiemetic ondansetron
• Pregnancy or were nursing
• Used inadequate birth control methods
• Are receiving central nervous system active therapy unless their pharmacotherapy doses had been stable for at least 28 days before baseline and were likely to remain stable for the duration of the trial</td></tr>
<tr><td>Details</td><td>Baseline characteristics:<table><tr><td>Characteristics</td><td>Rotigotine n=181</td><td>Placebo n=96</td></tr><tr><td>Age (yrs)</td><td>62(10.3)</td><td>64.5(10.7)</td></tr><tr><td>Years since diagnosis</td><td>1.3(1.3)</td><td>1.4(1.3)</td></tr><tr><td>UPDRS II</td><td>8.3(4.6)</td><td>8.7(4.0)</td></tr><tr><td>UPDRS III</td><td>21.6(8.9)</td><td>21.3(8.2)</td></tr></table>Data are given as mean (SD) unless otherwise indicated.</td></tr>
</table>

<table>
<tr><th>Bibliographic reference</th><th>Jankovic, Joseph, Watts, Ray L., Martin, Wayne, Boroojerdi, Babak, Transdermal rotigotine: double-blind, placebo-controlled trial in Parkinson disease, 64, 676-82, 2007</th></tr>
<tr><td>Interventions</td><td>Rotigotine transdermal system: 2, 4, or 6 mg during 24 hours</td></tr>
<tr><td>Primary outcomes</td><td>Percentage of subjects achieving a 20% response or greater (reduction) as assessed with the UPDRS II and III from baseline to the end of the maintenance phase.</td></tr>
<tr><td>Secondary outcomes</td><td>• Effects on subsets of the UPDRS
• Clinical Global Impression Scale rating
• Epworth Sleepiness Scale scores
• Quality of life measures
• Serum prolactin and rotigotine plasma concentration data</td></tr>
<tr><td>Results</td><td>
<table>
<tr><td></td><td>Rotigotine n=177</td><td>Placebo n=96</td><td>P value</td></tr>
<tr><td>Change in UPDRS II score</td><td>-0.39(0.26)</td><td>0.92(0.35)</td><td>0.002</td></tr>
<tr><td>Change in UPDRS III score</td><td>-3.58(0.54)</td><td>0.38(0.73)</td><td>0.001</td></tr>
</table>

Summary of the most common treatment-emergent adverse events with an incidence of 5% or greater:
<table>
<tr><td>Adverse event</td><td>Rotigotine n=181</td><td>Placebo n=96</td></tr>
<tr><td>Application site disorder</td><td>79(44)</td><td>11(11)</td></tr>
<tr><td>Accident, not otherwise specified</td><td>14(8)</td><td>2(2)</td></tr>
<tr><td>Fatigue</td><td>14(8)</td><td>5(5)</td></tr>
<tr><td>Pain</td><td>4(2)</td><td>7(7)</td></tr>
<tr><td>Leg pain</td><td>2(1)</td><td>6(6)</td></tr>
<tr><td>Dizziness</td><td>34(19)</td><td>12(13)</td></tr>
<tr><td>Headache</td><td>29(16)</td><td>9(9)</td></tr>
<tr><td>Tremor</td><td>11(6)</td><td>4(4)</td></tr>
</table>
</td></tr>
</table>

Bibliographic reference	Jankovic, Joseph, Watts, Ray L., Martin, Wayne, Boroojerdi, Babak, Transdermal rotigotine: double-blind, placebo-controlled trial in Parkinson disease, 64, 676-82, 2007

Parkinsonism aggravated	2(1)	5(5)
Nausea	75(41)	16(17)
Vomiting	16(9)	1(1)
Constipation	11(6)	4(4)
Dyspepsia	12(7)	1(1)
Diarrhoea	11(6)	2(2)
Arthralgia	10(6)	6(6)
Back pain	11(6)	3(3)
Skeletal pain	7(4)	6(6)
Somnolence	60(33)	19(20)
Insomnia	17(9)	3(3)
Coughing	9(5)	6(6)
Upper respiratory tract infection	8(4)	7(7)
Sinusitis	7(4)	6(6)
Rash	4(2)	5(5)

Data are given as number (%) of patients.

Overall Risk of Bias

1. Has an appropriate method of randomisation been used? Yes
2. Was there adequate concealment of allocation? Yes
3. Were the groups comparable at baseline for all major confounding/prognostic factors? Unclear
4. Did the comparison groups receive the same care apart from interventions studied? Unclear
5. Were participants receiving care kept blind to treatment allocation? Yes
6. Were the individuals administering care kept blind to treatment allocation? Yes
7. Were groups comparable with respect to availability of outcome data and for how many participants were no outcome

Bibliographic reference	Jankovic, Joseph, Watts, Ray L., Martin, Wayne, Boroojerdi, Babak, Transdermal rotigotine: double-blind, placebo-controlled trial in Parkinson disease, 64, 676-82, 2007
	data available? Yes 8. Did the study have an appropriate length of follow up? Yes 9. Did the study use a precise definition of outcome? Yes 10. Was a valid and reliable method used to determine that outcome? Yes 11. Were investigators kept blind to participant's exposure to the intervention? Yes 12. Were investigators kept blind to other important confounding and prognostic factors? Unclear

Bibliographic reference	Mizuno,Y., Nomoto,M., Kondo,T., Hasegawa,K., Murata,M., Takeuchi,M., Ikeda,J., Tomida,T., Hattori,N., Transdermal rotigotine in early stage Parkinson's disease: A randomised, double-blind, placebo-controlled trial, Movement Disorders.28 (10) (pp 1447-1450), 2013.Date of Publication: September 2013., 1447-1450, 2013
Country/ies where the study was carried out	Japan
Study type	Randomised, double-blind, placebo-controlled trial
Aim of the study	To determine the safety and efficacy of transdermal rotigotine in patients with early stage Parkinson's disease in Japan
Study dates	Study dates: September 2007 to April 2009 Study duration: 12 weeks
Source of funding	Otsuka Pharmaceutical Company Ltd
Sample size	In total: n=180; Rotigotine: n= 90; Placebo: n=90
Inclusion criteria	• Clinical diagnosis of PD • Patients with early PD and had no concomitant treatment with L-dopa • Age range 30-79 years • Hoehn & Yahr scale scores from I to III • UPDRS II and III scores ≥10 • Patients who had received L-dopa before study entry had to discontinue L-dopa at least 2 weeks before the date of the first treatment administration.
Exclusion criteria	Patients with any of the following symptoms: • Psychiatric symptoms, including confusion, hallucination, delusion, excitation, delirium, and abnormal behaviour at entry

<table>
<tr><th>Bibliographic reference</th><td>Mizuno,Y., Nomoto,M., Kondo,T., Hasegawa,K., Murata,M., Takeuchi,M., Ikeda,J., Tomida,T., Hattori,N., Transdermal rotigotine in early stage Parkinson's disease: A randomised, double-blind, placebo-controlled trial, Movement Disorders.28 (10) (pp 1447-1450), 2013.Date of Publication: September 2013., 1447-1450, 2013</td></tr>
<tr><td></td><td>• Symptomatic orthostatic hypotension
• A history of epilepsy and/or convulsion
• Complications or history of serious cardiac disease and/or arrhythmia
• Severe renal or hepatic impairments
• History of deep brain stimulation
• Dementia
• Had received L-dopa for >6 months by the time of acquisition of informed consent or other drugs that could possibly affect PD symptoms from at least 4 weeks before the date of first treatment</td></tr>
<tr><td>Details</td><td>Baseline characteristics:
<table>
<tr><td>Characteristics</td><td>Rotigotine n=88</td><td>Placebo n=88</td></tr>
<tr><td>Age (yrs): <65</td><td>36(40.9)</td><td>35(39.8)</td></tr>
<tr><td>Age (yrs): ≥65</td><td>52(59.1)</td><td>53(60.2)</td></tr>
<tr><td>Duration of disease (yrs)</td><td>2.0±1.8</td><td>1.8±1.9</td></tr>
<tr><td>UPDRS II</td><td>6.8±3.9</td><td>7.4±3.8</td></tr>
<tr><td>UPDRS III</td><td>20.2±9.2</td><td>20.8±9.5</td></tr>
<tr><td>Hoehn & Yahr stage (average)</td><td>2.1±0.7</td><td>2.2±0.6</td></tr>
</table>
Values are given in means ±SD or no. of patients (%).</td></tr>
<tr><td>Interventions</td><td>Rotigotine: Starting dose of 2mg/24 hrs with a weekly increment of 2mg/24 hrs, up to a maximum of 16mg/24 hrs during the 8 week titration period.</td></tr>
<tr><td>Primary outcomes</td><td>The change in UPDRS II and III scores from baseline to the end of treatment</td></tr>
<tr><td>Secondary outcomes</td><td>Not reported</td></tr>
<tr><td>Results</td><td>Change in UPDRS III scores from baseline to end of trial differed significantly (95% CI, -5.6 to -1.6; P<0.001) between groups, but changes in UPDRS II scores did not (95% CI, -1.6 to 0.2; P=0.125).

Seventy-eight patients (86.7%) in the rotigotine group and 65 patients (72.2%) in the placebo group experienced at least 1</td></tr>
</table>

Bibliographic reference	Mizuno,Y., Nomoto,M., Kondo,T., Hasegawa,K., Murata,M., Takeuchi,M., Ikeda,J., Tomida,T., Hattori,N., Transdermal rotigotine in early stage Parkinson's disease: A randomised, double-blind, placebo-controlled trial, Movement Disorders.28 (10) (pp 1447-1450), 2013.Date of Publication: September 2013., 1447-1450, 2013
	TEAE, and most were mild or moderate in intensity.
Overall Risk of Bias	1. Has an appropriate method of randomisation been used? Yes 2. Was there adequate concealment of allocation? Yes 3. Were the groups comparable at baseline for all major confounding/prognostic factors? Yes 4. Did the comparison groups receive the same care apart from interventions studied? Unclear 5. Were participants receiving care kept blind to treatment allocation? Yes 6. Were the individuals administering care kept blind to treatment allocation? Yes 7. Were groups comparable with respect to availability of outcome data and for how many participants were no outcome data available? Yes 8. Did the study have an appropriate length of follow up? Yes 9. Did the study use a precise definition of outcome? Yes 10. Was a valid and reliable method used to determine that outcome? Yes 11. Were investigators kept blind to participant's exposure to the intervention? Yes 12. Were investigators kept blind to other important confounding and prognostic factors? Unclear

Bibliographic reference	Pahwa, R., Lyons, K. E., Hauser, R. A., Fahn, S., Jankovic, J., Pourcher, E., Hsu, A., O'Connell, M., Kell, S., Gupta, S., Randomised trial of IPX066, carbidopa/levodopa extended release, in early Parkinson's disease, 20, 142-8, 2014
Country/ies where the study was carried out	US and Canada
Study type	Multicentre, multination, randomised, double-blind, parallel-group, fixed-dose, placebo-controlled trial
Aim of the study	To assess the efficacy, safety, and impact on quality of life of IPX066 (carbidopa/levodopa) in the treatment of levodopa-naive Parkinson's disease patients.
Study dates	Study dates: April 2009 to October 2010 Study duration: 30 weeks
Source of funding	Impax Pharmaceuticals
Sample size	In total: n=381; IPX066 145mg n=87; IPX066 245 n=104; IPX066 n=98; Placebo n=92
Inclusion criteria	• ≥30 years of age at PD diagnosis

<table>
<tr><th>Bibliographic reference</th><th>Pahwa, R., Lyons, K. E., Hauser, R. A., Fahn, S., Jankovic, J., Pourcher, E., Hsu, A., O'Connell, M., Kell, S., Gupta, S., Randomised trial of IPX066, carbidopa/levodopa extended release, in early Parkinson's disease, 20, 142-8, 2014</th></tr>
<tr><td></td><td>• Hoehn & Yahr stage I-III
• Levodopa- naive (not exposed to levodopa for >30 days and not within 4 weeks enrolment)
• MMSE ≥26
• Sum of UPDRS II and III scores ≥18
• Anticholinergics, amantadine, MAO-B inhibitors were allowed but dosages had to be stable for 4 weeks prior to study entry and unchanged throughout the study.</td></tr>
<tr><td>Exclusion criteria</td><td>• Atypical parkinsonism
• Females pregnant or breastfeeding
• Previous neurosurgical treatment for PD
• Use of nonselective MAO inhibitors
• Use of dopamine agonists within 30 days of screening
• Inability to tolerate a placebo regimen
• A history of sensitivity to carbidopa/levodopa
• Treatment of psychosis with any antipsychotic
• Seizure
• Active or prior medical conditions that would interfere with levodopa absorption
• Narrow-angle glaucoma
• Malignant melanoma
• Suspicious undiagnosed skin lesion
• Myocardial infarction with residual problems
• Abnormal kidney function
• Abnormal liver transaminase values</td></tr>
<tr><td>Details</td><td>There were no significant differences at baseline measures across treatment groups and patients who used non-levodopa PD medications were equally distributed across treatment groups.
<table>
<tr><td>Characteristics</td><td>Placebo n=92</td><td>145mg TID n=87</td><td>245mg TID n=104</td><td>390mg TID n=98</td></tr>
<tr><td>Age (yrs)</td><td>65.4(9.4)</td><td>63.8(9.8)</td><td>65.2(9.7)</td><td>64.8(9.3)</td></tr>
<tr><td>Total PDQ-39 score</td><td>24.0(15.5)</td><td>26.0(16.9)</td><td>25.2(18.6)</td><td>25.1(17.1)</td></tr>
</table></td></tr>
</table>

Bibliographic reference	Pahwa, R., Lyons, K. E., Hauser, R. A., Fahn, S., Jankovic, J., Pourcher, E., Hsu, A., O'Connell, M., Kell, S., Gupta, S., Randomised trial of IPX066, carbidopa/levodopa extended release, in early Parkinson's disease, 20, 142-8, 2014

Age at PD onset (yrs)	63.7(9.5)	61.7(10.7)	63.6(10.4)	63.0(9.4)
Duration of PD (yrs)	1.8(2.0)	2.3(3.1)	1.8(1.8)	2.0(2.3)
UPDRS II	10.2(4.5)	10.3(4.5)	10.3(5.0)	9.9(4.4)
UPDRS III	26.1(9.0)	25.9(10.6)	27.8(12.2)	26.4(10.1)
Hoehn & Yahr stage:				
I (n,%)	7(7.6)	6(6.9)	13(12.5)	14(14.3)
II (n,%)	69(75.0)	62(71.3)	65(62.5)	62(63.3)
III (n,%)	16(17.4)	19(21.8)	26(25.0)	22(22.4)

Interventions

IPX066 (carbidopa/levodopa) was initiated at 95 mg three times daily for all 3 intervention groups and then uptitrated to the maximum dose for each group:
Group 1: IPX066 36.25/145 mg tid
Group 2: IPX066 61.25/245 mg tid
Group 3: IPX066 97.5/390 mg tid
Group 4: Placebo tid

Primary outcomes

- Change in UPDRS II + III from baseline to end of the study
- Adverse events

Secondary outcomes

- Change from baseline in UPDRS I + II + III and in individual UPDRS subscores at the end of the study
- Total PDQ-39
- Patient Global Impression of Improvement
- Clinical Global Impression of Improvement

Results

Change from baseline to end of study (p-values and 95% confidence intervals compared with placebo):

Efficacy measure	Placebo n=90	145mg TID n=82	245mg TID n=99	390mg TID n=90
UPDRS II	0.2	-2.8; P<0.0001; (-4.4, -1.4)	-3.1; P<0.0001; (-4.7, -1.9)	-3.9; P<0.0001; (-5.5, -2.6)
UPDRS III	-0.7	-8.9; P<0.0001; (-11.2, -5.2)	-9.8; P<0.0001; (-11.9, -6.2)	-11.0; P<0.0001; (-13.2, -7.4)

Bibliographic reference	Pahwa, R., Lyons, K. E., Hauser, R. A., Fahn, S., Jankovic, J., Pourcher, E., Hsu, A., O'Connell, M., Kell, S., Gupta, S., Randomised trial of IPX066, carbidopa/levodopa extended release, in early Parkinson's disease, 20, 142-8, 2014

PDQ-39 total	0.6	-4.4; P<0.02; (9.3, -0.6)	-3.8; P<0.03; (-8.5, -0.3)	-6.0; P<0.0008; (-10.7, -2.3)

Adverse events occurring in greater than 5% of any treatment group:

Adverse event	Placebo n=92	145mg n=87	245mg n=104	390mg n=98	Total n=381
Nausea	8(8.7)	12(13.8)	20(19.2)	20(20.4)	60(15.7)
Headache	10(10.9)	6(6.9)	13(12.5)	17(17.3)	46(12.1)
Dizziness	5(5.4)	8(9.2)	20(19.2)	12(12.2)	45(11.8)
Insomnia	3(3.3)	2(2.3)	9(8.7)	6(6.1)	20(5.2)
Abnormal dreams	0	2(2.3)	6(5.8)	5(5.1)	13(3.4)
Dry mouth	1(1.1)	3(3.4)	2(1.9)	7(7.1)	13(3.4)
Vomiting	3(3.3)	2(2.3)	2(1.9)	5(5.1)	12(3.1)
Constipation	1(1.1)	2(2.3)	6(5.8)	2(2.0)	11(2.9)
Dyskinesia	0	2(2.3)	4(3.8)	5(5.1)	11(2.9)
Anxiety	0	2(2.3)	3(2.9)	5(5.1)	10(2.6)
Depression	5(5.4)	1(1.1)	2(1.9)	2(2.0)	10(2.6)
Orthostatic hypotension	1(1.1)	1(1.1)	1(1.0)	5(5.1)	8(2.1)

Overall Risk of Bias

1. Has an appropriate method of randomisation been used? Yes
2. Was there adequate concealment of allocation? Yes
3. Were the groups comparable at baseline for all major confounding/prognostic factors? Yes
4. Did the comparison groups receive the same care apart from interventions studied? Yes
5. Were participants receiving care kept blind to treatment allocation? Yes
6. Were the individuals administering care kept blind to treatment allocation? Yes
7. Were groups comparable with respect to availability of outcome data and for how many participants were no outcome

Bibliographic reference	Pahwa, R., Lyons, K. E., Hauser, R. A., Fahn, S., Jankovic, J., Pourcher, E., Hsu, A., O'Connell, M., Kell, S., Gupta, S., Randomised trial of IPX066, carbidopa/levodopa extended release, in early Parkinson's disease, 20, 142-8, 2014
	data available? Unclear 8. Did the study have an appropriate length of follow up? Yes 9. Did the study use a precise definition of outcome? Yes 10. Was a valid and reliable method used to determine that outcome? Yes 11. Were investigators kept blind to participant's exposure to the intervention? Yes 12. Were investigators kept blind to other important confounding and prognostic factors? Unclear

Bibliographic reference	Parkinson Study, Group, A controlled trial of rotigotine monotherapy in early Parkinson's disease, 60, 1721-8, 2003
Country/ies where the study was carried out	North America
Study type	Randomised, double-blind, placebo-controlled study
Aim of the study	To assess the efficacy and safety of rotigotine in patients with PD not receiving dopaminergic medications
Study dates	Study dates: Not reported Study duration: 11 weeks
Source of funding	Schwarz Pharma Inc.
Sample size	In total: n=242; Rotigotine 4.5mg n=49; Rotigotine 9mg n=47; Rotigotine 13.5mg n= 48; Rotigotine 18mg n=51; Placebo n=47
Inclusion criteria	• ≥30 years who were diagnosed as having idiopathic PD • Hoehn and Yahr stage of 3 or less • Subjects were permitted to take selegiline, amantadine, or anticholinergic agents if maintained at stable dosages for 28 days before baseline and throughout the trial.
Exclusion criteria	Patients who: • Had an MMSE score of less than 24 • Were unable to appropriately apply and remove the patches • Had a history of skin sensitivity to adhesives or other transdermal medications • Had taken a dopamine agonist or levodopa within 28 days of the baseline visit or had ever taken levodopa for longer than 6 months • Had an atypical parkinsonian syndrome

<table>
<tr><th>Bibliographic reference</th><th>Parkinson Study, Group, A controlled trial of rotigotine monotherapy in early Parkinson's disease, 60, 1721-8, 2003</th></tr>
<tr><td></td><td>

Had a clinically unstable medical or psychiatric condition
Had cardiac abnormalities such as arrhythmias, conduction blocks, congestive heart failure, QT-corrected interval of 500 milliseconds or more, unexplained syncope, symptomatic orthostatic hypotension, or a recent myocardial infarction
Had recent exposure to monoamine oxidase type A inhibitors, amphetamines, dopamine-depleting antihypertensive agents, neuroleptics, or antipsychotics or antiemetics that blocked central dopamine activity

</td></tr>
<tr><td>Details</td><td>There were no important differences among the 5 treatment groups in the baseline demographic and clinical variables.
<table>
<tr><td>Characteristics</td><td>Placebo (n=47)</td><td>Rotigotine 4.5mg (n=49)</td><td>Rotigotine 9mg (n=47)</td><td>Rotigotine 13.5mg (n=48)</td><td>Rotigotine 18mg (n=51)</td></tr>
<tr><td>Age (yrs)</td><td>62.3(10.5)</td><td>61.8(9.8)</td><td>60.9(8.3)</td><td>61.3(10.9)</td><td>60.5(10.7)</td></tr>
<tr><td>Years since PD diagnosis</td><td>1.3(1.4)</td><td>1.2(1.4)</td><td>1.5(2.0)</td><td>1.2(1.0)</td><td>1.1(1.2)</td></tr>
<tr><td colspan="6">Hoehn & Yahr stage:</td></tr>
<tr><td>I</td><td>27.7</td><td>36.7</td><td>25.5</td><td>35.4</td><td>35.3</td></tr>
<tr><td>II</td><td>57.5</td><td>57.1</td><td>70.2</td><td>56.3</td><td>56.9</td></tr>
<tr><td>III</td><td>14.9</td><td>6.1</td><td>4.3</td><td>8.3</td><td>7.8</td></tr>
<tr><td>UPDRS II</td><td>7.2(3.8)</td><td>6.9(3.3)</td><td>7.5(3.8)</td><td>7.4(4.3)</td><td>6.4(4.4)</td></tr>
<tr><td>UPDRS III</td><td>19.6(8.8)</td><td>19.8(8.9)</td><td>20.0(7.5)</td><td>19.8(10.7)</td><td>17.4(7.9)</td></tr>
</table>
Values are given as mean (SD) unless otherwise stated.</td></tr>
<tr><td>Interventions</td><td>Starting dose for all intervention groups were 4.5mg/day, then adjusted weekly by increments of 4.5mg until the maximum dosage for each group were reached:
Rotigotine patches: 4.5, 9, 13.5, or 18 mg</td></tr>
<tr><td>Primary outcomes</td><td>

The change in the sum of the scores of UPDRS II and III from baseline to the end of treatment
Adverse events and tolerability

</td></tr>
<tr><td>Secondary outcomes</td><td>

Changes in the UPDRS mental, ADL and motor subscale scores
Change in Hoehn and Yahr stage between baseline and week 11 visit

</td></tr>
<tr><td>Results</td><td>Treatment effects at week 11 on UPDRS scores:</td></tr>
</table>

Bibliographic reference	Parkinson Study, Group, A controlled trial of rotigotine monotherapy in early Parkinson's disease, 60, 1721-8, 2003

Dosage, mg	Difference in mean change between active treatment and placebo (95% CI)	P value
Motor score:		
4.5	-0.90(-3.2 to 1.40)	.44
9.0	-1.88 (-4.22 to 0.45)	.11
13.5	-3.91(-6.26 to -1.56)	.001
18.0	-3.82(-6.12 to -1.53)	.001
ADL score:		
4.5	-0.04(-1.05 to 0.97)	.94
9.0	-0.84(-1.87 to 0.18)	.11
13.5	-0.92(-1.95 to 0.11)	.08
18.0	-1.56(-2.57 to -0.56)	.003

Adverse events:

Adverse event	Placebo (n=47)	Rotigotine groups (n=195)
Nausea	7(15)	92(47)
Application site infection	10(21)	77(39)
Dizziness	6(13)	46(24)
Somnolence	2(4)	42(22)
Insomnia	5(11)	37(19)
Headache	6(13)	34(17)
Vomiting	1(2)	32(16)
Fatigue	1(2)	29(15)

Bibliographic reference	Parkinson Study, Group, A controlled trial of rotigotine monotherapy in early Parkinson's disease, 60, 1721-8, 2003
	<table><tr><td>Sweating</td><td>2(4)</td><td>12(6)</td></tr><tr><td>Diarrhoea</td><td>4(9)</td><td>8(4)</td></tr><tr><td>Anxiety</td><td>2(4)</td><td>9(5)</td></tr><tr><td>Peripheral oedema</td><td>0(0)</td><td>9(5)</td></tr><tr><td>Anorexia</td><td>0</td><td>9(5)</td></tr></table> Data are given as number (%) of participants.
Overall Risk of Bias	1. Has an appropriate method of randomisation been used? Yes 2. Was there adequate concealment of allocation? Yes 3. Were the groups comparable at baseline for all major confounding/prognostic factors? Yes 4. Did the comparison groups receive the same care apart from interventions studied? Unclear 5. Were participants receiving care kept blind to treatment allocation? Yes 6. Were the individuals administering care kept blind to treatment allocation? Yes 7. Were groups comparable with respect to availability of outcome data and for how many participants were no outcome data available? Unclear 8. Did the study have an appropriate length of follow up? Yes 9. Did the study use a precise definition of outcome? Yes 10. Was a valid and reliable method used to determine that outcome? Yes 11. Were investigators kept blind to participant's exposure to the intervention? Yes 12. Were investigators kept blind to other important confounding and prognostic factors? Unclear

Bibliographic reference	Caraceni,T., Musicco,M., Levodopa or dopamine agonists, or deprenyl as initial treatment for Parkinson's disease. A randomised multicenter study, Parkinsonism & Related Disorders, 7, 107-114, 2001
Country/ies where the study was carried out	Italy
Study type	Multi-centre, randomised, controlled, open trial
Aim of the study	To compare the occurrence of motor fluctuations and dyskinesias in previously untreated patients assigned to receive levodopa, a dopamine agonist or deprenyl.

<table>
<tr><th>Bibliographic reference</th><th>Caraceni,T., Musicco,M., Levodopa or dopamine agonists, or deprenyl as initial treatment for Parkinson's disease. A randomised multicenter study, Parkinsonism & Related Disorders, 7, 107-114, 2001</th></tr>
<tr><td>Study dates</td><td>Study dates: Not reported
Study duration: 3 years (median follow-up of 34 months)</td></tr>
<tr><td>Source of funding</td><td>Sandoz Italy, Chiesi Farmaceutici and by Italian Ministry of Health.</td></tr>
<tr><td>Sample size</td><td>In total: 473; Levodopa plus dopa decarboxylase inhibitor n=156; Dopamine agonist n=162; Deprenyl n=155</td></tr>
<tr><td>Inclusion criteria</td><td>Clinical diagnosis of PD (when hypokinesia was associated with tremor, rigidity or both for at least 6 months)</td></tr>
<tr><td>Exclusion criteria</td><td>• Interval from diagnosis greater than 2 years
• Dementia
• Secondary parkinsonism and parkinsonian syndromes
• Taking drugs that could give rise to extrapyramidal signs
• Previous treatment for more than 4 months with any of the studied drugs</td></tr>
<tr><td>Details</td><td>Baseline characteristics:
<table>
<tr><td>Characteristics</td><td>Levodopa n=156</td><td>Dopamine agonist n=162</td><td>Deprenyl n=155</td></tr>
<tr><td>Mean age (years)</td><td>63.4</td><td>63.0</td><td>63.4</td></tr>
<tr><td colspan="4">Hoehn & Yahr stage:</td></tr>
<tr><td>I-II</td><td>104(67.3)</td><td>102(69.1)</td><td>117(75.5)</td></tr>
<tr><td>III-IV</td><td>52(32.7)</td><td>60(30.9)</td><td>38(24.5)</td></tr>
<tr><td>Mean months from disease onset</td><td>16.21</td><td>17.7</td><td>16.0</td></tr>
<tr><td>UPDRS II</td><td>9.8</td><td>10.1</td><td>9.8</td></tr>
<tr><td>UPDRS III</td><td>16.8</td><td>16.7</td><td>16.9</td></tr>
</table></td></tr>
<tr><td>Interventions</td><td>The drug doses were increased slowly over 2-4 weeks until clinical efficacy was reached or adverse effects occurred. The maximum doses were:
Levodopa + dopa decarboxylase inhibitor: 750mg
Bromocriptine: 60mg
Lisuride: 6mg</td></tr>
</table>

Bibliographic reference	Caraceni,T., Musicco,M., Levodopa or dopamine agonists, or deprenyl as initial treatment for Parkinson's disease. A randomised multicenter study, Parkinsonism & Related Disorders, 7, 107-114, 2001
	Deprenyl: 10mg If deprenyl or dopamine agonists were, or subsequently became, ineffective levodopa was added. In cases of intolerance, the assigned drug was substituted with another.
Primary outcomes	• Motor dyskinesias • Motor fluctuations (wearing off and early morning akinesia)
Secondary outcomes	• Termination of the originally assigned therapy • Initiation of add-on therapy • A motor score worse than or equal to that recorded before the initiation of treatment
Results	Relative risks of occurrence of principal and secondary end-points by drug assigned:

	Levodopa (n=156)	Dopamine agonist (n=162)	Deprenyl (n=155)
Motor fluctuations:			
Number (%)	46(29.7)	27(16.7)	29(18.7)
RR (95% CI)	1*	0.5(0.3-0.8)	0.6(0.4-0.9)
Dyskinesias:			
Number (%)	42(27.1)	24(14.8)	32(20.6)
RR (95% CI)	1	0.6(0.3-0.9)	0.8(0.5-1.3)
Motor score equal to or worse than before treatment:			
Number (%)	43(27.7)	60(37.0)	51(32.9)
RR (95% CI)	1*	1.4(0.9-2.1)	1.3(0.8-1.9)
Withdrawal:			
Number (%)	10(6.4)	53(32.7)	30(19.4)
RR (95% CI)	1*	5.8(2.5-9.3)	3.2(1.6-6.4)

Bibliographic reference	**Caraceni,T., Musicco,M., Levodopa or dopamine agonists, or deprenyl as initial treatment for Parkinson's disease. A randomised multicenter study, Parkinsonism & Related Disorders, 7, 107-114, 2001**
	Add-on therapy: Number (%) 20(12.9) 66(40.7) 99(63.9) RR (95% CI) 1* 4.3(2.6-7.1) 9.1(5.6-14.7) *Reference group.
Overall Risk of Bias	1. Has an appropriate method of randomisation been used? Unclear 2. Was there adequate concealment of allocation? Unclear 3. Were the groups comparable at baseline for all major confounding/prognostic factors? Yes 4. Did the comparison groups receive the same care apart from interventions studied? Unclear 5. Were participants receiving care kept blind to treatment allocation? No 6. Were the individuals administering care kept blind to treatment allocation? No 7. Were groups comparable with respect to availability of outcome data and for how many participants were no outcome data available? Yes 8. Did the study have an appropriate length of follow up? Yes 9. Did the study use a precise definition of outcome? Yes 10. Was a valid and reliable method used to determine that outcome? Yes 11. Were investigators kept blind to participant's exposure to the intervention? No 12. Were investigators kept blind to other important confounding and prognostic factors? No

Bibliographic reference	**Caraceni,T., Musicco,M., Gasparini,M., Beghi,E., Scigliano,G., Carella,F., Cossutta,E., Chiaro,C., Lovicu,G., Giminiani,G., Currado,I., Solari,A., Nicolosi,A., Agnoli,A., Nappi,G., Giuliani,G., Angeleri,A., Moro,G., Franciosi,A., A multicenter Italian randomised study on early treatment of Parkinson disease: Comparison of 1-dopa, 1-deprenyl and dopaminoagonists. Study design and short term results, Italian Journal of Neurological Sciences, 13, 735-739, 1992**
Country/ies where the study was carried out	Italy
Study type	Multicentre, randomised open trial
Aim of the study	To find out whether early treatment of PD patients with levodopa, DA or deprenyl is associated with any difference in motor fluctuations occurrence on long term treatment.

<table>
<tr><th>Bibliographic reference</th><th>Caraceni,T., Musicco,M., Gasparini,M., Beghi,E., Scigliano,G., Carella,F., Cossutta,E., Chiaro,C., Lovicu,G., Giminiani,G., Currado,I., Solari,A., Nicolosi,A., Agnoli,A., Nappi,G., Giuliani,G., Angeleri,A., Moro,G., Franciosi,A., A multicenter Italian randomised study on early treatment of Parkinson disease: Comparison of 1-dopa, 1-deprenyl and dopaminoagonists. Study design and short term results, Italian Journal of Neurological Sciences, 13, 735-739, 1992</th></tr>
<tr><td>Study dates</td><td>Study dates: November 1988 to December 1991
Study duration: 3 years (this publication reports difference between first follow-up visit (2 months) and inclusion)</td></tr>
<tr><td>Source of funding</td><td>Supported by Chiesi and by contributions from Sandoz and Shering</td></tr>
<tr><td>Sample size</td><td>In total: n=475; Levodopa + dopa decarboxylase inhibitor n=159; Bromocriptine n=77; Lisuride n= 82; Deprenyl n=157</td></tr>
<tr><td>Inclusion criteria</td><td>Diagnosis of primary PD made on clinical grounds, when hypokinesia is associated with tremor or rigidity for up to 6 months</td></tr>
<tr><td>Exclusion criteria</td><td>• An interval from diagnosis longer than 2 years
• Dementia
• Secondary parkinsonism and parkinsonian syndrome
• Previous or current therapy with drugs possibly causing extrapyramidal signs
• Previous treatment for more than 4 months with 1 of the studied drugs
• Patients were excluded if, due to health or administrative reasons, there may be difficulty in follow-up</td></tr>
<tr><td>Details</td><td>Baseline characteristics:
<table>
<tr><td>Characteristics</td><td>Levodopa</td><td>Bromocriptine</td><td>Lisuride</td><td>Deprenyl</td></tr>
<tr><td>Age (mean)</td><td>63.0</td><td>63.9</td><td>62.8</td><td>64.1</td></tr>
<tr><td>Mean duration from onset (months)</td><td>17.2</td><td>17.1</td><td>17.1</td><td>17.1</td></tr>
<tr><td>UPDRS II</td><td>9.7</td><td>9.8</td><td>10.0</td><td>9.4</td></tr>
<tr><td>UPDRS III</td><td>13.3</td><td>12.7</td><td>13.5</td><td>13.6</td></tr>
<tr><td>Hoehn & Yahr stage</td><td>1.9</td><td>1.9</td><td>2.0</td><td>2.0</td></tr>
</table></td></tr>
<tr><td>Interventions</td><td>The drug doses were increased slowly over 2-4 weeks until clinical efficacy was reached or adverse effects occurred. The maximum doses were:
• Levodopa + dopa decarboxylase inhibitor: 750mg
• Bromocriptine: 60mg
• Lisuride: 3mg
• Deprenyl: 10mg</td></tr>
</table>

<table>
<tr><th>Bibliographic reference</th><th>Caraceni,T., Musicco,M., Gasparini,M., Beghi,E., Scigliano,G., Carella,F., Cossutta,E., Chiaro,C., Lovicu,G., Giminiani,G., Currado,I., Solari,A., Nicolosi,A., Agnoli,A., Nappi,G., Giuliani,G., Angeleri,A., Moro,G., Franciosi,A., A multicenter Italian randomised study on early treatment of Parkinson disease: Comparison of 1-dopa, 1-deprenyl and dopaminoagonists. Study design and short term results, Italian Journal of Neurological Sciences, 13, 735-739, 1992</th></tr>
<tr><td></td><td>If deprenyl or dopamine agonists were, or subsequently became, ineffective levodopa was added</td></tr>
<tr><td>Primary outcomes</td><td>The occurrence of motor fluctuations, in particular of wearing-off and of early morning akinesia</td></tr>
<tr><td>Secondary outcomes</td><td>Interruption of assigned therapy for untoward side effects, add-on therapy when the assigned therapy fails to control signs and symptoms</td></tr>
<tr><td>Results</td><td>Mean difference (± SE) of UPDRS scores between first follow-up visit and inclusion:
<table>
<tr><td></td><td>Levodopa</td><td>Bromocriptine</td><td>Lisuride</td><td>Deprenyl</td></tr>
<tr><td>UPDRS II</td><td>-2.5±0.21</td><td>-1.9±0.23</td><td>-2.6±0.29</td><td>-1.4±0.16*</td></tr>
<tr><td>UPDRS III</td><td>-3.4±0.39</td><td>-2.3±0.55</td><td>-3.2±0.44</td><td>-2.4±0.38</td></tr>
</table>
*Difference between inclusion and 1st examination is significantly lower than for levodopa and DA (p=0.03).</td></tr>
<tr><td>Overall Risk of Bias</td><td>1. Has an appropriate method of randomisation been used? Unclear
2. Was there adequate concealment of allocation? Unclear
3. Were the groups comparable at baseline for all major confounding/prognostic factors? Yes
4. Did the comparison groups receive the same care apart from interventions studied? Unclear
5. Were participants receiving care kept blind to treatment allocation? No
6. Were the individuals administering care kept blind to treatment allocation? No
7. Were groups comparable with respect to availability of outcome data and for how many participants were no outcome data available? Unclear
8. Did the study have an appropriate length of follow up? Yes
9. Did the study use a precise definition of outcome? Yes
10. Was a valid and reliable method used to determine that outcome? Yes
11. Were investigators kept blind to participant’s exposure to the intervention? No
12. Were investigators kept blind to other important confounding and prognostic factors? No</td></tr>
</table>

<table>
<tr><th>Bibliographic reference</th><th>Hauser,R.A., Schapira,A.H., Rascol,O., Barone,P., Mizuno,Y., Salin,L., Haaksma,M., Juhel,N., Poewe,W., Randomised, double-blind, multicenter evaluation of pramipexole extended release once daily in early Parkinson's disease, Movement Disorders.25 (15) (pp 2542-2549), 2010.Date of Publication: November 2010., 2542-2549, 2010</th></tr>
<tr><td>Country/ies where the study was carried out</td><td>Europe, US, South America, Asia</td></tr>
<tr><td>Study type</td><td>Randomised, double-blind, placebo and active comparator-controlled, parallel group clinical trial</td></tr>
<tr><td>Aim of the study</td><td>To evaluate the efficacy and safety of pramipexole extended release (ER) administered once daily in early PD.</td></tr>
<tr><td>Study dates</td><td>Study dates: Not reported
Study duration: 18 weeks</td></tr>
<tr><td>Source of funding</td><td>Boehringer Ingelheim International</td></tr>
<tr><td>Sample size</td><td>In total: n=259; Pramipexole ER n=106; Pramipexole IR n=103; Placebo n=50</td></tr>
<tr><td>Inclusion criteria</td><td>• ≥30 years or older
• Diagnosed with PD within 5 years and exhibiting at least 2 of 3 cardinal signs
• Hoehn and Yahr stages I-III and in need of dopaminergic therapy
• Patients could not have received a dopamine agonist within the last 4 weeks or L-dopa within the last 8 weeks before baseline and could not have previously received L-dopa for a total cumulative exposure of >3 months.
• Monoamine oxidase B inhibitors, amantadine, anticholinergics, and beta-blockers were permitted at stable doses, provided the dosage had been stable for at least 4 weeks before baseline.</td></tr>
<tr><td>Exclusion criteria</td><td>• Dementia (MMSE <24)
• Atypical and secondary parkinsonisms
• Clinically relevant medical and psychiatric conditions</td></tr>
<tr><td>Details</td><td>Baseline characteristics:
<table>
<tr><td>Characteristics</td><td>Placebo (n=50)</td><td>Pramipexole ER (n=106)</td><td>Pramipexole IR (n=103)</td></tr>
<tr><td>Age (yr), mean (SD)</td><td>63.2(8.7)</td><td>61.6(9.4)</td><td>62.0(8.3)</td></tr>
<tr><td>PD known duration (yr), mean (SD)</td><td>0.8(1.1)</td><td>1.1(1.3)</td><td>0.9(1.2)</td></tr>
<tr><td colspan="4">Modified Hoehn & Yahr stage (%)</td></tr>
<tr><td>I-I.5</td><td>28.0</td><td>29.2</td><td>26.2</td></tr>
<tr><td>II-III</td><td>72.0</td><td>70.8</td><td>73.8</td></tr>
</table></td></tr>
</table>

Bibliographic reference	Hauser,R.A., Schapira,A.H., Rascol,O., Barone,P., Mizuno,Y., Salin,L., Haaksma,M., Juhel,N., Poewe,W., Randomised, double-blind, multicenter evaluation of pramipexole extended release once daily in early Parkinson's disease, Movement Disorders.25 (15) (pp 2542-2549), 2010.Date of Publication: November 2010., 2542-2549, 2010
	UPDRS II: 7.6(4.3) / 7.9(4.3) / 7.8(3.7) UPDRS III: 22.4(13.6) / 22.6(10.1) / 20.4(9.0)
Interventions	Pramipexole ER or IR: 0.375, 0.75, 1.5, 2.25, 3.0, or 4.5 mg (7-week flexible up-titration phase) Pramipexole ER (extended release) was administered once daily and pramipexole IR (immediate release) was administered in equally divided doses TID.
Primary outcomes	• Change from baseline to week 18 in the sum of UPDRS II and III • Adverse events
Secondary outcomes	• Clinical Global Impression of Improvement and PGI-I responder rates at week 18 • Change from baseline to week 18 in individual UPDRS I, III, III • PDQ-39 • EQ-5D
Results	Efficacy results:

	Placebo	Pramipexole ER	Pramipexole IR
UPDRS II score, adjusted mean change (SE) [p vs. placebo] :			
No of subjects	50	102	101
Without levodopa data censored	-0.5(0.4)	-1.6(0.4) [0.0177]	-1.8(0.4) [0.0049]
With levodopa data censored	-0.0(0.5)	-1.5(0.4) [0.0023]	-1.8(0.4) [0.0005]
UPDRS III score, adjusted mean change (SE) [p vs. placebo]:			
No of patients	50	102	101
Without levodopa data censored	-4.6(1.0)	-6.5(0.9_ [0.0813]	-6.7(0.8) [0.0600]
With levodopa data censored	-2.7(1.0)	-5.9(0.9) [0.0039]	-5.9(0.8) [0.0038]
PDQ-39 score, adjusted mean change (SE) [P vs. placebo]:			

Bibliographic reference	Hauser,R.A., Schapira,A.H., Rascol,O., Barone,P., Mizuno,Y., Salin,L., Haaksma,M., Juhel,N., Poewe,W., Randomised, double-blind, multicenter evaluation of pramipexole extended release once daily in early Parkinson's disease, Movement Disorders.25 (15) (pp 2542-2549), 2010.Date of Publication: November 2010., 2542-2549, 2010

No of patients	49	91	95
Without levodopa data censored	-1.9(2.0)	-8.2(1.8) [0.0058]	-9.2(1.7) [0.0012]
With levodopa data censored	-1.7(2.1)	-8.2(1.8) [0.0052]	-9.2(1.7) [0.0010]
ED-5D VAS score, adjusted mean change (SE) [P vs. placebo]:			
No of patients	49	91	95
Without levodopa data censored	2.9(2.6)	7.1(2.3) [0.1445]	8.4(2.2) [0.0509]
With levodopa data censored	2.7(2.6)	6.7(2.3) [0.1631]	8.0(2.2) [0.0604]

Adverse events:

Adverse event	Placebo (n=50)	Pramipexole ER (n=106)	Pramipexole IR n=103)
Total discontinuations, n (%)	4(8.0)	21(19.8)	15(14.6)
AEs by category, n (%):			
Any	35(70.0)	81(76.4)	81(76.8)
Severea	1(2.0)	4(3.8)	6(5.8)
Seriousb	1(2.0)	5(4.7)	3(2.9)
Drug-related	19(38.0)	61(57.5)	66(64.1)
Leading to discontinuation	2(4.0)	11(10.4)	8(7.8)
AEs by type, n (%):			
Somnolence	7(14.0)	34(32.1)	34(33.0)
Nausea	2(4.0)	22(20.8)	22(21.4)

Bibliographic reference	**Hauser,R.A., Schapira,A.H., Rascol,O., Barone,P., Mizuno,Y., Salin,L., Haaksma,M., Juhel,N., Poewe,W., Randomised, double-blind, multicenter evaluation of pramipexole extended release once daily in early Parkinson's disease, Movement Disorders.25 (15) (pp 2542-2549), 2010.Date of Publication: November 2010., 2542-2549, 2010**
	<table><tr><td>Constipation</td><td>0(0.0)</td><td>13(12.3)</td><td>16(15.5)</td></tr><tr><td>Fatigue</td><td>1(2.0)</td><td>7(6.6)</td><td>7(6.8)</td></tr></table> [a]Incapacitating or causing inability to work or undertake usual activities. [b]Fatal, life-threatening, requiring hospitalization, or resulting in significant disability.
Overall Risk of Bias	1. Has an appropriate method of randomisation been used? Yes 2. Was there adequate concealment of allocation? Yes 3. Were the groups comparable at baseline for all major confounding/prognostic factors? Yes 4. Did the comparison groups receive the same care apart from interventions studied? Yes 5. Were participants receiving care kept blind to treatment allocation? Yes 6. Were the individuals administering care kept blind to treatment allocation? Yes 7. Were groups comparable with respect to availability of outcome data and for how many participants were no outcome data available? Yes 8. Did the study have an appropriate length of follow up? Yes 9. Did the study use a precise definition of outcome? Yes 10. Was a valid and reliable method used to determine that outcome? Yes 11. Were investigators kept blind to participant’s exposure to the intervention? Unclear 12. Were investigators kept blind to other important confounding and prognostic factors? Unclear

Bibliographic reference	**Holloway,R.G., Shoulson,I., Fahn,S., Kieburtz,K., Lang,A., Marek,K., McDermott,M., Seibyl,J., Weiner,W., Musch,B., Kamp,C., Welsh,M., Shinaman,A., Pahwa,R., Barclay,L., Hubble,J., LeWitt,P., Miyasaki,J., Suchowersky,O., Stacy,M., Russell,D.S., Ford,B., Hammerstad,J., Riley,D., Standaert,D., Wooten,F., Factor,S., Jankovic,J., Atassi,F., Kurlan,R., Panisset,M., Rajput,A., Rodnitzky,R., Shults,C., Petsinger,G., Waters,C., Pfeiffer,R., Biglan,K., Borchert,L., Montgomery,A., Sutherland,L., Weeks,C., DeAngelis,M., Sime,E., Wood,S., Pantella,C., Harrigan,M., Fussell,B., Dillon,S., Alexander-Brown,B., Rainey,P., Tennis,M., Rost-Ruffner,E., Brown,D., Evans,S., Berry,D., Hall,J., Shirley,T., Dobson,J., Fontaine,D., Pfeiffer,B., Brocht,A., Bennett,S., Daigneault,S., Hodgeman,K., O'Connell,C., Ross,T., Richard,K., Watts,A., Pramipexole vs levodopa as initial treatment for Parkinson disease: a 4-year randomised controlled trial, Archives of Neurology, 61, 1044-1053, 2004**

<table>
<tr><th>Bibliographic reference</th><td>Holloway,R.G., Shoulson,I., Fahn,S., Kieburtz,K., Lang,A., Marek,K., McDermott,M., Seibyl,J., Weiner,W., Musch,B., Kamp,C., Welsh,M., Shinaman,A., Pahwa,R., Barclay,L., Hubble,J., LeWitt,P., Miyasaki,J., Suchowersky,O., Stacy,M., Russell,D.S., Ford,B., Hammerstad,J., Riley,D., Standaert,D., Wooten,F., Factor,S., Jankovic,J., Atassi,F., Kurlan,R., Panisset,M., Rajput,A., Rodnitzky,R., Shults,C., Petsinger,G., Waters,C., Pfeiffer,R., Biglan,K., Borchert,L., Montgomery,A., Sutherland,L., Weeks,C., DeAngelis,M., Sime,E., Wood,S., Pantella,C., Harrigan,M., Fussell,B., Dillon,S., Alexander-Brown,B., Rainey,P., Tennis,M., Rost-Ruffner,E., Brown,D., Evans,S., Berry,D., Hall,J., Shirley,T., Dobson,J., Fontaine,D., Pfeiffer,B., Brocht,A., Bennett,S., Daigneault,S., Hodgeman,K., O'Connell,C., Ross,T., Richard,K., Watts,A., Pramipexole vs levodopa as initial treatment for Parkinson disease: a 4-year randomised controlled trial, Archives of Neurology, 61, 1044-1053, 2004</td></tr>
<tr><td>Country/ies where the study was carried out</td><td>US and Canada</td></tr>
<tr><td>Study type</td><td>Multicentre, parallel-group, double-blind, randomised controlled trial.</td></tr>
<tr><td>Aim of the study</td><td>To compare initial treatment with pramipexole vs levodopa in early Parkinson disease, followed by levodopa supplementation, with respect to the development of dopaminergic motor complications, other adverse events, and functional and quality of life outcomes.</td></tr>
<tr><td>Study dates</td><td>Study dates: October 1996 to August 2001
Study duration: A minimum of 4 years (2 year clinical trial + an extended follow-up for at least an additional 2 years)</td></tr>
<tr><td>Source of funding</td><td>Pharmacia Corporation, Boehringer Ingelheim Pharma, The National Parkinson Foundation Center of Excellence to the Parkinson Study Group, and by the National Institutes of Health for Clinical Research Center grants RR00044 and RR01066 at the University of Rochester and the Massachusetts General Hospital, respectively.</td></tr>
<tr><td>Sample size</td><td>In total: n=301; Pramipexole n=151; Levodopa/carbidopa n=150</td></tr>
<tr><td>Inclusion criteria</td><td>• ≥30 years of age
• Idiopathic Parkinson disease for fewer than 7 years and required dopaminergic antiparkinsonian therapy at the time of enrolment.
• Hoehn and Yahr stage I-III</td></tr>
<tr><td>Exclusion criteria</td><td>Patients who had taken levodopa or a dopaminergic agonist in the 2 months prior to enrolment</td></tr>
<tr><td>Details</td><td>The 2 treatment groups were similar at baseline with regard to demographic and clinical variables, except for lower quality-of-life scores in the pramipexole group.
<table>
<tr><td></td><td colspan="2">Completed Trial</td><td colspan="2">Withdrew from trial</td></tr>
<tr><td>Characteristics</td><td>Pramipexole (n=83)</td><td>Levodopa (n=100)</td><td>Pramipexole (n=68)</td><td>Levodopa (n=50)</td></tr>
<tr><td>Age (yrs)</td><td>61.1(9.6)</td><td>60.8(9.8)</td><td>62.1(10.8)</td><td>61.0(11.9)</td></tr>
</table></td></tr>
</table>

Bibliographic reference	**Holloway,R.G., Shoulson,I., Fahn,S., Kieburtz,K., Lang,A., Marek,K., McDermott,M., Seibyl,J., Weiner,W., Musch,B., Kamp,C., Welsh,M., Shinaman,A., Pahwa,R., Barclay,L., Hubble,J., LeWitt,P., Miyasaki,J., Suchowersky,O., Stacy,M., Russell,D.S., Ford,B., Hammerstad,J., Riley,D., Standaert,D., Wooten,F., Factor,S., Jankovic,J., Atassi,F., Kurlan,R., Panisset,M., Rajput,A., Rodnitzky,R., Shults,C., Petsinger,G., Waters,C., Pfeiffer,R., Biglan,K., Borchert,L., Montgomery,A., Sutherland,L., Weeks,C., DeAngelis,M., Sime,E., Wood,S., Pantella,C., Harrigan,M., Fussell,B., Dillon,S., Alexander-Brown,B., Rainey,P., Tennis,M., Rost-Ruffner,E., Brown,D., Evans,S., Berry,D., Hall,J., Shirley,T., Dobson,J., Fontaine,D., Pfeiffer,B., Brocht,A., Bennett,S., Daigneault,S., Hodgeman,K., O'Connell,C., Ross,T., Richard,K., Watts,A., Pramipexole vs levodopa as initial treatment for Parkinson disease: a 4-year randomised controlled trial, Archives of Neurology, 61, 1044-1053, 2004**
	Years since diagnosis: 1.4(1.3) / 1.8(1.7) / 1.6(1.6) / 1.8(1.7) UPDRS II: 8.7(4.1) / 7.8(3.8) / 9.5(4.0) / 9.2(4.2) UPDRS III: 21.9(8.9) / 20.8(9.4) / 22.7(9.5) / 24.3(9.8) No (%) of patients in Hoehn & Yahr stage: I: 12(14.5) / 18(18.0) / 8(11.8) / 5(10.0) I.5: 11(13.3) / 16(16.0) / 12(17.7) / 4(8.0) II: 43(51.8) / 58(58.0) / 35(51.5) / 26(52.0) II.5: 18(19.3) / 7(7.0) / 9(13.2) / 9(18.0) III: 1(1.2) / 1(1.0) / 4(5.9) / 6(12.0) Parkinson's Disease Quality-of-Life Scale: 28.2(9.9) / 24.5(10.4) / 30.6(13.6) / 31.0(12.2) EQ-VAS: 76.3(14.3) / 79.2(11.5) / 73.6(17.1) / 74.4(12.4) Values are expressed as mean (SD) unless otherwise indicated.
Interventions	Pramipexole: 0.25mg, 0.5mg or 1mg three times per day Carbidopa/Levodopa: 12.5/50mg or 25/100mg three times per day Subjects entered a 10-week dosage escalation period. All subjects were escalated initially to a daily dosage of 1.5mg pramipexole or 75/300mg carbidopa/levodopa. Subject requiring additional therapy could escalate to 3mg pramipexole or 112.5/450mg carbidopa/levodopa or 4.5mg pramipexole or 150/600mg carbidopa/levodopa. Thereafter (from week 11), investigators were permitted to add open-label levodopa or other antiparkinsonian medications to treat ongoing or emerging disability.

<table>
<tr><th>Bibliographic reference</th><td>Holloway,R.G., Shoulson,I., Fahn,S., Kieburtz,K., Lang,A., Marek,K., McDermott,M., Seibyl,J., Weiner,W., Musch,B., Kamp,C., Welsh,M., Shinaman,A., Pahwa,R., Barclay,L., Hubble,J., LeWitt,P., Miyasaki,J., Suchowersky,O., Stacy,M., Russell,D.S., Ford,B., Hammerstad,J., Riley,D., Standaert,D., Wooten,F., Factor,S., Jankovic,J., Atassi,F., Kurlan,R., Panisset,M., Rajput,A., Rodnitzky,R., Shults,C., Petsinger,G., Waters,C., Pfeiffer,R., Biglan,K., Borchert,L., Montgomery,A., Sutherland,L., Weeks,C., DeAngelis,M., Sime,E., Wood,S., Pantella,C., Harrigan,M., Fussell,B., Dillon,S., Alexander-Brown,B., Rainey,P., Tennis,M., Rost-Ruffner,E., Brown,D., Evans,S., Berry,D., Hall,J., Shirley,T., Dobson,J., Fontaine,D., Pfeiffer,B., Brocht,A., Bennett,S., Daigneault,S., Hodgeman,K., O'Connell,C., Ross,T., Richard,K., Watts,A., Pramipexole vs levodopa as initial treatment for Parkinson disease: a 4-year randomised controlled trial, Archives of Neurology, 61, 1044-1053, 2004</td></tr>
<tr><td>Primary outcomes</td><td>• Time to the first occurrence of dopaminergic complications wearing off, dyskinesias, on-off fluctuations, and freezing
• Adverse events</td></tr>
<tr><td>Secondary outcomes</td><td>Changes in scores of the UPDRS, Parkinson's Disease Quality of Life scale the EuroQol Visual Analog Scale, as well as the need for supplemental levodopa.</td></tr>
<tr><td>Results</td><td>Treatment effects on dopaminergic end points:
<table>
<tr><td>End points</td><td>Pramipexole no (%) (n=151)</td><td>Levodopa No. (%) (n=150)</td><td>HR (95% CI)</td><td>P value</td></tr>
<tr><td>First dopaminergic complication*</td><td>78(51.7)</td><td>111(74.0)</td><td>0.48(0.35-0.66)</td><td><.001</td></tr>
<tr><td>Wearing off</td><td>71(47.0)</td><td>94(62.7)</td><td>0.68(0.49-0.93)</td><td>.02</td></tr>
<tr><td>Dyskinesias</td><td>37(24.5)</td><td>81(54.0)</td><td>0.37(0.25-0.56)</td><td><.001</td></tr>
<tr><td>On-off fluctuations</td><td>10(6.6)</td><td>12(8.0)</td><td>0.64(0.26-1.59)</td><td>.34</td></tr>
<tr><td>Freezing</td><td>56(37.1)</td><td>38(25.3)</td><td>1.70(1.11-2.59)</td><td>.01</td></tr>
<tr><td>Off-period dystonia</td><td>53(35.1)</td><td>69(46.0)</td><td>0.73(0.51-1.06)</td><td>.10</td></tr>
</table>
*Defined as the first occurrence of wearing off, dyskinesia, or on-off fluctuations.

Mean changes from baseline to month 48 in UPDRS scores:
<table>
<tr><td>Scale score</td><td>Pramipexole (n=151)</td><td>Levodopa (n=150)</td><td>Treatment effect (95% CI)</td><td>P value</td></tr>
<tr><td>Total UPDRS</td><td>-3.2(17.3)</td><td>2.0(15.4)</td><td>-5.9(-9.6, -2.1)</td><td>.003</td></tr>
<tr><td>Motor</td><td>-1.3(13.3)</td><td>3.4(12.3)</td><td>-4.9(-7.8, -1.9)</td><td>.001</td></tr>
</table></td></tr>
</table>

Bibliographic reference	**Holloway,R.G., Shoulson,I., Fahn,S., Kieburtz,K., Lang,A., Marek,K., McDermott,M., Seibyl,J., Weiner,W., Musch,B., Kamp,C., Welsh,M., Shinaman,A., Pahwa,R., Barclay,L., Hubble,J., LeWitt,P., Miyasaki,J., Suchowersky,O., Stacy,M., Russell,D.S., Ford,B., Hammerstad,J., Riley,D., Standaert,D., Wooten,F., Factor,S., Jankovic,J., Atassi,F., Kurlan,R., Panisset,M., Rajput,A., Rodnitzky,R., Shults,C., Petsinger,G., Waters,C., Pfeiffer,R., Biglan,K., Borchert,L., Montgomery,A., Sutherland,L., Weeks,C., DeAngelis,M., Sime,E., Wood,S., Pantella,C., Harrigan,M., Fussell,B., Dillon,S., Alexander-Brown,B., Rainey,P., Tennis,M., Rost-Ruffner,E., Brown,D., Evans,S., Berry,D., Hall,J., Shirley,T., Dobson,J., Fontaine,D., Pfeiffer,B., Brocht,A., Bennett,S., Daigneault,S., Hodgeman,K., O'Connell,C., Ross,T., Richard,K., Watts,A., Pramipexole vs levodopa as initial treatment for Parkinson disease: a 4-year randomised controlled trial, Archives of Neurology, 61, 1044-1053, 2004**

ADL	-1.7(5.4)	-0.5(4.7)	-1.4(-2.5, -0.2)	.02
Mental	-0.3(1.6)	-0.8(1.6)	0.3(-0.1, 0.7)	.10

Values are mean (SD).

Adverse events by treatment group:

Adverse event	Pramipexole n (%) (n=151)	Levodopa n (%) (n=150)	P value
Oedema**	64(42.4)	22(14.7)	<.001
Peripheral oedema	34(22.5)	9(6.0)	<.001
Somnolence	56(36.4)	32(21.3)	.005
Hallucination	22(14.6)	12(8.0)	.10
Cellulitis	7(4.6)	0(0.0)	.01
Urinary frequency	5(3.3)	16(10.7)	.01
Hernia	1(0.7)	12(8.0)	.002

**Oedema includes peripheral oedema, localised oedema, generalised oedema, facial oedema, tongue oedema, periorbital oedema, and lymphedema.

Overall Risk of Bias	1. Has an appropriate method of randomisation been used? Yes 2. Was there adequate concealment of allocation? Yes 3. Were the groups comparable at baseline for all major confounding/prognostic factors? Yes 4. Did the comparison groups receive the same care apart from interventions studied? Yes

Bibliographic reference	**Holloway,R.G., Shoulson,I., Fahn,S., Kieburtz,K., Lang,A., Marek,K., McDermott,M., Seibyl,J., Weiner,W., Musch,B., Kamp,C., Welsh,M., Shinaman,A., Pahwa,R., Barclay,L., Hubble,J., LeWitt,P., Miyasaki,J., Suchowersky,O., Stacy,M., Russell,D.S., Ford,B., Hammerstad,J., Riley,D., Standaert,D., Wooten,F., Factor,S., Jankovic,J., Atassi,F., Kurlan,R., Panisset,M., Rajput,A., Rodnitzky,R., Shults,C., Petsinger,G., Waters,C., Pfeiffer,R., Biglan,K., Borchert,L., Montgomery,A., Sutherland,L., Weeks,C., DeAngelis,M., Sime,E., Wood,S., Pantella,C., Harrigan,M., Fussell,B., Dillon,S., Alexander-Brown,B., Rainey,P., Tennis,M., Rost-Ruffner,E., Brown,D., Evans,S., Berry,D., Hall,J., Shirley,T., Dobson,J., Fontaine,D., Pfeiffer,B., Brocht,A., Bennett,S., Daigneault,S., Hodgeman,K., O'Connell,C., Ross,T., Richard,K., Watts,A., Pramipexole vs levodopa as initial treatment for Parkinson disease: a 4-year randomised controlled trial, Archives of Neurology, 61, 1044-1053, 2004**
	5. Were participants receiving care kept blind to treatment allocation? Yes 6. Were the individuals administering care kept blind to treatment allocation? Yes 7. Were groups comparable with respect to availability of outcome data and for how many participants were no outcome data available? Unclear 8. Did the study have an appropriate length of follow up? Yes 9. Did the study use a precise definition of outcome? Yes 10. Was a valid and reliable method used to determine that outcome? Yes 11. Were investigators kept blind to participant's exposure to the intervention? Unclear 12. Were investigators kept blind to other important confounding and prognostic factors? Unclear

Bibliographic reference	**Parkinson Study, Group, Pramipexole vs levodopa as initial treatment for Parkinson disease: A randomised controlled trial. Parkinson Study Group, JAMA 284, 1931-8, 2000**
Country/ies where the study was carried out	US and Canada
Study type	Multicentre, parallel-group, double-blind, randomised controlled trial
Aim of the study	To compare the development of dopaminergic motor complications after initial treatment of early PD with pramipexole vs. levodopa.
Study dates	Study dates: Not reported Study duration: 23.5 months
Source of funding	Pharmacia Corp., the National Parkinson Foundation Center of Excellence to the Parkinson Study Group and by the National Institutes of Health for Clinical Research Center grants RR00044 and RR01066 to the University of Rochester and Massachusetts General Hospital, respectively.

<table>
<tr><th>Bibliographic reference</th><th>Parkinson Study, Group, Pramipexole vs levodopa as initial treatment for Parkinson disease: A randomised controlled trial. Parkinson Study Group, JAMA 284, 1931-8, 2000</th></tr>
<tr><td>Sample size</td><td>In total: n=301; Pramipexole n=151; Carbidopa/Levodopa n=150</td></tr>
<tr><td>Inclusion criteria</td><td>• ≥30 years or older who had idiopathic PD for fewer than 7 years and who required dopaminergic antiparkinsonian therapy at the time of enrolment
• Hoehn and Yahr stage I-III</td></tr>
<tr><td>Exclusion criteria</td><td>Patients who had taken levodopa or a dopaminergic agonist in the 2 months prior to enrolment
Subjects who had:
• A history of a previous dopaminergic complication
• Atypical parkinsonian syndromes
• Serious concurrent illness
• Treatment with methylphenidate, cinnarizine, reserpine, amphetamine, or monoamine oxidase A inhibitors in the past 3 months
• Treatment with pramipexole in the past 4 months
• Treatment with neuroleptics, metoclopramide, alphamethyldopa, or flunarizine in the past 6 months
• An unstable dosage of selegiline, amantadine, anticholinergic therapy, or other central nervous system active therapies in the past 2 months</td></tr>
<tr><td>Details</td><td>Baseline characteristics
<table>
<tr><td>Characteristics</td><td>Pramipexole (n=151)</td><td>Levodopa (n=150)</td></tr>
<tr><td>Age (yrs)</td><td>61.5(10.1)</td><td>60.9(10.5)</td></tr>
<tr><td>UPDRS II</td><td>9.1(4.1)</td><td>8.3(4.0)</td></tr>
<tr><td>UPDRS III</td><td>22.3(9.2)</td><td>22.0(9.6)</td></tr>
<tr><td colspan="3">No. (%) of patients in Hoehn & Yahr stage:</td></tr>
<tr><td>I</td><td>27(17.9)</td><td>33(22.0)</td></tr>
<tr><td>I.5</td><td>23(15.2)</td><td>17(11.3)</td></tr>
<tr><td>II</td><td>75(49.7)</td><td>78(52.0)</td></tr>
<tr><td>II.5</td><td>21(13.9)</td><td>13(8.7)</td></tr>
</table></td></tr>
</table>

<table>
<tr><th>Bibliographic reference</th><th>Parkinson Study, Group, Pramipexole vs levodopa as initial treatment for Parkinson disease: A randomised controlled trial. Parkinson Study Group, JAMA 284, 1931-8, 2000</th></tr>
<tr><td></td><td>
<table>
<tr><td>III</td><td>5(3.3)</td><td>9(6.0)</td></tr>
<tr><td>Parkinson's Disease Quality-of-Life Scale</td><td>30.5(10.7)</td><td>28.1(10.4)</td></tr>
<tr><td>EQ-VAS</td><td>75.1(15.6)</td><td>77.6(12.0)</td></tr>
</table>
Values are expressed as mean (SD) unless otherwise indicated.
</td></tr>
<tr><td>Interventions</td><td>Pramipexole: 0.25mg, 0.5mg or 1mg three times per day.
Carbidopa/Levodopa: 12.5/50mg or 25/100mg three times per day

Subjects entered a 10-week dosage escalation period. All subjects were escalated initially to a daily dosage of 1.5mg pramipexole or 75/300mg carbidopa/levodopa. Subject requiring additional therapy could escalate to 3mg pramipexole or 112.5/450mg carbidopa/levodopa or 4.5mg pramipexole or 150/600mg carbidopa/levodopa. Thereafter (from week 11), investigators were permitted to add open-label levodopa or other antiparkinsonian medications to treat ongoing or emerging disability.</td></tr>
<tr><td>Primary outcomes</td><td>Time to the first occurrence of dopaminergic complications: wearing off, dyskinesias, on-off fluctuations, and freezing
Adverse events</td></tr>
<tr><td>Secondary outcomes</td><td>Changes in scores of the UPDRS, Parkinson's Disease Quality of Life scale the EuroQol Visual Analog Scale, as well as the need for supplemental levodopa.</td></tr>
<tr><td>Results</td><td>Treatment effects on dopaminergic end points:
<table>
<tr><td>End points</td><td>Pramipexole no (%) (n=151)</td><td>Levodopa No. (%) (n=150)</td><td>HR (95% CI)</td><td>P value</td></tr>
<tr><td>First dopaminergic complication*</td><td>42(27.8)</td><td>76(50.7)</td><td>0.45(0.30-0.66)</td><td><.001</td></tr>
<tr><td>Wearing off</td><td>36(23.8)</td><td>57(38.0)</td><td>0.57(0.37-0.88)</td><td>.01</td></tr>
<tr><td>Dyskinesias</td><td>15(9.9)</td><td>46(30.7)</td><td>0.33(0.18-0.60)</td><td><.001</td></tr>
<tr><td>On-off fluctuations</td><td>2(1.3)</td><td>8(5.3)</td><td>0.27(0.06-1.32)</td><td>.11</td></tr>
</table>
*Defined as the first occurrence of wearing off, dyskinesia, or on-off fluctuations.

Mean changes from baseline to month 48 in UPDRS scores:</td></tr>
</table>

Bibliographic reference	Parkinson Study, Group, Pramipexole vs levodopa as initial treatment for Parkinson disease: A randomised controlled trial. Parkinson Study Group, JAMA 284, 1931-8, 2000

Scale score	Pramipexole (n=151)	Levodopa (n=150)	Treatment effect (95% CI)	P value
Total UPDRS	4.5(12.7)	9.2(10.8)	-5.0(-7.6 to -2.4)	<.001
Motor	3.4(8.6)	7.3(8.6)	-3.9(-5.7 to -2.1)	<.001
ADL	1.1(4.5)	2.2(3.2)	-1.4(-2.2 to -0.5)	.001
Mental	0.0(1.6)	-0.2(1.2)	0.1(-0.2 to 0.3)	.72

Values are mean (SD). Positive values indicate improvement.

Adverse events by treatment group:

Adverse event	Pramipexole n (%) (n=151)	Levodopa n (%) (n=150)
Somnolence	49(32.4)	26(17.3)a
Hallucination	14(9.3)	5(3.3)b
Generalised oedema	27(17.9)	12(8.0)b
Peripheral oedema	22(14.6)	6(4.0)a
Nausea	55(36.4)	55(36.7)
Dizziness	39(25.8)	36(24.0)
Insomnia	39(25.8)	33(22.0)
Headache	31(20.5)	23(15.3)
Constipation	31(20.5)	19(12.7)
Depression	23(15.2)	20(13.3)
Abnormal dreams	21(13.9)	19(12.7)
Anxiety	17(11.3)	10(6.7)

Bibliographic reference	Parkinson Study, Group, Pramipexole vs levodopa as initial treatment for Parkinson disease: A randomised controlled trial. Parkinson Study Group, JAMA 284, 1931-8, 2000
	<table><tr><td>Postural hypotension</td><td>9(6.0)</td><td>15(10)</td></tr></table> [a]p<.01 for comparison of pramipexole with levodopa. [b]p<.05 for comparison of pramipexole with levodopa.
Overall Risk of Bias	1. Has an appropriate method of randomisation been used? Yes 2. Was there adequate concealment of allocation? Yes 3. Were the groups comparable at baseline for all major confounding/prognostic factors? Yes 4. Did the comparison groups receive the same care apart from interventions studied? Unclear 5. Were participants receiving care kept blind to treatment allocation? Yes 6. Were the individuals administering care kept blind to treatment allocation? Yes 7. Were groups comparable with respect to availability of outcome data and for how many participants were no outcome data available? Unclear 8. Did the study have an appropriate length of follow up? Yes 9. Did the study use a precise definition of outcome? Yes 10. Was a valid and reliable method used to determine that outcome? Yes 11. Were investigators kept blind to participant's exposure to the intervention? Yes 12. Were investigators kept blind to other important confounding and prognostic factors? Unclear

Bibliographic reference	Poewe,W., Rascol,O., Barone,P., Hauser,R.A., Mizuno,Y., Haaksma,M., Salin,L., Juhel,N., Schapira,A.H.V., Extended-release pramipexole in early Parkinson disease A 33-week randomised controlled trial, Neurology.77 (8) (pp 759-766), 2011.Date of Publication: 23 Aug 2011., 759-766, 2011
Country/ies where the study was carried out	Argentina, Austria, Czech Republic, Finland, Germany, Hungary, India, Japan, Malaysia, Russia, Slovakia, Taiwan, Ukraine, and the US
Study type	Multicentre, randomised, double-blind, parallel study
Aim of the study	To assess the clinical efficacy, safety, tolerability of a novel once-daily extended-release (ER) formulation of the dopamine agonist pramipexole as monotherapy in patients with early Parkinson disease and establish its non-inferiority vs standard immediate-release (IR) pramipexole.
Study dates	Study dates: Not reported Study duration: 33 weeks

<table>
<tr><th>Bibliographic reference</th><th>Poewe,W., Rascol,O., Barone,P., Hauser,R.A., Mizuno,Y., Haaksma,M., Salin,L., Juhel,N., Schapira,A.H.V., Extended-release pramipexole in early Parkinson disease A 33-week randomised controlled trial, Neurology.77 (8) (pp 759-766), 2011.Date of Publication: 23 Aug 2011., 759-766, 2011</th></tr>
<tr><td>Source of funding</td><td>Boehringer Ingelheim</td></tr>
<tr><td>Sample size</td><td>In total: n=539; Pramipexole ER n=223; Pramipexole IR n=213; Placebo n=103</td></tr>
<tr><td>Inclusion criteria</td><td>• A diagnosis of PD based on the presence of bradykinesia and either resting tremor or rigidity
• Hoehn & Yahr I-III
• Had disease duration of no more than 5 years
• ≥30 years of age at the time of diagnosis
• Had reached a level of clinical disability requiring initiation or augmentation of dopaminergic therapy
• Current treatment with antiparkinsonian anticholinergics, monoamine oxidase B inhibitors, amantadine or beta-blockers(when given for PD) was allowed, provided the dose had been kept stable for at least 4 weeks.
• Previous therapy with levodopa of less than 3 months total duration was also permitted if discontinued at least 8 weeks before randomisation.
• Previous dopamine agonist exposure was allowed if discontinued at least 4 weeks before randomisation.</td></tr>
<tr><td>Exclusion criteria</td><td>• MMSE score <24
• Signs suggestive of an atypical parkinsonian syndrome
• Medical or DSM-IV psychiatric disorders capable of impeding the patient's trial participation
• Clinically significant hypotension or electrocardiographic abnormalities
• Creatinine clearance <50 mL/min
• Women with childbearing potential were excluded for pregnancy or inadequate contraception</td></tr>
<tr><td>Details</td><td>Baseline demographics were similar among the 3 patient groups. Use of PD medication at baseline was also similar.
<table>
<tr><td>Characteristics</td><td>Placebo (n=103)</td><td>Pramipexole ER (n=223)</td><td>Pramipexole IR (n=213)</td></tr>
<tr><td>Mean age, y, mean (SD)</td><td>62.0(9.6)</td><td>61.3(9.8)</td><td>61.7(9.6)</td></tr>
<tr><td>Mean PD duration, y, mean (SD)</td><td>0.9(1.0)</td><td>1.0(1.2)</td><td>1.1(1.4)</td></tr>
<tr><td colspan="4">Modified Hoehn & Yahr stage, %</td></tr>
<tr><td>I-I.5</td><td>29.1</td><td>33.6</td><td>29.6</td></tr>
<tr><td>II-III</td><td>70.9</td><td>66.4</td><td>70.4</td></tr>
</table></td></tr>
</table>

Bibliographic reference	**Poewe,W., Rascol,O., Barone,P., Hauser,R.A., Mizuno,Y., Haaksma,M., Salin,L., Juhel,N., Schapira,A.H.V., Extended-release pramipexole in early Parkinson disease A 33-week randomised controlled trial, Neurology.77 (8) (pp 759-766), 2011.Date of Publication: 23 Aug 2011., 759-766, 2011**

Native to PD therapy, %	38.3	40.8	36.2
UPDRS II, mean (SD)	7.6(4.4)	7.9(4.3)	7.8(3.7)
UPDRS III, mean (SD)	21.4(11.7)	21.9(9.9)	21.1(9.3)

Interventions

7-week flexible titration using the following dose escalation levels per week:
Pramipexole ER: 0.375, 0.75, 1.5, 2.25, 3.0, 3.75, or 4.5 mg once daily
Pramipexole IR: 0.125, 0.25, 0.50, 0.75, 1.0, 1.25, 1.5 mg 3 times daily

Primary outcomes

- Change from baseline to week 33 in combined score on UPDRS II and III
- Adverse events

Secondary outcomes

- Responder rates on the PGI-I and on the Clinical Global Impression Improvement scales
- UPDRS II+III responder rate
- UPDRS I, II, III scores separately
- Proportions of patients requiring levodopa rescue
- Quality of life assessment on PDQ-39 and the EQ-5D

Results

Efficacy results at week 33 with levodopa rescue censored (adjusted mean change (95% CI), p vs. placebo):

	Placebo (n=103)a	Pramipexole ER (n=213)b	Pramipexole IR (n=207)c
UPDRS II	-0.2(-0.9 to 0.4)	-2.1(-2.5 to -1.6) (<0.0001)	-2.4(-2.8 to -1.9) (<0.0001)
UPRDS III	-1.1(-2.5 to 0.3)	-6.1(-7.1 to -5.1) (<0.0001)	-6.4(-7.4 to -5.4) (<0.0001)
PDQ-39	-1.5(-4.4 to 1.5)	-3.8(-5.9 to -1.8) (0.1802)	-6.5(-8.6 to -4.5) (0.0043
EQ-5D VAS	2.1(-1.8 to 6.1)	4.2(1.5 to 7.0) (0.3820)	5.9(3.2 to 8.7) (0.1090)

Adverse events, 33-week analysis:

Adverse event	Placebo (n=103)	Pramipexole ER (n=223)	Pramipexole IR (n=213)
Total discontinuation, n (%)	12(11.7)	49(22.0)	37(17.4)

Bibliographic reference	Poewe,W., Rascol,O., Barone,P., Hauser,R.A., Mizuno,Y., Haaksma,M., Salin,L., Juhel,N., Schapira,A.H.V., Extended-release pramipexole in early Parkinson disease A 33-week randomised controlled trial, Neurology.77 (8) (pp 759-766), 2011.Date of Publication: 23 Aug 2011., 759-766, 2011

AEs by category, n (%)			
Any	80(77.7)	189(84.8)	172(80.8)
Severe*	4(3.9)	12(5.4)	11(5.2)
Serious**	4(3.9)	16(7.2)	11(5.2)
Drug-related	40(38.8)	141(63.2)	134(62.9)
Leading to discontinuation	4(3.9)	24(10.8)	20(9.4)
AEs by type, n(%)***			
Somnolence	15(14.6)	81(36.3)	70(32.9)
Nausea	9(8.7)	48(21.5)	51(23.9)
Constipation	2(1.9)	32(14.3)	25(11.7)
Dizziness	7(6.8)	26(11.7)	25(11.7)
Dry mouth	1(1.0)	12(5.4)	8(3.8)

*Incapacitating or causing inability to work or undertake usual activities.

**Fatal, immediately life-threatening, requiring or prolonging hospitalization, or resulting in significant disability.

*** With frequency ≥5% in either pramipexole group and >3 percentage points more frequent for pramipexole than for placebo.

Overall Risk of Bias	1. Has an appropriate method of randomisation been used? Yes 2. Was there adequate concealment of allocation? Yes 3. Were the groups comparable at baseline for all major confounding/prognostic factors? Yes 4. Did the comparison groups receive the same care apart from interventions studied? Unclear 5. Were participants receiving care kept blind to treatment allocation? Yes 6. Were the individuals administering care kept blind to treatment allocation? Yes 7. Were groups comparable with respect to availability of outcome data and for how many participants were no outcome data available? Unclear

Bibliographic reference	Poewe,W., Rascol,O., Barone,P., Hauser,R.A., Mizuno,Y., Haaksma,M., Salin,L., Juhel,N., Schapira,A.H.V., Extended-release pramipexole in early Parkinson disease A 33-week randomised controlled trial, Neurology.77 (8) (pp 759-766), 2011.Date of Publication: 23 Aug 2011., 759-766, 2011
	8. Did the study have an appropriate length of follow up? Yes 9. Did the study use a precise definition of outcome? Yes 10. Was a valid and reliable method used to determine that outcome? Yes 11. Were investigators kept blind to participant's exposure to the intervention? Unclear 12. Were investigators kept blind to other important confounding and prognostic factors? Unclear

Bibliographic reference	Rascol, O., Brooks, D. J., Brunt, E. R., Korczyn, A. D., Poewe, W. H., Stocchi, F., Ropinirole in the treatment of early Parkinson's disease: a 6-month interim report of a 5-year levodopa-controlled study. 056 Study Group, Movement Disorders, 13, 39-45, 1998
Country/ies where the study was carried out	Europe, Israel and Canada
Study type	Multicentre, randomised, double-blind trial
Aim of the study	To compare the efficacies and side-effect profiles of ropinirole and L-dopa plus benserazide in patients with early PD.
Study dates	Study dates: Not reported Study duration: 6-month interim analysis of a 5-year study
Source of funding	Not reported
Sample size	In total: n=282; Ropinirole n=179; L-dopa n=89
Inclusion criteria	• ≥30 years old • Fulfilled criteria consistent with the Parkinson's disease Society of the United Kingdom Brain Tissue Bank for a clinical diagnosis of idiopathic PD • Hoehn and Yahr stages I-III • Required dopamine therapy • Patients cannot have received prior L-dopa or dopamine agonist therapy for more than 6 weeks, and any such treatment must be discontinued at least 2 weeks before study entry. • Concurrent treatment with selegiline was permitted at a constant dose but the use of other monoamine oxidase inhibitors must be discontinued at least 2 weeks before the start of treatment. Patients were allowed to continue receiving anticholinergics and amantadine, provided that the doses remained constant. Concurrent administration of other

<table>
<tr><th>Bibliographic reference</th><th>Rascol, O., Brooks, D. J., Brunt, E. R., Korczyn, A. D., Poewe, W. H., Stocchi, F., Ropinirole in the treatment of early Parkinson's disease: a 6-month interim report of a 5-year levodopa-controlled study. 056 Study Group, Movement Disorders, 13, 39-45, 1998</th></tr>
<tr><td></td><td>dopaminergic agents, apart from L-dopa rescue therapy, was not permitted, nor was the introduction of selegiline, anticholinergics, or amantadine after the start of the study.</td></tr>
<tr><td>Exclusion criteria</td><td>Patients with:
• Severe systemic or psychiatric disease
• A history of drug or alcohol dependence
• Severe dementia or other clinically relevant abnormalities
• Evidence of postural hypotension
• Previous treatment with ropinirole or a contraindication to L-dopa</td></tr>
<tr><td>Details</td><td>The baseline characteristics of the two study populations were similar:
<table>
<tr><td>Characteristics</td><td>Ropinirole (n=179)</td><td>L-dopa (n=89)</td></tr>
<tr><td>Mean age (yrs)</td><td>63(9)</td><td>63(9)</td></tr>
<tr><td>Mean duration of disease (months)</td><td>30(34)</td><td>29(27)</td></tr>
<tr><td colspan="3">Hoehn & Yahr stage (%):</td></tr>
<tr><td>I</td><td>12.8</td><td>22.5</td></tr>
<tr><td>I.5</td><td>15.1</td><td>9.0</td></tr>
<tr><td>II</td><td>36.9</td><td>37.1</td></tr>
<tr><td>II.5</td><td>25.7</td><td>23.1</td></tr>
<tr><td>III</td><td>9.5</td><td>10.1</td></tr>
<tr><td>Mean baseline UPDRS III score</td><td>21.5(10.5)</td><td>21.7(11.3)</td></tr>
</table>
Values are given in mean (SD).</td></tr>
<tr><td>Interventions</td><td>Ropinirole: Starting dose of 0.25mg three times a day to a maximum of 24mg per day (8mg three times daily)
L-dopa: Starting dose of 50mg once a day to a maximum of 1200mg per day (400mg three times daily)
The doses were titrated at weekly intervals according to patient's clinical response. There were 13 dose titration levels for each treatment group. L-dopa was given twice daily at dose level 2, and tid from dose level 3 and beyond.</td></tr>
</table>

<table>
<tr><th>Bibliographic reference</th><th>Rascol, O., Brooks, D. J., Brunt, E. R., Korczyn, A. D., Poewe, W. H., Stocchi, F., Ropinirole in the treatment of early Parkinson's disease: a 6-month interim report of a 5-year levodopa-controlled study. 056 Study Group, Movement Disorders, 13, 39-45, 1998</th></tr>
<tr><td></td><td>If therapeutic efficacy could not be maintained, open L-dopa was administered as rescue therapy.</td></tr>
<tr><td>Primary outcomes</td><td>• Percentage improvement in the UPDRS III score
• Adverse events</td></tr>
<tr><td>Secondary outcomes</td><td>• UPDRS total
• Clinical Global Impression</td></tr>
<tr><td>Results</td><td>After 6 months of treatment, the UPDRS scores were 15.7 (SD 9.0) in the ropinirole group and 13.3. (SD 8.6) in the L-dopa group. The percentage improvement was 32% in the ropinirole group and 44% in the L-dopa group, a significant difference of 12% points (-12%) (95% CI [-20%, -5%]).

Emergent adverse events occurring in >5% of patients:
<table>
<tr><td>Adverse events</td><td>Ropinirole n (%) (n=179)</td><td>L-dopa n (%) (n=89)</td></tr>
<tr><td>Nausea</td><td>70(39.1)</td><td>29(32.6)</td></tr>
<tr><td>Insomnia</td><td>22(12.3)</td><td>9(10.1)</td></tr>
<tr><td>Somnolence</td><td>22(12.3)</td><td>12(13.5)</td></tr>
<tr><td>Dizziness</td><td>21(11.7)</td><td>11(12.4)</td></tr>
<tr><td>Dyspepsia</td><td>21(11.7)</td><td>12(13.5)</td></tr>
<tr><td>Headache</td><td>19(10.6)</td><td>12(13.5)</td></tr>
<tr><td>Vomiting</td><td>17(9.5)</td><td>5(5.6)</td></tr>
<tr><td>Abnormal pain</td><td>15(8.4)</td><td>7(7.9)</td></tr>
<tr><td>Psychiatric symptoms</td><td>15(8.4)</td><td>4(4.5)</td></tr>
<tr><td>Tremor</td><td>14(7.8)</td><td>2(2.2)</td></tr>
<tr><td>Anxiety</td><td>13(7.3)</td><td>2(2.2)</td></tr>
<tr><td>Anorexia</td><td>10(5.6)</td><td>3(3.4)</td></tr>
</table></td></tr>
</table>

Bibliographic reference	Rascol, O., Brooks, D. J., Brunt, E. R., Korczyn, A. D., Poewe, W. H., Stocchi, F., Ropinirole in the treatment of early Parkinson's disease: a 6-month interim report of a 5-year levodopa-controlled study. 056 Study Group, Movement Disorders, 13, 39-45, 1998
	Postural Hypotension: 8(4.5); 5(5.6) Increased sweating: 8(4.5); 5(5.6) Abnormal Involuntary movements: 5(2.8); 10(11.2) Depression: 4(2.2); 5(5.6)
Overall Risk of Bias	1. Has an appropriate method of randomisation been used? Unclear 2. Was there adequate concealment of allocation? Yes 3. Were the groups comparable at baseline for all major confounding/prognostic factors? Yes 4. Did the comparison groups receive the same care apart from interventions studied? Yes 5. Were participants receiving care kept blind to treatment allocation? Yes 6. Were the individuals administering care kept blind to treatment allocation? Yes 7. Were groups comparable with respect to availability of outcome data and for how many participants were no outcome data available? Unclear 8. Did the study have an appropriate length of follow up? Yes 9. Did the study use a precise definition of outcome? Yes 10. Was a valid and reliable method used to determine that outcome? Yes 11. Were investigators kept blind to participant's exposure to the intervention? Unclear 12. Were investigators kept blind to other important confounding and prognostic factors? Unclear

Bibliographic reference	Rascol, O., Brooks, D. J., Korczyn, A. D., De Deyn, P. P., Clarke, C. E., Lang, A. E., A five-year study of the incidence of dyskinesia in patients with early Parkinson's disease who were treated with ropinirole or levodopa, New England Journal of Medicine, 342, 1484-91, 2000
Country/ies where the study was carried out	Europe, Israel and Canada
Study type	Multicentre, randomised, double-blind trial
Aim of the study	To compare the risk of dyskinesia in early Parkinson's disease among patients treated with ropinirole with that among patients treated with a combination of levodopa and benserazide over a period of 5 years.

<table>
<tr><th>Bibliographic reference</th><th>Rascol, O., Brooks, D. J., Korczyn, A. D., De Deyn, P. P., Clarke, C. E., Lang, A. E., A five-year study of the incidence of dyskinesia in patients with early Parkinson's disease who were treated with ropinirole or levodopa, New England Journal of Medicine, 342, 1484-91, 2000</th></tr>
<tr><td>Study dates</td><td>Study dates: Not reported
Study duration: 5 years</td></tr>
<tr><td>Source of funding</td><td>SmithKline Beecham Pharmaceuticals</td></tr>
<tr><td>Sample size</td><td>In total: n=268; Ropinirole n=179; Levodopa n=89</td></tr>
<tr><td>Inclusion criteria</td><td>• ≥30 years old
• Hoehn and Yahr stages I-III
• Prior short-term treatment with levodopa or dopamine agonists was limited to a maximum of 6 weeks and had to be discontinued at least 2 weeks before study entry.</td></tr>
<tr><td>Exclusion criteria</td><td>Patients with:
• Severe dizziness or fainting
• Severe systemic disease
• Major psychosis
• Severe dementia
• Alcoholism or drug dependence
• A contraindication to levodopa
• Treatment with a monoamine oxidase inhibitor within 2 weeks before study entry (with the exception of selegiline) or previous treatment with ropinirole</td></tr>
<tr><td>Details</td><td>The demographic characteristics of the two groups were similar:
<table>
<tr><td>Characteristics</td><td>Ropinirole (n=179)</td><td>L-dopa (n=89)</td></tr>
<tr><td>Mean age (yrs)</td><td>63(9)</td><td>63(9)</td></tr>
<tr><td>Mean duration of disease (months)</td><td>30(34)</td><td>29(27)</td></tr>
<tr><td colspan="3">Hoehn & Yahr stage (%):</td></tr>
<tr><td>I</td><td>23(12.8)</td><td>20(22.5)</td></tr>
<tr><td>I.5</td><td>27(15.1)</td><td>8(9.0)</td></tr>
</table></td></tr>
</table>

Bibliographic reference	Rascol, O., Brooks, D. J., Korczyn, A. D., De Deyn, P. P., Clarke, C. E., Lang, A. E., A five-year study of the incidence of dyskinesia in patients with early Parkinson's disease who were treated with ropinirole or levodopa, New England Journal of Medicine, 342, 1484-91, 2000
	<table><tr><td>II</td><td>66(36.9)</td><td>33(37.1)</td></tr><tr><td>II.5</td><td>46(25.7)</td><td>19(21.3)</td></tr><tr><td>III</td><td>17(9.5)</td><td>9(10.1)</td></tr><tr><td>Mean baseline UPDRS III score</td><td>21.5(10.5)</td><td>21.7(11.3)</td></tr><tr><td>Mean baseline UPDRS II score</td><td>8.0(5.0)</td><td>8.0(4.6)</td></tr></table>Values are given in mean (SD).
Interventions	Ropinirole: Starting dose of 0.25mg three times a day to a maximum of 24mg per day (8mg three times daily) L-dopa: Starting dose of 50mg once a day to a maximum of 1200mg per day (400mg three times daily) The doses were titrated at weekly intervals according to patient's clinical response. There were 13 dose titration levels for each treatment group. L-dopa was given twice daily at dose level 2, and tid from dose level 3 and beyond. If therapeutic efficacy could not be maintained, open L-dopa was administered as rescue therapy.
Primary outcomes	• Dyskinesia • Adverse events
Secondary outcomes	• Scores of UPDRS II and III • UPDRS item 39 assessing "Wearing off" period • UPDRS item 14 assessing "Freezing when walking"
Results	Hazard ratio for remaining free dyskinesia in the ropinirole group, as compared with the levodopa group, 2.82; 95% CI, 1.78 to 4.44; P<0.001. Overall, dyskinesia developed in 36 of the 177 patients in the ropinirole group (20%) and in 40 of the 88 in the levodopa group (45%), as assessed by item 32 in the UPDRS and by reports of adverse events. Before the addition of supplementary levodopa, 9 of 177 patients in the ropinirole group (5%) and 32 of 88 in the levodopa group (36%) had dyskinesia. Adverse events occurring in 10% or more of either group in the ITT analysis: <table><tr><td>Adverse event*</td><td>Ropinirole n (%) (n=179)</td><td>Levodopa n (%) (n=89)</td></tr></table>

Bibliographic reference	Rascol, O., Brooks, D. J., Korczyn, A. D., De Deyn, P. P., Clarke, C. E., Lang, A. E., A five-year study of the incidence of dyskinesia in patients with early Parkinson's disease who were treated with ropinirole or levodopa, New England Journal of Medicine, 342, 1484-91, 2000		
	Nausea	87(48.6)	44(49.4)
	Somnolence	49(27.4)	17(19.1)
	Insomnia	45(25.1)	21(23.6)
	Aggravated PD	40(22.3)	18(20.2)
	Dyspepsia	37(20.7)	15(16.9)
	Dizziness	36(20.1)	17(19.1)
	Hallucinations	31(17.3)	5(5.6)
	Vomiting	29(16.2)	10(11.2)
	Tremor	29(16.2)	11(12.4)
	Abdominal pain	27(15.1)	13(14.6)
	Depression	26(14.5)	20(22.5)
	Headache	25(14.0)	16(18.0)
	Edema of the legs	25(14.0)	5(5.6)
	Ataxia	25(14.0)	8(9.0)
	Anxiety	21(11.7)	8(9.0)
	Postural hypotension	21(11.7)	11(12.4)
	Constipation	17(9.5)	11(12.4)
	Dyskinesia	16(8.9)	23(25.8)
	Dystonia	12(6.7)	11(12.4)
	Increased sweating	11(6.1)	9(10.1)

Bibliographic reference	Rascol, O., Brooks, D. J., Korczyn, A. D., De Deyn, P. P., Clarke, C. E., Lang, A. E., A five-year study of the incidence of dyskinesia in patients with early Parkinson's disease who were treated with ropinirole or levodopa, New England Journal of Medicine, 342, 1484-91, 2000
	*Patients often had more than one adverse event.
Overall Risk of Bias	1. Has an appropriate method of randomisation been used? Yes 2. Was there adequate concealment of allocation? Yes 3. Were the groups comparable at baseline for all major confounding/prognostic factors? Yes 4. Did the comparison groups receive the same care apart from interventions studied? Unclear 5. Were participants receiving care kept blind to treatment allocation? Yes 6. Were the individuals administering care kept blind to treatment allocation? Yes 7. Were groups comparable with respect to availability of outcome data and for how many participants were no outcome data available? Unclear 8. Did the study have an appropriate length of follow up? Yes 9. Did the study use a precise definition of outcome? Yes 10. Was a valid and reliable method used to determine that outcome? Yes 11. Were investigators kept blind to participant's exposure to the intervention? Unclear 12. Were investigators kept blind to other important confounding and prognostic factors? Unclear

Bibliographic reference	Whone, A. L., Watts, R. L., Stoessl, A. J., Davis, M., Reske, S., Nahmias, C., Lang, A. E., Rascol, O., Ribeiro, M. J., Remy, P., Poewe, W. H., Hauser, R. A., Brooks, D. J., Slower progression of Parkinson's disease with ropinirole versus levodopa: The REAL-PET study, Annals of Neurology, 54, 93-101, 2003
Country/ies where the study was carried out	Not reported
Study type	Randomised, double-blind, multinational study
Aim of the study	To compare the rates of loss of dopamine-terminal function in de novo patients with clinical and F-dopa PET evidence of early PD.
Study dates	Study dates: June 1997 to April 1999 Study duration: 2 years
Source of funding	GlaxoSmithKline
Sample size	In total: n=162; Ropinirole n= 87; L-dopa n=75

<table>
<tr><th>Bibliographic reference</th><th>Whone, A. L., Watts, R. L., Stoessl, A. J., Davis, M., Reske, S., Nahmias, C., Lang, A. E., Rascol, O., Ribeiro, M. J., Remy, P., Poewe, W. H., Hauser, R. A., Brooks, D. J., Slower progression of Parkinson's disease with ropinirole versus levodopa: The REAL-PET study, Annals of Neurology, 54, 93-101, 2003</th></tr>
<tr><td>Inclusion criteria</td><td>• Aged 30 to 75 years with a clinical diagnosis of idiopathic PD
• Hoehn and Yahr stages I-II.5 with a symptom duration of 2 years or less
• Patients who had not previously received treatment with L-dopa or dopamine agonist and were considered by their local neurologist to require such therapy
• Amantadine and anticholinergic antiparkinsonian medications were permitted but at a fixed dose from study onset. Concomitant selegiline was not allowed and was discontinued at least 6 weeks before the study started.</td></tr>
<tr><td>Exclusion criteria</td><td>Patients with:
• Pronounced head tremor or postural dizziness
• Potentially producing difficulty with imaging
• Severe psychiatric or severe systemic physical illness, including diabetes and other severe endocrine disorders</td></tr>
<tr><td>Details</td><td>Baseline demographics and disease characteristics of the groups were similar:
<table>
<tr><td>Characteristics</td><td>Ropinirole, mean (SD) (n=87)</td><td>L-dopa, mean (SD) (n=75)</td></tr>
<tr><td>Age (yr)</td><td>61.0(8.60)</td><td>59.9(9.23)</td></tr>
<tr><td>Age range (yr)</td><td>34-79</td><td>32-76</td></tr>
<tr><td>Symptom of duration (months)</td><td>15.6(6.79)</td><td>16.3(6.55)</td></tr>
<tr><td>Symptom of duration range (months)</td><td>1-27</td><td>3-35</td></tr>
<tr><td colspan="3">Hoehn & Yahr score, n (%):</td></tr>
<tr><td>I</td><td>19(21.8%)</td><td>22(29.3%)</td></tr>
<tr><td>I.5</td><td>13(14.9%)</td><td>9(12.0%)</td></tr>
<tr><td>II</td><td>39(44.8%)</td><td>34(45.3%)</td></tr>
<tr><td>II.5</td><td>16(18.4%)</td><td>10(13.3%)</td></tr>
<tr><td>UPDRS III</td><td>19.2(8.74)</td><td>17.7(8.20)</td></tr>
<tr><td>UPDRS III range</td><td>5+40</td><td>3-38</td></tr>
</table></td></tr>
</table>

Bibliographic reference	**Whone, A. L., Watts, R. L., Stoessl, A. J., Davis, M., Reske, S., Nahmias, C., Lang, A. E., Rascol, O., Ribeiro, M. J., Remy, P., Poewe, W. H., Hauser, R. A., Brooks, D. J., Slower progression of Parkinson's disease with ropinirole versus levodopa: The REAL-PET study, Annals of Neurology, 54, 93-101, 2003**
Interventions	Ropinirole: Initial doses of 0.75mg/d (0.25mg three times a day) Carbidopa/L-dopa: 50mg/day Over the first 4 weeks of the study, doses were escalated to three times daily regimens of ropinirole, 3mg/day, or L-dopa, 300mg/day. Titration was then flexible, based on clinical response and tolerability, to a maximum 24mg/day ropinirole or 1000mg/day L-dopa. If symptoms were inadequately controlled, patients could receive open-label, supplementary L-dopa.
Primary outcomes	The rates of loss of dopamine-terminal function
Secondary outcomes	• Change from baseline to completion in UPDRS III (motor) scores • The proportion of patients scoring 1 or 2 on the Clinical Global Impression Improvement scale • Incidence and time to development of dyskinesias
Results	Incidence of dyskinesia: Significantly fewer patients in the ropinirole group (3/87, 3.4%; one receiving open-label L-dopa) developed dyskinesias compared with the L-dopa group (20/75, 26.7%; OR, 0.09; 95% CI, 0.02-0.29; p<0.001). There was also a significant difference in favour of ropinirole in the time to develop dyskinesias (hazard ratio, 8.28; 95% CI, 2.46-27.93, p<0.001). Adverse events: Similar proportions of patients (87 ropinirole, 75 L-dopa) reported nonserious adverse events (ropinirole, 95.4%l L-dopa, 86.7%). nausea and somnolence were the most commonly reported adverse events, and both were more common in patients receiving ropinirole than in those receiving L-dopa. Hallucinations, depression, and confusion occurred in less than 10% of patients on each treatment (six and one patients; six and seven patients, five and one patients, ropinirole vs. L-dopa, respectively). Serious adverse events were experienced by 18 ropinirole and 17 L-dopa-treated patients with no contribution of concern from any one event.
Overall Risk of Bias	1. Has an appropriate method of randomisation been used? Yes 2. Was there adequate concealment of allocation? Unclear 3. Were the groups comparable at baseline for all major confounding/prognostic factors? Yes 4. Did the comparison groups receive the same care apart from interventions studied? Unclear 5. Were participants receiving care kept blind to treatment allocation? Yes 6. Were the individuals administering care kept blind to treatment allocation? Yes 7. Were groups comparable with respect to availability of outcome data and for how many participants were no outcome

Bibliographic reference	**Whone, A. L., Watts, R. L., Stoessl, A. J., Davis, M., Reske, S., Nahmias, C., Lang, A. E., Rascol, O., Ribeiro, M. J., Remy, P., Poewe, W. H., Hauser, R. A., Brooks, D. J., Slower progression of Parkinson's disease with ropinirole versus levodopa: The REAL-PET study, Annals of Neurology, 54, 93-101, 2003**
	data available? Yes 8. Did the study have an appropriate length of follow up? Yes 9. Did the study use a precise definition of outcome? Yes 10. Was a valid and reliable method used to determine that outcome? Yes 11. Were investigators kept blind to participant's exposure to the intervention? Unclear 12. Were investigators kept blind to other important confounding and prognostic factors? Unclear

Bibliographic reference	**Gray,R.FAU, Ives,N.FAU, Rick,C.FAU, Patel S FAU - Gray,Alastair, Gray,A.FAU, Jenkinson,C.FAU, McIntosh E FAU - Wheatley,Keith, Wheatley,K.FAU, Williams,A.FAU, Clarke,C.E., Long-term effectiveness of dopamine agonists and monoamine oxidase B inhibitors compared with levodopa as initial treatment for Parkinson's disease (PD MED): a large, open-label, pragmatic randomised trial, Lancet, -1196, 2014**
Country/ies where the study was carried out	UK, Czech Republic, Russia
Study type	Open-label, pragmatic, randomised trial
Aim of the study	To establish which of the three classes of drug, as initial treatment, provides the most effective long-term control of symptoms and best quality of life for people with early Parkinson's disease.
Study dates	Study dates: 09 Nov 2000 to 22 Dec 2009 Study duration: 7 years
Source of funding	UK National Institute for Health Research Health Technology Assessment Programme, UK department of Health, UK Medical Research Council, Parkinson's UK.
Sample size	In total: 1620; Levodopa n=528; Dopamine agonist n=632; MAOBI n=460
Inclusion criteria	• People diagnosed with idiopathic Parkinson's disease • Previously untreated or had been treated for less than 6 months with dopaminergic drugs and if there was uncertainty as which class of drug to use.
Exclusion criteria	• Dementia • Inability to complete questionnaires
Details	1058 (65%) of 1620 were randomly assigned three ways between dopamine agonists, MAOBI, and levodopa, 348 (21%) were

Bibliographic reference	**Gray,R.FAU, Ives,N.FAU, Rick,C.FAU, Patel S FAU - Gray,Alastair, Gray,A.FAU, Jenkinson,C.FAU, McIntosh E FAU - Wheatley,Keith, Wheatley,K.FAU, Williams,A.FAU, Clarke,C.E., Long-term effectiveness of dopamine agonists and monoamine oxidase B inhibitors compared with levodopa as initial treatment for Parkinson's disease (PD MED): a large, open-label, pragmatic randomised trial, Lancet, -1196, 2014**

assigned two ways between dopamine agonists and levodopa, and 214 (13%) were assigned two ways between dopamine agonists and MAOBI. Therefore, in total, 1406 were randomised between levodopa-sparing therapy and levodopa, and 919 between the two levodopa-sparing therapies, dopamine agonists and MAOBI. Patients assigned only between dopamine agonists and MAOBI had less severe disease and were younger. Other patient characteristics were balanced between randomisation and treatment groups:

Characteristics	Levodopa vs. levodopa sparing comparison		Levodopa-sparing comparison (dopamine agonist vs. MAOBI)	
	Levodopa (n=528)	Levodopa-sparing (n=878)	Dopamine agonist (n=459)	MAOBI (n=460)
Age (years)	71(34-94)	71(42-92)	69(27-92)	69(36-92)
Duration of PD (years)	0.6(0-10)	0.6(0-13)	0.6(0-6)	0.7(0-13)
Hoehn & Yahr stage:				
I-I.5	254(48%)	414(47%)	232(51%)	235(51%)
II	155(29%)	262(30%)	130(28%)	130(28%)
II.5-V	119(23%)	202(23%)	97(21%)	95(21%)
Previously received anti-PD treatments	46(9%)	74(8%)	37(8%)	38(8%)
PDQ-39 mobility score	31.2(25.5)	30.5(26.2)	28.3(26.5)	27.7(24.6)
PDQ-39 summary index	22.6(13.2)	22.3(14.0)	21.7(13.5)	21.4(13.2)

Data are in mean (range), n(%), or mean (SD).

Interventions	Levodopa: Mean daily dose was 347 (SD 139) at 1 year rising to 531mg (SD 229) at 7 years

<table>
<tr><th>Bibliographic reference</th><td>Gray,R.FAU, Ives,N.FAU, Rick,C.FAU, Patel S FAU - Gray,Alastair, Gray,A.FAU, Jenkinson,C.FAU, McIntosh E FAU - Wheatley,Keith, Wheatley,K.FAU, Williams,A.FAU, Clarke,C.E., Long-term effectiveness of dopamine agonists and monoamine oxidase B inhibitors compared with levodopa as initial treatment for Parkinson's disease (PD MED): a large, open-label, pragmatic randomised trial, Lancet, -1196, 2014</td></tr>
<tr><td></td><td>Dopamine agonists;
Ropinirole: Mean daily dose was 9mg/day (SD 4.5) at 1 year rising to 13mg/day (SD 6.7) at 7 years
Pramipexole: Mean daily dose was 2.2mg/day (SD 1.10; salt) at 1 year rising to 3.4mg/day (SD 1.5) at 7 years
MAOBI:
Selegiline: 8.4mg/day (SD 3.1) at 1 year and 8.6mg/day (SD 2.7) at 7 years
Rasagiline: 1mg/day (SD 0.1) at 1 and 7 years.</td></tr>
<tr><td>Primary outcomes</td><td>• Patient-rated functional status on the mobility subscale of the PDQ-39
• Cost-effectiveness</td></tr>
<tr><td>Secondary outcomes</td><td>• QALYs derived from the EQ-5D generic quality-of-life measure and a resource usage questionnaire
• PDQ-39 domains and overall score and compliance
• MMSE
• Onset of dementia
• Dyskinesias
• Motor fluctuations
• Admissions to hospital or institutional care
• Mortality</td></tr>
<tr><td>Results</td><td>Exposure to levodopa was similar in the dopamine agonists and MAOBI groups: averaging in all patients at 1 year, 96mg/d (SD 157) for dopamine agonists and 131mg/d (SD 172) for MAOBI, rising at 7 years to 526mg/d (SD 266) for dopamine agonists and 489mg/d (SD 246) for MAOBI. The mean daily dose in patients allocated to levodopa was 347mg (SD 139 at 1 year rising to 531mg (SD 229) at 7 years.

Estimated average differences between levodopa and levodopa-sparing groups, and between dopamine agonist and MAOBI, in the different PDQ-39 subscales and in EQ-5D:
<table>
<tr><td rowspan="2"></td><td colspan="2">Levodopa vs. levodopa-sparing</td><td colspan="2">Dopamine agonist vs. MAOBI</td><td rowspan="2">MID*</td></tr>
<tr><td>Estimate+ (95% CI)</td><td>p value</td><td>Estimate++ (95% CI)</td><td>p value</td></tr>
<tr><td>Mobility</td><td>1.8 (0.5 to 3.0)</td><td>0.005</td><td>1.4 (0.0 to 2.9)</td><td>0.05</td><td>3.2</td></tr>
</table></td></tr>
</table>

Bibliographic reference	Gray,R.FAU, Ives,N.FAU, Rick,C.FAU, Patel S FAU - Gray,Alastair, Gray,A.FAU, Jenkinson,C.FAU, McIntosh E FAU - Wheatley,Keith, Wheatley,K.FAU, Williams,A.FAU, Clarke,C.E., Long-term effectiveness of dopamine agonists and monoamine oxidase B inhibitors compared with levodopa as initial treatment for Parkinson's disease (PD MED): a large, open-label, pragmatic randomised trial, Lancet, -1196, 2014

ADL	1.9 (0.7 to 3.0)	0.002	0.3 (-1.1 to 1.7)	0.7	4.4
Emotional wellbeing	-0.2 (-1.1 to 0.7)	0.7	0.3 (-0.8 to 1.4)	0.6	4.2
Stigma	1.3 (0.2 to 2.3)	0.02	1.3 (0.0 to 2.5)	0.06	5.6
Social support	0.1 (-0.6 to 0.8)	0.8	0.8 (-0.1 to 1.7)	0.07	11.4
Cognition	1.0 (0.0 to 2.0)	0.05	1.7 (0.5 to 2.9)	0.005	1.8
Communication	0.9 (0.0 to 1.8)	0.05	0.5 (-0.6 to 1.5)	0.4	4.2
Bodily discomfort	1.4 (0.3 to 2.4)	0.01	0.7 (-0.6 to 2.0)	0.3	2.1
PDQ-39 summary index	1.0 (0.3 to 1.7)	0.008	0.8 (0.0 to 1.7)	0.05	1.6
EQ-5D utility score	0.03 (0.01 to 0.05)	0.0002	0.004 (-0.01 to 0.02)	0.6	-

*MID=minimally important difference.

+Positive numbers favour levodopa.

++Positive numbers favour MAOBI.

The side effects (mainly psychological, sleep disturbance, and gastrointestinal) were usually mild, only 16 patients (9 given dopamine agonists, 4 given MAOBI, and 3 given levodopa) had serious adverse events believed to be possibly related to trial treatment.

Patients in the levodopa group were more likely to develop dyskinesias than those in the levodopa-sparing group: HR: 1.52, 95% CI 1.16 to 2.00, p=0.003) but there was no difference in motor fluctuations (1.11, 0.90 to 1.37, p=0.3).

Rates of dyskinesias were similar (HR: 0.85, 95% CI 0.60 to 1.22, p=0.4) but motor fluctuations were higher (HR: 1.32, 95% CI 1.01 to 1.72, p=0.04) in the dopamine agonist group than in the MAOBI group.

Overall Risk of Bias	1. Has an appropriate method of randomisation been used? Yes 2. Was there adequate concealment of allocation? No 3. Were the groups comparable at baseline for all major confounding/prognostic factors? No

Bibliographic reference	Gray,R.FAU, Ives,N.FAU, Rick,C.FAU, Patel S FAU - Gray,Alastair, Gray,A.FAU, Jenkinson,C.FAU, McIntosh E FAU - Wheatley,Keith, Wheatley,K.FAU, Williams,A.FAU, Clarke,C.E., Long-term effectiveness of dopamine agonists and monoamine oxidase B inhibitors compared with levodopa as initial treatment for Parkinson's disease (PD MED): a large, open-label, pragmatic randomised trial, Lancet, -1196, 2014
	4. Did the comparison groups receive the same care apart from interventions studied? No 5. Were participants receiving care kept blind to treatment allocation? No 6. Were the individuals administering care kept blind to treatment allocation? No 7. Were groups comparable with respect to availability of outcome data and for how many participants were no outcome data available? Yes 8. Did the study have an appropriate length of follow up? Yes 9. Did the study use a precise definition of outcome? Yes 10. Was a valid and reliable method used to determine that outcome? Yes 11. Were investigators kept blind to participant's exposure to the intervention? No 12. Were investigators kept blind to other important confounding and prognostic factors? No

Bibliographic reference	Parkinson Study Group, Safety and efficacy of pramipexole in early Parkinson disease. A randomised dose-ranging study. Parkinson Study Group, JAMA, 125-130, 1997
Country/ies where the study was carried out	Not reported
Study type	Multicentre, multidosage, parallel-group, double-blind, placebo-controlled, randomised clinical trial
Aim of the study	To evaluate dose-response relationships for tolerability, safety, and efficacy of the synthetic dopamine agonist pramipexole.
Study dates	Study dates: April to September 1994 Study duration: 11 weeks
Source of funding	Pharmacia & Upjohn, Inc.
Sample size	In total: n=264; Pramipexole 1.5mg/d n=54; Pramipexole 3.0mg/d n=50; Pramipexole 4.5mg/d n=54; Pramipexole 6.0mg/d n=55; Placebo n=51
Inclusion criteria	• Adults who had idiopathic PD for less than 7 years • Did not require anti-PD treatment with levodopa or dopamine agonists and had not taken such medication within the 3 months prior to enrolment • Hoehn & Yahr stage I-III

<table>
<tr><th>Bibliographic reference</th><th>Parkinson Study Group, Safety and efficacy of pramipexole in early Parkinson disease. A randomised dose-ranging study. Parkinson Study Group, JAMA, 125-130, 1997</th></tr>
<tr><td></td><td>• The use of levodopa or other dopamine agonists was not permitted during the study; however, selegiline, anticholinergics and amantadine were permitted if administered at a stable dosage for 30 days prior to and throughout the duration of the study.</td></tr>
<tr><td>Exclusion criteria</td><td>Subjects with:
• Atypical parkinsonian syndromes
• Dementia, as defined by a MMSE score of 22 or less
• Serious concurrent illness, such as active cardiac, renal, liver or neoplastic disease
• Age younger than 30 years
• Treatment with an antipsychotic, neuroleptic, metoclopramide, methyldopa, flunarizine, methylphenidate, cinnarizine, reserpine, or amphetamine in the past 6 months</td></tr>
<tr><td>Details</td><td>Baseline characteristics:
<table>
<tr><td>Characteristics</td><td>Placebo (n=51)</td><td>Pramipexole 1.5mg/d (n=54)</td><td>Pramipexole 3.0mg/d (n=50)</td><td>Pramipexole 4.5mg/d (n=54)</td><td>Pramipexole 6.0mg/d (n=55)</td></tr>
<tr><td>Age, mean (SD), y</td><td>60.4(12.0)</td><td>60.3(10.5)</td><td>62.2(11.1)</td><td>62.8(10.5)</td><td>62.8(11.4)</td></tr>
<tr><td>Time since onset of symptoms, mean (SD), y</td><td>1.7(1.5)</td><td>1.8(1.5)</td><td>2.0(1.6)</td><td>1.9(1.5)</td><td>2.2(1.8)</td></tr>
<tr><td>UPDRS Total, mean (SD)</td><td>28.7(12.3)</td><td>29.0(13.7)</td><td>28.3(11.9)</td><td>27.3(12.9)</td><td>32.9(18.6)</td></tr>
<tr><td>Hoehn & Yahr stage, mean (SD)</td><td>1.8(0.5)</td><td>1.8(0.6)</td><td>1.9(0.5)</td><td>1.8(0.5)</td><td>1.9(0.6)</td></tr>
</table></td></tr>
<tr><td>Interventions</td><td>Pramipexole: 1.5, 3.0, 4.5, or 6.0mg per day.
A 6-week dosage escalation period was followed by a 4-week maintenance period and a 1-week period during which active treatment was withdrawn.</td></tr>
<tr><td>Primary outcomes</td><td>• The proportion of subjects completing the study on the assigned treatment
• Change from baseline to 10 weeks in the total score of UPDRS</td></tr>
<tr><td>Secondary outcomes</td><td>• Changes between baseline and 8 and 10 weeks in the mental, motor and activities of daily living subscale scores of the UPDRS
• Changes between baseline and 10 weeks in Hoehn and Yahr scores
• Adverse events</td></tr>
</table>

Bibliographic reference	Parkinson Study Group, Safety and efficacy of pramipexole in early Parkinson disease. A randomised dose-ranging study. Parkinson Study Group, JAMA, 125-130, 1997

Results

Changes from baseline to 10 weeks in Total UPDRS score:

Pramipexole dosage, mg/d	Difference* between treatment group mean and placebo group mean (98.75% CI)
1.5	-5.24 (-8.95 to -1.54)
3.0	-5.08 (-8.86 to -1.29)
4.5	-5.86 (-9.59 to -2.13
6.0	-5.24 (8.96 to -1.53

*Negative values indicate improvement.

The same pattern of treatment effect was apparent for the UPDRS II and UPDRS III score (data not reported in this publication).

Adverse effects:

Adverse event	Placebo n(%) (n=51)	Pramipexole 1.5mg/d, n(%) (n=54)	Pramipexole 3.0mg/d, n(%) (n=50)	Pramipexole 4.5mg/d, n(%) (n=54)	Pramipexole 6.0mg/d n(%) (n=55)	Combined pramipexole groups, n(%) (n=213)
Any event	40(78.4)	43(79.6)	42(84.0)	47(87.0)	49(89.1)	181(85.0)
Any event (moderate and severe intensity)	19(37.3)	24(44.4)	18(36.0)	23(42.6)	37(67.3)	102(47.9)
Somnolence	7(13.7)	9(16.7)	15(30.0)	17(31.5)	17(30.9)	58(27.2)
Dizziness	10(19.6)	10(18.5)	10(20.0)	9(16.7)	10(18.2)	39(18.3)
Nausea	5(9.8)	9(16.7)	9(18.0)	12(22.2)	12(21.8)	42(19.7)
Musculoskeletal pain	10(19.6)	8(14.8)	6(12.0)	3(5.6)	4(7.3)	21(9.8)
Headache	5(9.8)	5(9.2)	7(14.0)	8(14.8)	4(7.3)	24(11.3)
Constipation	3(5.9)	4(7.4)	6(12.0)	3(5.6)	10(18.2)	23(10.8)

Bibliographic reference	Parkinson Study Group, Safety and efficacy of pramipexole in early Parkinson disease. A randomised dose-ranging study. Parkinson Study Group, JAMA, 125-130, 1997

Insomnia	4(7.8)	2(3.7)	2(4.0)	7(13.0)	5(9.1)	16(7.5)
Fatigue	5(9.8)	4(7.4)	2(4.0)	2(3.7)	6(10.9)	14(6.6)
Hallucination	0(0)	4(7.4)	4(8.0)	1(1.9)	5(9.1)	14(6.6)
Confusion	0(0)	3(5.6)	2(4.0)	1(1.9)	3(5.5)	9(4.2)

Overall Risk of Bias

1. Has an appropriate method of randomisation been used? Yes
2. Was there adequate concealment of allocation? Yes
3. Were the groups comparable at baseline for all major confounding/prognostic factors? Yes
4. Did the comparison groups receive the same care apart from interventions studied? Unclear
5. Were participants receiving care kept blind to treatment allocation? Yes
6. Were the individuals administering care kept blind to treatment allocation? Yes
7. Were groups comparable with respect to availability of outcome data and for how many participants were no outcome data available? Yes
8. Did the study have an appropriate length of follow up? Yes
9. Did the study use a precise definition of outcome? Yes
10. Was a valid and reliable method used to determine that outcome? Yes
11. Were investigators kept blind to participant's exposure to the intervention? Unclear
12. Were investigators kept blind to other important confounding and prognostic factors? Unclear

Bibliographic reference	Parkinson Study Group, A controlled trial of rasagiline in early Parkinson disease: the TEMPO Study, Arch Neurol., 1937-1943, 2002
Country/ies where the study was carried out	US and Canada
Study type	Multi-centre, parallel-group, randomised, double-blind, placebo-controlled clinical trial.
Aim of the study	To evaluate the safety and efficacy of the selective monoamine oxidase type B inhibitor rasagiline on parkinsonian characteristics in untreated patients with early PD who had not developed sufficient disability to require dopaminergic therapy.
Study dates	Study dates: November 1997 to June 1999 Study duration: 26 weeks

<table>
<tr><th>Bibliographic reference</th><th>Parkinson Study Group, A controlled trial of rasagiline in early Parkinson disease: the TEMPO Study, Arch Neurol., 1937-1943, 2002</th></tr>
<tr><td>Source of funding</td><td>Teva Pharmaceuticals Industries, Ltd and Teva Neuroscience LLC</td></tr>
<tr><td>Sample size</td><td>In total: n=404; Rasagiline 1mg/d n=134; Rasagiline 2mg/d n=132; Placebo n=138</td></tr>
<tr><td>Inclusion criteria</td><td>• Older than 35 years who had the presence of at least 2 of the cardinal signs of PD
• Hoehn & Yahr I-III
• Patients could be treated with anticholinergic medications, but other antiparkinsonian medications, including levodopa, dopamine agonists, selegiline or amantadine were not permitted.</td></tr>
<tr><td>Exclusion criteria</td><td>Patients who had:
• Atypical or secondary parkinsonism
• Unstable medical problems, including congestive heart failure of New York Heart Association class II or greater
• Psychiatric problems that compromised the ability of the subjects to give informed consent
• An MMSE score of 23 or less
• Clinically significant depression
• Patients on antidepressants and sympathomimetics</td></tr>
<tr><td>Details</td><td>Baseline characteristics:
<table>
<tr><td>Characteristics</td><td>Placebo (n=138)</td><td>Rasagiline 1mg/d (n=134)</td><td>Rasagiline 2mg/d (n=132)</td><td>P value</td></tr>
<tr><td>Age (yrs)</td><td>60.5(10.8)</td><td>61.6(10.3)</td><td>60.4(11.4)</td><td>.76</td></tr>
<tr><td>Disease duration (yrs)</td><td>0.94(1.10)</td><td>0.92(1.24)</td><td>1.15(1.32)</td><td>.35</td></tr>
<tr><td>UPDRS II</td><td>6.2(3.5)</td><td>5.9(3.4)</td><td>6.7(3.2)</td><td>.04</td></tr>
<tr><td>UPDRS III</td><td>17.6(8.8)</td><td>17.9(8.9)</td><td>18.0(7.5)</td><td>.71</td></tr>
<tr><td>Hoehn and Yahr stage</td><td>1.9(0.5)</td><td>1.9(0.5)</td><td>1.9(0.5)</td><td>.93</td></tr>
<tr><td>PDQUALIF scale</td><td>26.9(15.7)</td><td>28.3(15.2)</td><td>30.2(16.8)</td><td>.29</td></tr>
<tr><td>Beck Depression Inventory</td><td>2.54(2.79)</td><td>2.39(2.47)</td><td>3.05(3.22)</td><td>.33</td></tr>
</table>
Data are presented as mean (SD) unless otherwise indicated.</td></tr>
<tr><td>Interventions</td><td>Rasagiline: 1mg or 2mg per day. A 1-week escalation period was followed by a 25-week maintenance period.</td></tr>
<tr><td>Primary outcomes</td><td>The change in the UPDRS Total score between baseline and 26 weeks of treatment, comparing active treatment group with</td></tr>
</table>

<table>
<tr><th>Bibliographic reference</th><th>Parkinson Study Group, A controlled trial of rasagiline in early Parkinson disease: the TEMPO Study, Arch Neurol., 1937-1943, 2002</th></tr>
<tr><td></td><td>the placebo group.</td></tr>
<tr><td>Secondary outcomes</td><td>Changes in:
Mental, ADL and motor subscales of the UPDRS as well as symptom-based subscores (tremor, rigidity, bradykinesia, and postural instability/gait disorder)
Hoehn & Yahr stage
Schwab-England ADL scale
Beck Depression Inventory score
Timed motor tests
PDQUALIF scale</td></tr>
<tr><td>Results</td><td>Changes between baseline and 26 weeks:<table>
<tr><td></td><td colspan="2">Effect size (95% CI)</td></tr>
<tr><td>Characteristic</td><td>Rasagiline 1mg/d vs. placebo</td><td>Rasagiline 2mg/d vs. placebo</td></tr>
<tr><td>UPDRS III</td><td>-2.71 (-3.86 to -1.55)</td><td>-1.68 (-2.84 to -0.51</td></tr>
<tr><td>UPDRS II</td><td>-1.04 (-1.60 to -0.48)</td><td>-1.22 (-1.78 to -0.65)</td></tr>
<tr><td>PDQUALIF scale</td><td>-2.91 (-5.19 to -0.64)</td><td>-2.74 (-5.02 to -0.45)</td></tr>
<tr><td>Beck Depression Inventory</td><td>-0.35 (-0.86 to 0.16)</td><td>-0.21 (-0.72 to 0.30)</td></tr>
</table>
Adverse events by treatment group:<table>
<tr><td>Adverse events</td><td>Placebo, n(%) (n=138)</td><td>Rasagiline 1mg/d, n(%) (n=134)</td><td>Rasagiline 2mg/d, n(%) (n=132)</td><td>Combined rasagiline groups, n(%) (n=266)</td></tr>
<tr><td>Any event</td><td>110(79.7)</td><td>109(81.3)</td><td>111(84.1)</td><td>220(82.7)</td></tr>
<tr><td>Any event (moderate or severe intensity)</td><td>63(45.7)</td><td>58(43.3)</td><td>60(45.5)</td><td>118(44.4)</td></tr>
</table></td></tr>
</table>

Bibliographic reference	Parkinson Study Group, A controlled trial of rasagiline in early Parkinson disease: the TEMPO Study, Arch Neurol., 1937-1943, 2002

Infection	22(15.9)	20(14.9)	21(15.9)	41(15.4)
Headache	14(10.1)	19(14.2)	16(12.1)	35(13.2)
Accidental injury	14(10.1)	10(7.5)	10(7.6)	20(7.5)
Dizziness	15(10.9)	9(6.7)	10(7.6)	19(7.1)
Asthenia*	15(10.9)	6(4.5)	6(4.5)	12(4.5)
Nausea	10(7.2)	7(5.2)	9(6.8)	16(6.0)
Arthralgia	6(4.3)	5(3.7)	14(10.6)	19(7.1)
Back pain	7(5.1)	7(5.2)	8(6.1)	15(5.6)
Pain	8(5.8)	8(6.0)	6(4.5)	14(5.3)

*P=.03 for the difference between placebo and combined groups; P=.05 difference between placebo and each of the individual treatment groups.

Overall Risk of Bias

1. Has an appropriate method of randomisation been used? Yes
2. Was there adequate concealment of allocation? Yes
3. Were the groups comparable at baseline for all major confounding/prognostic factors? Yes
4. Did the comparison groups receive the same care apart from interventions studied? Unclear
5. Were participants receiving care kept blind to treatment allocation? Yes
6. Were the individuals administering care kept blind to treatment allocation? Yes
7. Were groups comparable with respect to availability of outcome data and for how many participants were no outcome data available? Yes
8. Did the study have an appropriate length of follow up? Yes
9. Did the study use a precise definition of outcome? Yes
10. Was a valid and reliable method used to determine that outcome? Yes
11. Were investigators kept blind to participant's exposure to the intervention? Unclear
12. Were investigators kept blind to other important confounding and prognostic factors? Unclear

Bibliographic reference	Watts,R.L., Jankovic,J.FAU, Waters,C.FAU, Rajput,A.FAU, Boroojerdi,B.FAU, Rao,J., Randomised, blind, controlled trial of transdermal rotigotine in early Parkinson disease, Neurology, 272-276, 2007
Country/ies where the study was carried out	US and Canada
Study type	Phase III, multi-centre, randomised, double-blind, placebo-controlled, two-arm, parallel-group clinical trial.
Aim of the study	To compare safety and therapeutic effects between transdermally applied rotigotine and placebo in patients with early-stage PD.
Study dates	Study dates: November 2001 to April 2003 Study duration: 28 weeks
Source of funding	Schwarz Pharma
Sample size	In total: 277; Rotigotine n=181; Placebo n=96
Inclusion criteria	• ≥30 years old • A diagnosis of idiopathic PD of less than or equal to 5 years in duration • UPDRS III score of at least 10 at baseline • Hoehn & Yahr stage score I-III • Two or more of the cardinal signs of PD • MMSE score of 25 or more • No other known or suspected cause of parkinsonism • Patients previously receiving an anticholinergic agent, monoamine oxidase B inhibitor, or an N-methyl-D-aspartate antagonist (amantadine) must have been on a stable dose for at least 28 days prior to study baseline and must be maintained on that dose for the duration of the trial
Exclusion criteria	• Prior or concurrent therapy with a dopamine agonist or carbidopa/levodopa therapy within 28 days of the baseline visit • Carbidopa/levodopa therapy lasting for more than 6 months since diagnosis • Atypical parkinsonism • Surgical intervention for PD • Clinically relevant hepatic, renal, or cardiac dysfunction • A diagnosis of epilepsy • A history of seizures as an adult, stroke, a TIA within the last year • Significant skin hypersensitivity to adhesive or other intolerance/hypersensitivity to the antiemetic ondansetron • Pregnancy or nursing

<table>
<tr><th>Bibliographic reference</th><td>Watts,R.L., Jankovic,J.FAU, Waters,C.FAU, Rajput,A.FAU, Boroojerdi,B.FAU, Rao,J., Randomised, blind, controlled trial of transdermal rotigotine in early Parkinson disease, Neurology, 272-276, 2007</td></tr>
<tr><td></td><td>• Inadequate birth control methods
• Patients receiving CNS active therapy were excluded unless their pharmacotherapy dose(s) had been stable for at least 28 days prior to baseline and was likely to remain stable for the duration of the trial</td></tr>
<tr><td>Details</td><td>Baseline characteristics:
<table>
<tr><td>Characteristics</td><td>Placebo n=96</td><td>Rotigotine n=181</td></tr>
<tr><td>Mean (SD) age, years</td><td>64.5(10.7)</td><td>62.0(10.3)</td></tr>
<tr><td>Mean (SD) years since diagnosis</td><td>1.4(1.3)</td><td>1.3(1.3)</td></tr>
<tr><td colspan="3">Hoehn & Yahr stage:</td></tr>
<tr><td>I</td><td>19(18)</td><td>27(49)</td></tr>
<tr><td>II</td><td>63(60)</td><td>54(97)</td></tr>
<tr><td>III</td><td>19(18)</td><td>19(34)</td></tr>
</table></td></tr>
<tr><td>Interventions</td><td>Rotigotine: starting at 2mg/day, titrated weekly up to 6mg/day, and then maintained for 6 months.</td></tr>
<tr><td>Primary outcomes</td><td>• The change in UPDRS II and III from baseline to end of treatment
• Responder rates (patients with ≥20% improvement)</td></tr>
<tr><td>Secondary outcomes</td><td>Not reported.</td></tr>
<tr><td>Results</td><td>Superior scoring in the UPDRS III was the greatest numerical contributor for the rotigotine group's subtotal improvements: the mean change in UPDRS III from baseline to end of the maintenance phase was -3.50 (±7.26) and the mean change in the UPDRS II score was -0.30 (±3.54).

Summary of the most common treatment-emergent adverse events:
<table>
<tr><td>Adverse event</td><td>Placebo n (%) (n=95)</td><td>Rotigotine n (%) (n=181)</td></tr>
<tr><td>Application site disorders*</td><td>11(12)</td><td>79(44)</td></tr>
<tr><td>Accident NOS*</td><td>2(2)</td><td>14(8)</td></tr>
<tr><td>Fatigue*</td><td>5(5)</td><td>14(8)</td></tr>
</table></td></tr>
</table>

Bibliographic reference	Watts,R.L., Jankovic,J.FAU, Waters,C.FAU, Rajput,A.FAU, Boroojerdi,B.FAU, Rao,J., Randomised, blind, controlled trial of transdermal rotigotine in early Parkinson disease, Neurology, 272-276, 2007		
	Pain	7(7)	4(2)
	Leg pain	6(6)	2(1)
	Dizziness*	12(13)	34(19)
	Headache*	9(9)	29(16)
	Tremor*	4(4)	11(6)
	PD aggravated	5(5)	2(1)
	Nausea*	16(17)	75(41)
	Vomiting*	1(1)	16(9)
	Constipation*	4(4)	11(6)
	Dyspepsia*	1(2	12(7)
	Diarrhoea*	2(2)	11(6)
	Arthralgia*	6(6)	10(6)
	Back pain*	3(3)	11(6)
	Skeletal pain	6(6)	7(4)
	Somnolence*	19(20)	60(33)
	Insomnia*	3(3)	17(9)
	Coughing*	6(6)	9(5)
	Upper respiratory tract infection	7(7)	8(4)
	Sinusitis	6(6)	7(4)
	Rash	5(5)	4(2)
	*Adverse events with an incidence of >5% in the rotigotine-treatment group.		

Bibliographic reference	Watts,R.L., Jankovic,J.FAU, Waters,C.FAU, Rajput,A.FAU, Boroojerdi,B.FAU, Rao,J., Randomised, blind, controlled trial of transdermal rotigotine in early Parkinson disease, Neurology, 272-276, 2007
	NOS=not otherwise specified
Overall Risk of Bias	1. Has an appropriate method of randomisation been used? Yes 2. Was there adequate concealment of allocation? Yes 3. Were the groups comparable at baseline for all major confounding/prognostic factors? Yes 4. Did the comparison groups receive the same care apart from interventions studied? Yes 5. Were participants receiving care kept blind to treatment allocation? Yes 6. Were the individuals administering care kept blind to treatment allocation? Yes 7. Were groups comparable with respect to availability of outcome data and for how many participants were no outcome data available? Unclear 8. Did the study have an appropriate length of follow up? Yes 9. Did the study use a precise definition of outcome? Yes 10. Was a valid and reliable method used to determine that outcome? Yes 11. Were investigators kept blind to participant's exposure to the intervention? Yes 12. Were investigators kept blind to other important confounding and prognostic factors? Unclear

Bibliographic reference	Zhang,Z., Shang,H., Hu,X., Chen,S., Zhao,Z., Du,Z., Surmann,E., Bauer,L., Asgharnejad,M., Rotigotine transdermal patch in Chinese patients with early Parkinson's disease: a randomized, double-blind, placebo-controlled pivotal study, Parkinsonism and Related Disorders, 28,29-55, 2016
Country/ies where the study was carried out	China
Study type	Randomised, double-blind, placebo-controlled trial
Aim of the study	To determine the efficacy and safety of transdermal rotigotine in Chinese patients with early stage Parkinson's disease
Study dates	Study dates: June 2012 to May 2014 Study duration: 24 weeks
Source of funding	UCB Pharma
Sample size	In total: n=247; Rotigotine: n= 124; Placebo: n=123
Inclusion criteria	• Idiopathic Parkinson's disease of less than 5 years duration • Hoehn and Yahr stage ≤3

<table>
<tr><th>Bibliographic reference</th><th>Zhang,Z., Shang,H., Hu,X., Chen,S., Zhao,Z., Du,Z., Surmann,E., Bauer,L., Asgharnejad,M., Rotigotine transdermal patch in Chinese patients with early Parkinson’s disease: a randomized, double-blind, placebo-controlled pivotal study, Parkinsonism and Related Disorders, 28,29-55, 2016</th></tr>
<tr><td></td><td>• MMSE ≥25
• UPDRS III ≥10
• Patients who were being treated with anticholinergics, MAOBIs and amantadine has to be on stable doses at least 28 days prior to the start of trial and maintain those doses for its duration</td></tr>
<tr><td>Exclusion criteria</td><td>Patients with any of the following symptoms:
• Dementia
• Active psychosis or hallucinations
• Severe depression
• Evidence of an impulse control disorder
• History of epilepsy or stroke
• Hepatic, renal or cardiac dysfunction</td></tr>
<tr><td>Details</td><td>Baseline characteristics:
<table>
<tr><td>Characteristics</td><td>Rotigotine n=124</td><td>Placebo n=123</td></tr>
<tr><td>Mean age (years)</td><td>59.1 (10.3)</td><td>59.7 (10.1)</td></tr>
<tr><td>Male (%)</td><td>74 (60)</td><td>76 (62)</td></tr>
<tr><td>Duration of disease (years)</td><td>0.94 (1.17)</td><td>1.08 (1.27)</td></tr>
</table>
Values are given in means (SD) or no. of patients (%).</td></tr>
<tr><td>Interventions</td><td>Rotigotine: Starting dose of 2mg/24 hrs with a weekly increment of 2mg/24 hrs, up to a maximum of 8mg/24 hrs during the 4 week titration period.</td></tr>
<tr><td>Primary outcomes</td><td>The change in UPDRS II + III scores from baseline to the end of treatment</td></tr>
<tr><td>Secondary outcomes</td><td>• Clinical global impression
• PDQ-8</td></tr>
<tr><td>Results</td><td>Significantly greater reduction in UPDRS II + III scores with rotigotine versus placebo</td></tr>
<tr><td>Overall Risk of Bias</td><td>1. Has an appropriate method of randomisation been used? Yes
2. Was there adequate concealment of allocation? Yes</td></tr>
</table>

Bibliographic reference	Zhang,Z., Shang,H., Hu,X., Chen,S., Zhao,Z., Du,Z., Surmann,E., Bauer,L., Asgharnejad,M., Rotigotine transdermal patch in Chinese patients with early Parkinson's disease: a randomized, double-blind, placebo-controlled pivotal study, Parkinsonism and Related Disorders, 28,29-55, 2016
	3. Were the groups comparable at baseline for all major confounding/prognostic factors? Yes 4. Did the comparison groups receive the same care apart from interventions studied? Unclear 5. Were participants receiving care kept blind to treatment allocation? Yes 6. Were the individuals administering care kept blind to treatment allocation? Yes 7. Were groups comparable with respect to availability of outcome data and for how many participants were no outcome data available? Yes 8. Did the study have an appropriate length of follow up? Yes 9. Did the study use a precise definition of outcome? Yes 10. Was a valid and reliable method used to determine that outcome? Yes 11. Were investigators kept blind to participant's exposure to the intervention? Yes 12. Were investigators kept blind to other important confounding and prognostic factors? Unclear

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 - Changes in parkinsonian rating

	motor complications **Source of funding** Not reported					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 Placebo (n=10): 20.2 ± 5.5	**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

				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 with 203 participants examined tolcapone vs. pergolide and the	**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

		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. **Source of funding** Novartis Pharma AG	**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 MAOB other than selegiline, antipsychotics, or other COMT inhibitors within 2 months prior to	**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

			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** Randomised, double-blind, active-controlled trial	**Country/ies where the study was carried out** 32 centres in Finland, France, Germany,	**Inclusion/ exclusion criteria** Inclusion criteria: - Patients with PD diagnosed ≥5 years previously, with significant fluctuations (≥3 hrs/d OFF time) despite best medical therapy,	**Baseline characteristics** Mean age (yrs) - Entacapone (n=75): 63.1 ± 8.1 - Tolcapone (n=75): 65.1 ± 8.9 Mean disease duration	**Intervention(s)** - Entacapone: 200mg with each dose of L-dopa - Tolcapone: 100mg three times daily, while	**Primary outcomes** The proportion of patients with a mean increase in ON-time (without

	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	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	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): 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%)	maintaining their other antiparkinsonian treatments	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-blind, placebo-controlled study	**Country/ies where the study was carried out** 20 centres in France and 5 in Spain	**Inclusion/ exclusion criteria** Inclusion criteria: - People aged 30-80years; fulfilled the UK PD Brain Bank clinical criteria; were responsive to L-dopa therapy; with Hoehn and Yahr stage 2-4 during ON periods; and	**Baseline characteristics** Mean age (yrs) Entacapone (n=99): 63.5 ± 9.96 Placebo (n=63): 65.0 ± 6.61 Hoehn & Yahr stage Entacapone (n=99): 2.6 ±	**Intervention(s)** Entacapone: 200mg taken with each dose of L-dopa	**Primary outcomes** Improvement of ON and OFF time while awake as measured by Patient Diary and UPDRS part IV item

	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	**Study dates/duration** Study duration 3 months **Sample size** Total (n): 162 Group 1 (n): Entacapone: 99 Group 2 (n): Placebo: 63	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 days; MAOBs except selegiline, provided that it had been prescribed at an unchanged dose for a minimum of 4 weeks prior to	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)		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

			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** Schwarz Pharma (Monheim, Germany)	**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 12mg/d: 111 Placebo: 120	**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 the baseline visit Exclusion criteria: - A Da or COMT inhibitor was not permitted within 28 days of	**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 Mean UPDRS ADL score Rotigotine patches 8mg/d (n=118): 13.3 ± 6.7 Rotigotine patches 12mg/d	**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)

			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	(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 with motor fluctuations **Source of funding** SmithKline Beecham	**Country/ies where the study was carried out** 16 medical centres in the USA **Study dates/duration** Study duration 6 months **Sample size** Total (n): 149 Group 1 (n): Ropinirole: 95	**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 - Anticholinergic, amantadine, or selegiline treatment was permitted if the dose was stable for at least 4 weeks before entry and throughout	**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): 843 ± 517 mg/d	**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 and by 3.0mg/d each week to a maximal dose of 24mg/d. - All patients had to be titrated to a	**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 visits. **Secondary outcomes**

	Pharmaceuticals	Group 2 (n): Placebo: 54	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		minimum dose of 7.5mg/d.	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** To determine whether the efficacy of pramipexole (PPX) is significantly inferior to	**Country/ies where the study was carried out** 38 sites in Japan **Study dates/duration** Study duration 12 weeks **Sample size**	**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 effects or therapeutic strategy - Patients had received an individual dosage of L-dopa and were stable for at least 28 days before the	**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 ± 4.07 Bromocriptine (n=104): 5.03 ± 3.96 Placebo (n=107): 5.73 ± 7.05	**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. **Secondary outcomes** Total score of

	bromocriptine (BR) in patients with advanced PD as an adjunct to Lo-dopa therapy **Source of funding** Nippon Boehringer Ingelheim Co., Ltd., Hyogo, Japan	Total (n): - Total: 313 - Pramipexole: 102 - Bromocriptine: 104 - Placebo: 107	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	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		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** Randomized, double-blind, placebo-controlled study	**Country/ies where the study was carried out** 25 medical institutions in Japan	**Inclusion/ exclusion criteria** Inclusion criteria: - 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	**Baseline characteristics** Mean age (yrs) Ropinirole (n=121): 64.9 ± 9.53 Placebo (n=120): 64.7 ± 9.31 Mean disease duration Ropinirole (n=121): 66.4 ±	**Intervention(s)** Ropinirole: 0.25mg 3 times daily (0.75mg/d) and uptitrated to a maximum of 15.0 mg/d (final mean dose: 7.12 ±	**Primary outcomes** Change in UPDRS III from baseline as assessed by the Japanese version of the UPDRS III

	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	**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	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	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)	2.88 mg/d)	**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-controlled trial **Aim/ objective of the study**	**Country/ies where the study was carried out** 62 sites in Japan **Study dates/duration** Study duration 16 treatment weeks + a taper period of up to	**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 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	**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 ± 7.9 Mean disease duration Rotigotine patches (n=164): 7.0 ± 4.9 years Ropinirole (n=166): 6.8 ±	**Intervention(s)** - Rotigotine patches: Initial dose of 2mg/d and increased to 16mg/d in weekly increments of 2mg/d - Ropinirole: Initial dose of 0.75mg/d and increase to 3mg/d in weekly increments of 0.75mg/d and then	**Primary outcomes** Change in the UPDRS III (ON state) sum score from baseline to week 16 of the treatment period **Secondary**

	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	4 weeks **Sample size** Total (n): - Total: 414 - Rotigotine patches: 164 - Ropinirole: 166 - Placebo: 84	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 prolongation, or interact with ropinirole	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-PD drugs, rotigotine patches (n=164)vs. ropinirole (n=166) vs. placebo (n=84) (n (%)): - Entacapone: 40(24.4) vs.	increased to 15mg/d in weekly increments of 1.5mg/d	**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)

				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 Neuroscience	**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: 406 Group 2 (n): Placebo: 108	**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 benserazide or carbidopa, with an average "off" time of ≥2.5h/d - Permitted PD drugs included anticholinergics, MAOBs, N-Methyl-D-aspartate antagonists,	**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 Rotigotine patches 8mg/d (n=94): 7.79 ± 3.92 years Placebo (n=108): 7.49 ± 4.75 years Mean UPDRS motor score	**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" with or without troublesome dyskinesias or "off", UPDRS II, III, and IV

			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 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 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** To investigate the efficacy and safety of rotigotine transdermal patches delivering up to 16mg of rotigotine per	**Country/ies where the study was carried out** 38 centres in Japan **Study dates/duration** Study duration 15 weeks Study dates August 2006 and September 2006	**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 - 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	**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 Rotigotine patches (n=86): 28.1 ± 12.2 Placebo (n=86): 26.2 ± 10.4 Mean UPDRS ADL score Rotigotine patches (n=86):	**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** The absolute changes in off-time, UPDRS II (average ON and OFF state)

	day in combination with L-dopa in patients with advanced-stage PD **Source of funding** Otsuka Pharmaceutical Co., Ltd., Japan	**Sample size** Total (n): 214 Group 1 (n): Rotigotine patches: 87 Group 2 (n): Placebo: 87	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	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)		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 **Aim/ objective of the study** Not reported	**Country/ies where the study was carried out** United States **Study dates/duration** Study duration 12 weeks	**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 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	**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 ± 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):	**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 1.5mg tablets) and was maintained for the remainder of the study	**Primary outcomes** The reduction in total daily off as determined by an average of the % of off time reported at weeks 10 and 12 **Secondary outcomes**

	Source of funding Not reported	**Sample size** Total (n): 180 Group 1 (n): Selegiline Orally Disintegrated Tablet (ODT): 98 Group 2 (n): Placebo: 50	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	6.8 ± 2.2 hr/d		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 fluctuations **Source of funding**	**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 2 years **Sample size** Total (n): 393 Group 1 (n):	**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 - Patients with incapacitating peak dose or biphasic dyskinesia - Any dopamine agonist use within 4 weeks of screening; significant or uncontrolled psychiatric,	**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 Ropinirole 24-hour (n=201): 13.9 ± 6.2; n=199 Placebo (n=190): 14.2 ± 6.8; n=189 Hoehn & Yahr stage	**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-39 subscales of mobility, ADL, emotional well-being, stigma and communication, and

	GlaxoSmithKline and Skye Pharma	Ropinirole 24-hour: 202 Group 2 (n): Placebo: 191	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): 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		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) dosed once daily at bedtime for the treatment of LID in PD patients	**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 **Sample size** Total (n): Total: 83 Group 1 (n): Amantadine ER	**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 unchanged for at least 30 days prior to screening and throughout study - L-dopa preparations had to be administered at least 3 times daily	**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 ± 3.5 years Mean UPDRS motor score Movement Disorder Society-UDRS: - Placebo (n=22): 11.7 ± 3.1 - 260mg	**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 Dyskinesia Rating Scale for 260mg and 420mg of ADS-5102, Fatigue Severity Scale,

	Source of funding Adamas Pharmaceuticals, Inc.	overall: 61 Group 2 (n): Placebo: 22	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	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		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	**Country/ies where the study was carried out** 77 centres in Europe, South Africa, Australia,	**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,	**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 ±	**Intervention(s)** - Rotigotine patches: Initial dose of 4mg/d with weekly increments of 2mg/d up to an optimum	**Primary outcomes** - Absolute change in total hours "off" from baseline to end of study and responder

	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)	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	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, monoamine oxidase A inhibitors, dopamine-releasing drugs, tolcapone, neuroleptics, cimetidine, ranitidine, diltiazem, triamterene, verapamil, quinidine, or quinine	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 (n=100): 814 ± 398 mg/d	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	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

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 Health for Clinical Research Center grant at the University of Rochester	**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 screen	**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
Rektorova (2003)	**Study type**	**Study dates/duration** Study duration	**Inclusion/ exclusion criteria** Inclusion criteria:	**Baseline characteristics** Mean age (yrs)	**Intervention(s)**	**Primary outcomes**

	Prospective randomised, open-label trial **Source of funding** Not reported	8 months **Sample size** Total (n): 41 Group 1 (n): Pramipexole: 22 Group 2 (n): Pergolide: 19	- 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	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	Pramipexole: 1.5 - 4.5mg/d Pergolide: 1.5 - 4.5mg/d	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-blind, parallel trial **Aim/ objective of the study**	**Country/ies where the study was carried out** 76 centres in Austria, Czech Republic, Hungary, India, Italy, Philippines, Poland, Russia, Slovakia,	**Inclusion/ exclusion criteria** Inclusion criteria: - Subjects ≥30 years old and had 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	**Baseline characteristics** Mean age (yrs) Placebo (n=178): 60.9 ± 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	**Intervention(s)** - Pramipexole ER: 0.375, 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,	**Primary outcomes** Changes in UPDRS II + III score at 18 weeks, with further assessments at 33 weeks in a subset of patients

	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	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	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	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 vs. 88.4 vs. 79.4 - OFF state 4-5: 14 vs. 11.6 vs. 20 Other anti-parkinsonian medication Placebo (n=178) vs.	1.25, or 1.5mg 3 times daily (over a 7-week flexible titration period)	**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

				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 complications **Source of funding** Nippon Boehringer Ingelheim	**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/Entacapone: 46 Group 2 (n): Levodopa/Carbidopa: 49	**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 treated with entacapone; symptoms, signs or history of atypical or secondary Parkinsonism; hallucinations or psychiatric disorders related to dopaminergic treatments; major	**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) - 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	**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

			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	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 after up to 3 years of therapy with less than 600 mg/d delays the onset of dyskinesia compared with increasing doses of	**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 prolonged release: 105 Group 2 (n): Carbidopa-levodopa: 104	**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 initiated during the study Exclusion criteria: - A clinical history of dyskinesia, clinically relevant laboratory abnormalities, recent history of severe symptomatic postural	**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 ± 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	**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 PPRS scales

	levodopa **Source of funding** GlaxoSmithKline Research and Development		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	Mean levodopa dose Ropinirole prolonged-release (n=102): 369 ± 168 mg/d L-dopa (n=102): 364 ± 212 mg/d		
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 Chinese PD patients **Source of funding** Chongqing Pharmaceutical	**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): Rasagiline: 119 Group 2 (n): Placebo: 125	**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 screening visit - Required washout periods were 60 days for selegiline and 35 days for fluoxetine and fluvoxamine Exclusion criteria: - Parkinson's syndrome or	**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): 16.30 ± 5.59 Other anti-parkinsonian medication Treated with other anti-PD agents (n (%)): - Rasagiline (n=119): 18	**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 "off" time, as well as UPDRS Total, I, II, and III scores at weeks 4. 8. and 12 from baseline

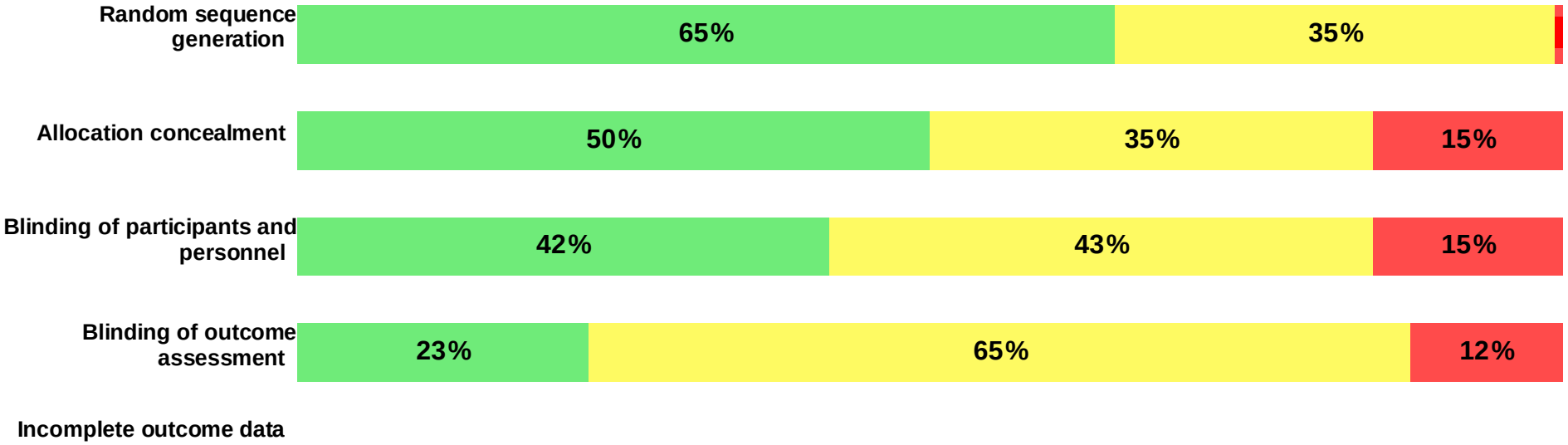
	Research Institute Co., Ltd.		Parkinson's plus syndrome; significant cognitive dysfunction or psychiatric problems compromising the ability to complete the study or give informed consent; surgery history of PD or stereotactic brain surgery; any severe illness, such as heart, liver, renal diseases or 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	(15.1) - Placebo (n=125): 17 (13.6)		

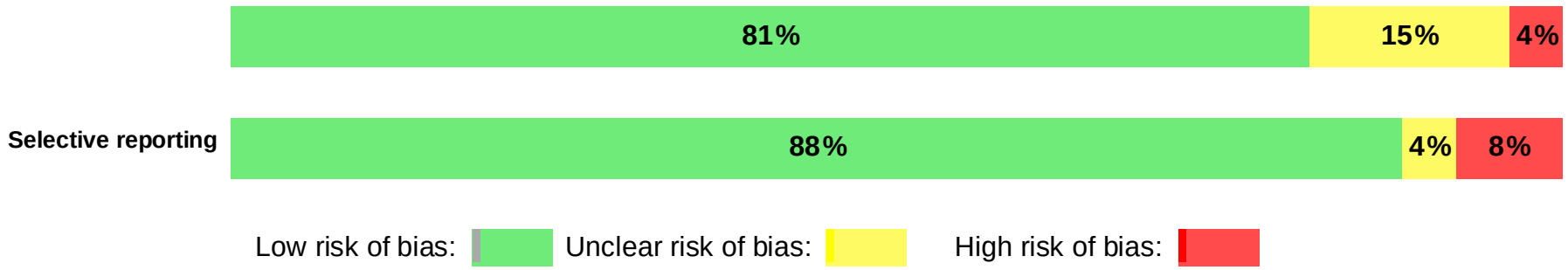
Risk of Bias

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)	+	+	+	?	+	+




81%
15%
4%
Selective reporting
88%
4%
8%
Low risk of bias:
Unclear risk of bias:
High risk of bias:

D.3 Pharmacological management of non-motor symptoms

D.3.1 Daytime hypersomnolence

What sleep disorders are seen in Parkinson's disease and how are they best treated?	
Bibliographic reference	Adler CH, Caviness JN, Hentz JG, Lind M, Tiede J. Randomized trial of modafinil for treating subjective daytime sleepiness in patients with Parkinson's disease. Movement Disorders 2003;18:287-93.
Study type	Randomised, double-blind, placebo controlled cross over study (1 week washout period)
Evidence level	1++ (low risk of bias)
Study objective	To assess the safety and efficacy of modafinil for the treatment of excessive daytime sleepiness in patients with Parkinson's disease
Number of patients	N=21 Parkinson's disease (PD) patients N=11 started on modafinil N=10 started on placebo Location: USA Site: single
Patient characteristics	27 consecutive patients with PD who admitted having excessive daytime sleepiness were questioned using the Epworth Sleepiness Scale (ESS). Patients were included if they scored ≥ 10. 21 of the 27 patients questioned met these criteria and were included in the study. Patients were not allowed to start new PD medications during the study. Inclusion criteria: ≥ 30 years of age, a Folstein Mini-Mental Status Exam score >24, and ability to complete diary forms. Mean baseline characteristics: mean age 65 years, F:M was 6:14, duration of PD 7.4 years, ESS 16.9 Of the 20 patients who completed the trial 19 had motor fluctuations
Intervention	Modafinil 200mg/d for 3 weeks
Comparison	Matching placebo for 3 weeks
Length of follow-up	Baseline, week 3, week 4 (baseline visit 2), week 7 and week 8 (1 week after discontinuation)
Outcome measures	ESS, Excessive Daytime Sleepiness Rating Scale (EDSRS), modified Fatigue Assessment Inventory (FAI), Excessive Daytime Fatigue Rating Scale (EDFRS), Unified Parkinson's Disease Rating Scale (UPDRS), Hoehn and Yahr stage (H&Y), Schwab and England Activities of Daily Living Scale, Timed Tapping Test, and a Clinical Global Impression of

What sleep disorders are seen in Parkinson's disease and how are they best treated?	
	Change (CGI-C) scale
Effect size	Drug compliance was 93% ± 28% while on modafinil and 113% ± 36% on placebo ESS Demonstrated a carry-over effect (p=0.013) from period to 1 to period 2 At visit 3, before the second treatment period the modafinil group/placebo group had decreased 2.3 ± 4.2 from a baseline of 17.8 ± 4.2 The placebo/modafinil group increased 2.0 ± 2.5 from a baseline of 16.0 ± 4.2 The carry-over effect was replicated after period 2 (p=0.006) At visit 5 (end of second washout period) modafinil/placebo group had increased 0.9 ± 2.1 from 15.5 ± 4.1 at visit 3 Placebo/modafinil group decreased 3.3 ± 3.8 from 18.0 ± 5.1 at visit 3 Comparing changes from baseline- the ESS for patients treated with 200 mg/d modafinil was better (p=0.039) than placebo treated patients ESS for patients treated with modafinil was 4.4 points better than placebo (95%CI –8.6 to –0.2) Two patients had an ESS <10 while receiving modafinil The ESS scores for the placebo group went from 16.0 +/- 4.2 (mean +/- SD) to 17.0 +/- 5.1 ESS scores for the modafinil group went from 17.8 +/- 4.2 to 14.4 +/- 5.7 (P = 0.039). CGI-C Patient-rated CGI-C improved +0.75 on modafinil compared with +0.15 for placebo (p=0.07) Physician-rated CGI-C improved +0.75 on modafinil compared to +0.25 placebo (p=0.12) Improvements were reported by 7 (35%) of patients on modafinil only, 1 (5%) patient on placebo-only, 2 patients (10%) receiving both modafinil and placebo, and 10 patients (50%) reported no change on either treatment (p=0.070) No significant differences were found in any of the other secondary outcome measures of sleepiness or fatigue Modafinil did not have an effect on sleep time based on diary analysis The patient Clinical Global Impression of Change (+3 to -3) improved by 0.75 on modafinil compared with 0.15 for placebo (P = 0.07). A total of 7 of 20 (35%) of the patients reported some improvement on modafinil but not placebo Parkinson's disease scores Modafinil did not cause any worsening or improvement of PD signs

What sleep disorders are seen in Parkinson's disease and how are they best treated?	
	No significant differences between modafinil and placebo treatment periods on UPDRS, H&Y, timed tapping test, or diaries Modafinil had no effect on the percentage 'on' time There was no significant carryover effect for any other measure.. There was no significant improvement or worsening of the UPDRS subscores I-III, Timed Tap test, or time on. Vital signs, electrocardiograms, and lab tests were unchanged. Modafinil was very well tolerated. Our data demonstrate that, in a small sample size, administration of 200 mg/day of modafinil was associated with few side effects and was modestly effective for the treatment of excessive daytime sleepiness in patients with PD. Adverse effects There were no clinically or statistically significant effects of modafinil compared with placebo The following treatment-emergent effects were reported by one patient each: atrial fibrillation (patient with known paroxysmal atrial fibrillation), bruise, elevated blood pressure, flu, insomnia, rectal prolapse, and skin redness One patient reported: hot flashes, gas, increased 'off' time Another patient reported: pruritic rash and sore tongue On placebo one patient reported: allergy symptoms, anxiety, back spasm, headache, and heart burn No patients described any episodes of 'sleep attacks'
Source of funding	Pharmaceutical company
Additional comments	Exams were performed when patients were in their 'on' states Modafinil and placebo tablets were identical in size, colour, and taste Methods of randomisation and allocation concealment stated Pills were counted at each visit to monitor compliance Elimination half-life of modafinil after multiple doses in 15 hours in healthy controls- no data regarding the duration of benefit that might occur after discontinuation of drug in patients with PD The sample size (n=16) was based on 80% power to detect differences of 0.75 standard deviations used the paired T-test Sample size was increased to n=21 in case of premature withdrawals 1 patient dropped out of modafinil group a few days after starting trial

What sleep disorders are seen in Parkinson's disease and how are they best treated?	
Bibliographic reference	Hogl B, Saletu M, Brandauer E, Glatzl S, Frauscher B, Seppi K et al. Modafinil for the treatment of daytime sleepiness in

What sleep disorders are seen in Parkinson’s disease and how are they best treated?	
	Parkinson's disease: A double-blind, randomized, crossover, placebo-controlled polygraphic trial. Sleep 2002; 25:905-9.
Study type	Double-blind, randomised, placebo-controlled, cross-over study (2-week washout phase)
Evidence level	1++ (low risk of bias)
Study objective	To assess the therapeutic efficacy of modafinil in the treatment of increased daytime sleepiness in patients with Parkinson’s disease
Number of patients	N=15 patients with Parkinson’s disease Location: Austria Sites: single
Patient characteristics	Recruited from outpatient clinic at University Hospital Department of Neurology All patients had a score of 10 or more on Epworth Sleepiness Scale (ESS) Exclusion criteria: see paper 12 patients completed study- 9 men, 3 women; mean age 65.0, mean symptomatic PD duration 6.8 years, all patients were on levodopa therapy
Intervention	Modafinil dose was 100mg in first week and 200mg in second week
Comparison	Placebo
Length of follow-up	2 week treatment phase, 2 week washout and 2 week treatment phase
Outcome measures	ESS, maintenance of wakefulness test (MWT) sleep log and depression scale, Unified Parkinson’s disease Rating Scale (UPDRS) and Hoehn and Yahr (H&Y) staging, adverse effects
Effect size	ESS Modafinil improved perceived sleepiness ESS scores at baseline did not differ between treatment and placebo Subjective sleepiness improved by 0.83 ± 1.99 points with placebo and by 3.42 ± 3.90 with modafinil Analysis of variance revealed a significant interaction (p=0.011) between medication condition and ESS changes from baseline to end MWT Latency to stage 1 sleep was calculated using (MWT) No significant difference was found between the treatment groups at baseline (p=0.26) and at the end of the treatment

	phase (p=0.114) The mean changes of sleep latencies at the end versus beginning of each block were also not significantly different (p=0.139) Sleep logs Similar amounts of sleep were obtained in both treatment groups Estimated time of sleep 390 ± 80 min at baseline of placebo treatment, 360 ± 94 min at end of placebo treatment, 375 ± 86 min at baseline of modafinil treatment, and 360 ± 50min at the end of modafinil treatment (median standard deviation, p=0.3) Depression scores Beck depression scores were not statistically different between baseline and end of treatment for placebo and modafinil Side effects Modafinil: insomnia (n=1), constipation (n=1), diarrhoea (n=2), dizziness (n=1) Placebo: constipation (n=1), flatulence (n=1), diarrhoea (n=1), insomnia (n=1) In no case did side effects lead to study withdrawal
Source of funding	Pharmaceutical
Additional comments	Method of randomisation and allocation concealment stated Modafinil and placebo were prepared in identical-looking capsules 3 patients did not complete study Not intention-to-treat analysis

Study details	Participants	Methods	Results	Comments
Full citation Lou,J.-S., Dimitrova,D.M., Park,B.S., Johnson,S.C., Eaton,R., Arnold,G., Nutt,J.G., Using modafinil to treat fatigue in Parkinson's disease: A double-blind, placebo-	Sample size 19 PD patients Inclusion criteria Diagnosis idiopathic PD	Details: Sample of 19 PD patients from movement disorders clinic participated. Potential participants filled out	Results EPSWORTH SLEEP SCALE — baseline / month 1 / Month 2 Modafinil: 8.3 (1.6) / 6.4 (1.6) / 6.0 (1.6) Placebo: 9.8 (1.5) / 8.9(1.5) / 9.0(1.5)	Overall Risk of Bias SERIOUS: very small sample size gender bias: only men in modafinil group

controlled pilot study, Clinical Neuropharmacology.32 (6) (pp 305-310), 2009.Date of Publication: November-December 2009., 305-310, 2009 Ref Id 215655 Country/ies where the study was carried out USA Study type Intervention: RCT Aim of the study To determine if modafinil improves subjective fatigue and physical fatigability Study dates Nov/Dec 2009 Source of funding National Parkinson's foundation	with at least 2 of these 4: rigidity; tremor; bradykinesia; postural instability. All were dopa-responsive No patients had motor fluctuations. Exclusion criteria patients with other neurological disorders. Also excluded patients with medical conditions that might cause excessive fatigue i.e. heart failure, endocrine disorders, pulmonary disease, renal failure, anaemia, arthritis, chronic fatigue	multidimensional fatigue inventory (MFI) to assess subjective fatigue. Only those who scored >48 were enrolled into study. They were then randomly assigned by the pharmacy to the treatment group or placebo. Modafinil and placebo capsules had same appearance. Study required 3 visits per participant: baseline, month 1 and month 2. Each visit, subjects performed 2 motor tasks to evaluate physical fatigability quantitatively and filled out questionnaires to evaluate their subjective fatigue, depression, and sleepiness. Patients performed motor tasks within 1-2 house of their last	UPDRS / baseline / month / month 2 modafinil / 26(3) / 25(3) / 26(4) placebo / 40(3) / 39(4) / 39(4) Paper reports: ESS scores tended to decrease at months 1 and 2 in Modafinil group, but not placebo ($p<0.12$). Non-significant difference between groups in ESS. Non-reported interaction effects =no significant difference between modafinil and placebo. Neither group showed a decrement in UPDRS score over the study period.	subjects in placebo group had significantly higher (almost double modafinil group) scores in UPDRS Other information Motor tasks are irrelevant to current review as fatigue is not a primary outcome. Only Epworth sleep scale values were evaluated, in line with existing research on efficacy of modafinil on daytime hypersomnolence/EDS

What sleep disorders are seen in Parkinson's disease and how are they best treated?				
	syndrome, fibromyalgia, psychosis.	dose of antiparkinsonian medication at each visit. Interventions Modafinil: 100mg PO twice a day for 2 months. Placebo: placebo PO twice a day for 2 months.		

What sleep disorders are seen in Parkinson's disease and how are they best treated?	
Bibliographic reference	Ondo WG, Faye R, Atassi F, Jankovic J. Modafinil for daytime somnolence in Parkinson's disease: double blind, placebo controlled parallel trial. J Neurol Neurogurg Psychiatry 2005;76:1636-1639
Study type	Randomised, double-blind, placebo controlled trial
Evidence level	1++ (low risk of bias)
Study objective	To determine whether modafinil is effective in reversing daytime sleepiness in people with PD
Number of patients	N=40 Parkinson's disease (PD) patients (37 completed the study). N=20 started on modafinil N=20 started on placebo Location: USA Site: Single
Patient characteristics	40 patients satisfying diagnostic criteria for PD between 35 and 80 years of age and who reported daytime somnolence as measured by an ES score of greater than 10. Exclusion criteria: Serious medical conditions, known narcolepsy, known sleep apnoea and pregnancy. Patients were not allowed to take prescription stimulant medications.

What sleep disorders are seen in Parkinson's disease and how are they best treated?	
	Mean baseline characteristics: 29 men/ 11 women, mean age 64.8, mean duration of PD 6.8 years, mean dopaminergic dose 8.5mg/day, 12/40 fluctuating response, UPDRS activities of daily living mean score 13.7, UPDRS mean/motor score 26.7 and mean Epworth score (ES) 15.8.
Intervention	Modafinil one 100mg upon waking and at lunch (200mg/day). After one week the dose was increased to two pills twice a day (400mg/day).
Comparison	Matching placebo administered as for intervention
Length of follow-up	Visit 1 at baseline and visit 2 at 4 weeks.
Outcome measures	ES, UPDRS activities of daily living and motor scores, Multiple sleep latency test (MSLT), SF-36, Fatigue Severity Scale (FFS), Hamilton Depression scale, change in sleepiness "much or very much improved", adverse events.
Effect size	Three patients dropped out: 2 men on placebo and 1 woman on modafinil)the latter was instructed to stop taking study medication by her local physician due to back pain). All drop-outs were prior to post drug evaluation. ES and MSLT There was no significant change in the primary endpoint, the ES score. Patients on modafinil showed an improvement of 2.7 points compared with the placebo group who improved by 1.5 points (p=0.28). MSLT results were not significantly different although the scores worsened less with modafinil (-0.16 (3.59) minutes) than with placebo (-0.70 (3.28) minutes), p=0.14. Other outcomes The UPDRS, Fatigue Severity Scale, Hamilton Depression Scale, SF-36 and global impression scores did not significantly change compared to placebo. In fluctuating subjects, there was no change in on/off time. Adverse effects Only one patient taking modafinil elected to return to the lower dose, secondary to nausea and anxiety. Other adverse events thought to be at least possibly drug related included dry mouth N=1), dizziness (N=1), and back pain (N=1).
Source of funding	Cephalon Pharmaceuticals, the makers of Provigil.
Additional comments	The authors performed a power analysis and found that they required a total of 28 participants (14 per group) to achieve a power of 0.81. Modafinil and placebo tablets were identical in size and appearance. Methods of randomisation and allocation concealment stated. The authors concluded that "Modafinil failed to significantly improve EDS in PD compared with placebo. The drug did not alter motor symptoms and was well tolerated".

D.3.2 Nocturnal akinesia

Bibliographic reference	Trenkwalder,C., Kies,B., Rudzinska,M., Fine,J., Nikl,J., Honczarenko,K., Dioszeghy,P., Hill,D., Anderson,T., Myllyla,V., Kassubek,J., Steiger,M., Zucconi,M., Tolosa,E., Poewe,W., Surmann,E., Whitesides,J., Boroojerdi,B., Chaudhuri,K.R., Rotigotine effects on early morning motor function and sleep in Parkinson's disease: A double-blind, randomized, placebo-controlled study (RECOVER), Movement Disorders.26 (1) (pp 90-99), 2011.Date of Publication: January 2011., 90-99, 2011
Country/ies where the study was carried out	Germany
Study type	Double-blind placebo controlled randomized controlled trial
Aim of the study	To reduce motor disability and improve sleep in patients with Parkinson's disease
Study dates	Paper received 22 June, accepted August 2010, published Nov 2010
Source of funding	RECOVER study supported by Schwartz Biosciences GmbH, a member of UCB group
Sample size	N=287; rotigotine n=2190, placebo n = 97
Inclusion criteria	Subjects with diagnosis of PD and unsatisfactory early-morning motor symptom control. Patients were age >18 years, PD H&Y stage1-4 (both fluctuators and non-fluctuators), and unsatisfactory control of early morning motor symptoms as determined by the investigator . PD defined by presence of bradykinesia and at least 1 of the following: resting tremor, rigidity, impairment of postural reflexes subjects taking immediate release L-dopa or not taking L-dopa were included as long as had been on stable dose for <28 days prior to baseline
Exclusion criteria	None
Details	Antiemetics without central dopaminergic activity were permitted. ACTHI#s MOABI's, NMDA's, entacapone, sedatives, hypnotics, SSRIs, anxiolytics, and other CNS medications were permitted providing dose was stable for >28 days prior to baseline. Controlled-release L-dopa, other centrally acting dopaminergic agents MOA-B inhibitors, tolcapone, budipine, neuroleptics (except olanzapine, ziprasidone, ariprazole, clozapine, or quetiapine) were prohibited from 28 days prior to baseline screening took place 4 weeks before baseline. subjects randomizes 2:1 to receive rotigotine or placebo, stratified by site, using computerized randomization schedule. clinic visits took place at screening, and baseline. Every 2 weeks. during dose titration, start and end of maintenance, 30 days post treatment ending. Efficacy assessments performed after first or second night of hospitalization at baseline and at end of maintenance or withdrawal

Bibliographic reference	**Trenkwalder,C., Kies,B., Rudzinska,M., Fine,J., Nikl,J., Honczarenko,K., Dioszeghy,P., Hill,D., Anderson,T., Myllyla,V., Kassubek,J., Steiger,M., Zucconi,M., Tolosa,E., Poewe,W., Surmann,E., Whitesides,J., Boroojerdi,B., Chaudhuri,K.R., Rotigotine effects on early morning motor function and sleep in Parkinson's disease: A double-blind, randomized, placebo-controlled study (RECOVER), Movement Disorders.26 (1) (pp 90-99), 2011.Date of Publication: January 2011., 90-99, 2011**
	safety and tolerability assessed throughout study and up to 30 days after treatment discontinuation by monitoring frequency and severity of AE's and any changes in vital signs. Emergence of ICD monitored using modified Minnesota impulsive disorder interview (mMIDI)
Interventions	Rotigotine transdermal patch; Day 1, treatment administered once daily in morning using 24hr transdermal patch with identical-looking placebo patch Treatment titrated to optimal dose over 1-8 weeks. starting at 2mg/24hr and increasing in weekly increments of 2mg/24hr up to a maximum of 16mg/24hr Dose maintained at optimal or maximal dose for 4 weeks during which dose reduction not permitted During titration, dose could be back-titrated once if adverse events occurred that were thought to be because of excessive dopaminergic action. Subjects requiring back-titration immediately entered into maintenance period
Results	Baseline characteristics were similar between treatment groups. 80/97 completed placebo: 7 withdrew consent, 6 adverse events, 4 lack of efficacy; 89 included in efficacy analysis, 96 included in safety analysis 166/190 completed rotigotine: 11 withdrew consent, 11 adverse events, 2 other reasons. 178 included in efficacy, 191 in safety NB* q subject in placebo group received 1 dose of rotigotine during de-escalation to counted in this group for safety. Efficacy outcome: Improvement in UPDRS III-motor score MD = -3.55 (-5.37to -1.73) Improvement PDSS-2 total score MD = -4.26 (-6.08 to -2.45) Improvement in NADCS total score MD = -0.41 (-0.79 to -0.04) No significant effect on number of nocturias MD = -0.02 (-0.29 to 0.25) Mean NMS improved MD = -6.65 (-11.99 to -1.31) Improvement in UPDRS II (ADL) MD = -1.49 (-2.32 to -0.65) Improvement in health related quality of life PDQ8 MD = -5.74 (-8.74 to -2.75) Safety and tolerability Mean duration drug exposure 73 days in placebo and 71 in rotigotine 80% subjects compliant overall

Bibliographic reference	**Trenkwalder,C., Kies,B., Rudzinska,M., Fine,J., Nikl,J., Honczarenko,K., Dioszeghy,P., Hill,D., Anderson,T., Myllyla,V., Kassubek,J., Steiger,M., Zucconi,M., Tolosa,E., Poewe,W., Surmann,E., Whitesides,J., Boroojerdi,B., Chaudhuri,K.R., Rotigotine effects on early morning motor function and sleep in Parkinson's disease: A double-blind, randomized, placebo-controlled study (RECOVER), Movement Disorders.26 (1) (pp 90-99), 2011.Date of Publication: January 2011., 90-99, 2011**
	Most frequently reported AE = nausea, application and installation site reaction, dizziness, dyskinesia, headache. total 54/96 placebo, 137/191 rotigotine, - (Risk ratio calculated using RevMan: RR= 3.07, 95%CI = 0.08 to 11.3
Overall Risk of Bias	NICE RCT checklist: 1. An appropriate method of randomization was used to allocate pts to treatment groups? Yes - computer randomized sequence. 2. There was adequate concealment of allocation: Yes - double blind 3. The groups were comparable at baseline, including all major confounding and prognostic factors? Yes - comparable at baseline 4. Comparison groups received same care apart from interventions: yes 5. Pts receiving care were kept blind to tmt allocation: Yes - patients and practitioners were blind 6. Individuals administering care were kept blind to tmt allocation: Yes - blind assessors 7. All groups followed up for an equal length of time: yes - equal time follow-up 8. Groups comparable for treatment completion? Yes - similar completion in both arms 9. Groups were comparable with respect to availability of outcome data? Yes 10. Study had appropriate length of follow up Yes - 30 days follow up. Drug exposure average 78 days 11. Study used a precise definition of outcome Yes - clearly defined outcomes 12. Valid and reliable method was used to determine the outcome: yes- well-validated outcome measures 13. Investigators were kept blind to participants' exposure to the intervention: yes - blind assessors 14. Investigators were kept blind to other important confounding and prognostic factors: not clear whether assessor had access to medical notes. Overall quality = HIGH (risk of bias = low)
Other information	None

Evidence Table Q TxCM8 What is the effect of controlled-release levodopa vs. immediate-release levodopa in the treatment of later Parkinson's disease?	
Bibliographic reference	The U.K.Madopar CR Study Group. A comparison of Madopar CR and standard Madopar in the treatment of nocturnal and early-morning disability in Parkinson's disease. Clin Neuropharmacol 1989;12:498-505.
Study type	Double-blind crossover study
Evidence level	1+
Study objective	To compare the effects of Madopar CR with that of conventional Levodopa/benserazide (Madopar) on nocturnal and early morning disability in patients with Parkinson's disease.
Number of patients	N=103 patients with Parkinson's disease (PD) Location: UK Sites: 11 centres
Patient characteristics	Majority of patients had difficulty turning in bed or getting out of bed and suffered from cramps and pain at night; foot spasms and spontaneous jerks were also common. The mean age was 67.7 years and 67% of the population was male. Disease duration ranged from 1 to 29 years, with a mean of 8 years. Mean duration of levodopa therapy was 6.4 years. The majority of patients (52%) were rated as Hoehn and Yahr stage III, 26% were stage II, 19% were stage IV and 2% were stage I. Daytime fluctuations in response to levodopa and/or abnormal involuntary movements were reported by 42 of 103 patients (41%).
Intervention	Controlled-release Madopar 125 mg (CR) immediately before going to bed. If insufficient effect on symptoms was observed, the dose was increased by 125mg weekly to a maximum of 4 capsules at night. Once optimum night time dose was determined, patients remained at this dosage for 2 weeks. They then transferred to alternative treatment, starting at one capsule, the procedure was repeated.
Comparison	Standard Madopar 125 mg immediate-release (IR) immediately before going to bed
Length of follow-up	Trial duration: 6 weeks (3 weeks per arm). No follow-up stated
Outcome measures	Patient diaries and opinion of investigator
Effect size	82/103 patients completed the study Dosage Mean optimum dosages for the treatments was similar (2.4 capsules for CR, 2.2 for IR) Sleep On entry to study mean time taken to fall asleep (recoded by investigator) was 47 min During optimum treatment periods this time was reduced to 38 min (CR) and 39 min (IR) Mean time taken to fall asleep (patient diaries) was little different between treatments

	Both CR and IR reduced total nocturnal and early-morning disability scores recorded by investigator compared with baseline to a statistically significant degree Little difference between total scores for two optimum treatment periods for either nocturnal or early-morning disability Nocturnal and early-morning disability scores taken from patient diaries and averaged over the periods of optimum treatment were also very similar for IR and CR Patient ratings of early morning condition also improved from baseline but not between treatments The majority of patients considered their overall nocturnal condition was better after optimum treatment with either IR or CR than on entry to study 62% of patients felt better after CR and 59% felt better after IR The number of patients who felt their nocturnal condition was worse from baseline was 4% CR and 10% IR Overall early-morning condition was rated as better than on entry to the study was 46% after CR and 45 after IR Percentage of patients who felt overall condition was worse was 2% cr and 6% IR 2/3 of patients gave the same response for both treatments with respect to their effect on overall condition compared to baseline Only 27% felt the two treatments were the same in relation to their effect on nocturnal condition 41% felt CR was better 33% felt it was worse Corresponding percentages for early-morning condition are 41% the same, 33% felt CR was better and 26% felt CR was worse CR was considered to be advantageous by 61% of patients and IR by 60% Patients who found treatments to be disadvantageous: 23% CR and 28% IR After the optimum treatment period the investigator (patient) felt it was justified to continue treatment with CR 55% (63%) of cases and with IR in 50% (55%) of cases Good agreement between patient and investigatory opinions Despite many little differences between treatments investigator thought that there was a difference between the two treatments in 60% of cases Of these CR was felt to be preferable in 65% and IR in 35% Adverse effects 63 adverse events were reported by 37 patients (32 CR and 31 IR)

Evidence Table Q TxCM8 What is the effect of controlled-release levodopa vs. immediate-release levodopa in the treatment of later Parkinson's disease?	
	Majority were consistent with levodopa profile Dyskinesia was the most commonly reported adverse event (8 CR, 7 IR) Other adverse events: disorders of movement, gastrointestinal, central effects such as confusion, expression, hallucinations etc was evenly distributed between the 2 treatments Withdrawal rates 21 patients withdrew Lack of effect was the reason given in 3 cases (one on IR and 2 on CR) Adverse side effects in 11 cases (4 on IR and 7 on CR) 7 due to other reasons
Source of Funding	Not stated
Additional comments	There was no washout period between arms and no first arm results were reported Period and carry-over effects were analysed Differences from baseline to the end of the first treatment period were assessed within each treatment group separately, also using analysis of variance techniques Methods of randomisation or allocation concealment not stated No sample size calculations Intention-to-treat not stated Centre comparisons were performed No details of blinding procedure No details of clinical diagnosis criteria

D.3.3 Orthostatic hypotension

Bibliographic reference	Hauser,R.A., Hewitt,L.A., Isaacson,S., 20141014, Droxidopa in patients with neurogenic orthostatic hypotension associated with Parkinson's disease (NOH306A), Journal of Parkinson's Disease Print, 4, 57-65, 2014
Country/ies where the study was carried out	USA
Study type	Intervention, Randomised Controlled Trial
Aim of the study	Determine efficiency and safety of droxidopa in treating Orthostatic Hypotension as a symptom of Parkinson's disease
Study dates	June 2010 - December 2010
Source of funding	Chelsea Therapeutics, Inc.
Sample size	51
Inclusion criteria	• Age >=18 years • PD clinical diagnosis • Symptomatic nOH (Decrease >=20mmHg systolic/>=10mmHg diastolic b.p. within 3 minutes after going from supine to standing) • Patient reported composite score >=3 on Orthostatic Hypotension Questionnaire • Study investigator rating >=3 on Clinical Global Impression-Severity Scale)
Exclusion criteria	• Use of vasoconstrictive agents or long-acting antihypertensive medications • Sustained severe hypertension (>=180/110 mmHg while seated or supine on 3 consecutive measurements over 1h) • Mini-Mental State Examination score <=23
Details	Enrolled patients underwent up to 2 weeks of dosage optimisation by titration in 100mg increments until becoming asymptomatic, reaching the maximum permitted dosage, or experiencing intolerable adverse effects. In the third case, patients were eligible to continue the study under a lower dose if effects occurred at a dosage of more than 100mg twice daily. During study, all PD medications were held stable. Midodrine was disallowed, but fludrocortisone could be continued at a dosage that had been held steady for 2 weeks prior to start of study drug. Primary efficacy measure was mean change in Orthostatic Hypotension Questionnaire from baseline to end of study, recorded on weeks 1, 2, 4 and 8 of treatment Key secondary efficacy variables included dizziness/light-headedness score on OHQ and patient-reported falls from baseline to end of study, which patients were instructed to record by daily entries in an electronic diary, with falls defined as "unexpectedly coming to rest on the ground, floor, or a lower level from where the patient started." Additional secondary effect variables included OHQ symptom and symptom impact composite scores and individual item scores, and hemodynamic efficacy variables such as standing systolic b.p.

Bibliographic reference	**Hauser,R.A., Hewitt,L.A., Isaacson,S., 20141014, Droxidopa in patients with neurogenic orthostatic hypotension associated with Parkinson's disease (NOH306A), Journal of Parkinson's Disease Print, 4, 57-65, 2014**
Interventions	Droxidopa: 100, 200, 300, 400, 500 or 600mg twice daily Placebo: placebo twice daily
Results	

	Droxidopa	Placebo
Total assigned	24	27
Discontinued	3	3
Completed Study	21	24

	Droxidopa	Placebo
Patients receiving maximum allowable dosage	6	13
Mean (SD) dosage/mg twice daily	433.3 (155.1)	488.9 (134.0)

	Droxidopa	Placebo
Mean (SD) decrease in OHQ composite week 1	-2.7 (2.6)	-2.1 (2.5)
Mean (SD) decrease in OHQ composite week 2	-2.3 (2.4)	-1.7 (2.2)
Mean (SD) decrease in OHQ composite week 8	-2.2 (2.4)	-2.1 (2.5)
Mean (SD) decrease in dizziness/light-headedness score week 1	-3.1 (3.4)	-1.6 (3.1)
Mean (SD) decrease in dizziness/light-headedness score week 2	-2.3 (3.0)	-1.0 (3.0)
Mean (SD) change in standing systolic bp week 1	+8.4 (17.4)	-4.1 (20.5)
Mean (SD) change in standing systolic bp week 8	+7.0 (18.7)	+7.7 (22.2)

	Droxidopa	Placebo

Bibliographic reference	Hauser,R.A., Hewitt,L.A., Isaacson,S., 20141014, Droxidopa in patients with neurogenic orthostatic hypotension associated with Parkinson's disease (NOH306A), Journal of Parkinson's Disease Print, 4, 57-65, 2014

# (%) patients recording falls	13 (54)	16 (59)
Repeat fallers	9	13
Total falls	79	192
Mean falls/patient/week	0.4	0.8
Mean (SD) falls/repeat faller/week	1.0 (1.2)	1.9 (2.1)
Number of patients (%) reporting AEs	17 (71)	23 (85)
Fall related injuries	4	8
Most frequently reported AEs	Nausea (3), Headache (3), Skin Laceration (2)	Diarrhoea (4), Nausea (3), Skin Laceration (3)

	Droxidopa	Placebo
Mean (SD) decrease MDS-UPDRS total	-19.0 (18.4)	-11.3 (24.9)
Mean (SD) decrease MDS-UPDRS I	-7.3 (7.1)	-5.2 (6.9)
Mean (SD) decrease MDS-UPDRS II	-5.3 (7.7)	-3.1 (6.7)
Mean (SD) decrease MDS-UPDRS III	-4.7 (8.4)	-0.6 (12.9)
Mean (SD) decrease MDS-UPDRS IV	-1.7 (5.3)	-0.7 (4.0)
Mean (SD) decrease H&Y stage	-0.4 (0.9)	0.0 (1.2)

Overall Risk of Bias	Not much information given for method of randomisation, level of blinding present beyond description of study as "randomized, double-blind, placebo-controlled phase 3 trial". However, study groups appear to have been comparable and treated comparably, and results collected would seem to be valid and reasonably connected to the outcomes measured. Overall there is likely high risk of bias.
Other information	1. An appropriate method of randomization was used to allocate pts to treatment groups? not mentioned 2. There was adequate concealment of allocation - not mentioned

Bibliographic reference	Hauser,R.A., Hewitt,L.A., Isaacson,S., 20141014, Droxidopa in patients with neurogenic orthostatic hypotension associated with Parkinson's disease (NOH306A), Journal of Parkinson's Disease Print, 4, 57-65, 2014
	3. The groups were comparable at baseline, including all major confounding and prognostic factors? approximately similar - possible slight difference in progression of PD, but probably not enough to make much of a difference 4. Comparison groups received same care apart from interventions - yes 5. Pts receiving care were kept blind to tmt allocation - not discussed 6. Individuals administering care were kept blind to tmt allocation - not discussed 7. All groups followed up for an equal length of time - yes, when possible 8. Groups comparable for treatment completion? yes 9. Groups were comparable with respect to availability of outcome data? yes 10. Study had appropriate length of followup - 8 weeks 11. Study used a precise definition of outcome - difference in questionnaire scores, standing Systolic Blood Pressure, number of falls/fall-related injuries sustained, change in H&Y score 12. Valid and reliable method was used to determine the outcome - see above 13. Investigators were kept blind to participants exposure to the intervention - not discussed 14. Investigators were kept blind to other important confounding and prognostic factors - not discussed

Bibliographic reference	Hauser,R.A., Isaacson,S., Lisk,J.P., Hewitt,L.A., Rowse,G., Droxidopa for the Short-Term Treatment of Symptomatic Neurogenic Orthostatic Hypotension in Parkinson's Disease (nOH306B), Movement Disorders.30 (5) (pp 646-654), 2015.Date of Publication: 15 Apr 2015., 646-654, 2015
Country/ies where the study was carried out	USA
Study type	RCT: Intervention
Aim of the study	To determine efficacy and safety of droxidopa as a short term treatment of Orthostatic Hypotension in PD
Study dates	June 2010 - October 2012
Source of funding	Lundbeck NA Ltd.
Sample size	174
Inclusion criteria	• Age >=18 years • Clinical diagnosis of Parkinson's disease

<table>
<tr><th>Bibliographic reference</th><th>Hauser,R.A., Isaacson,S., Lisk,J.P., Hewitt,L.A., Rowse,G., Droxidopa for the Short-Term Treatment of Symptomatic Neurogenic Orthostatic Hypotension in Parkinson's Disease (nOH306B), Movement Disorders.30 (5) (pp 646-654), 2015.Date of Publication: 15 Apr 2015., 646-654, 2015</th></tr>
<tr><td></td><td>• B.P. decrease >=20mmHg systolic or >=10mmHg diastolic upon standing for up to 3 minutes
• Orthostatic Hypotension Questionnaire score >=3
• Study-investigator Orthostatic Hypotension rating >=3 on clinician reported Clinical Global Impression-Severity scale</td></tr>
<tr><td>Exclusion criteria</td><td>• Use of vasoconstricting agents or long acting antihypertensive medications
• Sustained, sever hypertension (>=180/110 mmHg while seated or supine)
• Mini-Mental State Examination score <=23
• Significant uncontrolled cardiac arrhythmia, unstable angina, congestive heart failure, or a history of myocardial infarction</td></tr>
<tr><td>Details</td><td>Subjects were randomised in a 1:1 ratio to double-blind droxidopa or placebo titration for up to 2 weeks, followed by 8 weeks of double-blind maintenance at the personally optimised dosage
During titration, assigned drug was increased in 100mg increments thrice daily until subject's cCGI-S score fell to 1 or 2, the maximum dosage was reached, subject's blood pressure reached >=180mmHg systolic or >=110mmHg diastolic after ten minutes supine 3 times consecutively over an hour, or subject experienced intolerable adverse effects. If either of the last 2 criteria were met at a dosage of >100mg, subjects were eligible to continue the trial at a lower dosage.
During study, all PD medications were to be held steady; Midodrine was disallowed, but fludrocortisone could be allowed at a dosage that had been kept stable for at least 2 weeks prior to the trial. Bedtime usage of a short-acting antihypertensive was permitted.
An orthostatic standing test, OHQ, cCGI-S and subject reported pCGI-S ratings were completed for each subject at randomisation, and on weeks 1, 2, 4 and 8 of maintenance; patient and clinician reported Clinical Global Impression-Improvement ratings were obtained in weeks 1, 2, 4 and 8; and MDS-UPDRS and PDQ-39 were completed at randomisation and week 8. All assessments were conducted ~3h after the subject's first daily dose, and subjects were instructed to record all falls, defined as "unexpectedly coming to rest on the ground, floor, or a lower level from where the patient started", in a daily electronic diary.</td></tr>
<tr><td>Interventions</td><td>Droxidopa: 100, 200, 300, 400, 500 or 600mg thrice daily
Placebo: placebo thrice daily</td></tr>
<tr><td>Results</td><td><table><tr><td></td><td>Droxidopa</td><td>Placebo</td></tr><tr><td>N</td><td>89</td><td>85</td></tr><tr><td>Treated</td><td>87</td><td>84</td></tr></table></td></tr>
</table>

Bibliographic reference	Hauser,R.A., Isaacson,S., Lisk,J.P., Hewitt,L.A., Rowse,G., Droxidopa for the Short-Term Treatment of Symptomatic Neurogenic Orthostatic Hypotension in Parkinson's Disease (nOH306B), Movement Disorders.30 (5) (pp 646-654), 2015.Date of Publication: 15 Apr 2015., 646-654, 2015

Provided week 1 data	69	78
Completed study	62	67
Mean (SD) study drug dosage/mg	436 (163)	468 (165)

Mean (SD) improvement in OHSA item 1 score	Droxidopa	Placebo
To week 1	2.3 (2.95)	1.3 (3.16)
To week 2	1.9 (2.86)	1.6 (2.97)
To week 4	2.0 (3.08)	1.5 (2.74)
To week 8	2.1 (3.03	1.5 (2.91)

Mean (SD) change in OHQ composite score	Droxidopa	Placebo
To week 1	-2.3 (2.12)	-1.9 (2.39)
To week 2	-2.5 (1.98)	-2.0 (2.26)
To week 4	-2.5 (1.93)	-1.9 (2.28)
To week 8	-2.2 (2.29)	-2.0 (2.18)

	Droxidopa	Placebo
Aggregate falls per patient-week	0.38	1.09
Total falls	229	716
Total falls to end of titration	46	232

Bibliographic reference	Hauser,R.A., Isaacson,S., Lisk,J.P., Hewitt,L.A., Rowse,G., Droxidopa for the Short-Term Treatment of Symptomatic Neurogenic Orthostatic Hypotension in Parkinson's Disease (nOH306B), Movement Disorders.30 (5) (pp 646-654), 2015.Date of Publication: 15 Apr 2015., 646-654, 2015

Patients experiencing Treatment Emergent Adverse Effects	82%	79.3%
Subjects experiencing fall related AEs	16.9%	25.6%
Severe AEs	8	9
Serious AEs	5	4
AEs leading to discontinuation	11	5
Patients experiencing Supine Hypertension	7	4
Most Common AEs	Headache (12), Dizziness (9), Fatigue (7)	Contusion (10), Excoriation (7), Skin Laceration (7)

Mean (SD) change in lowest standing Systolic Blood Pressure	Droxidopa	Placebo
To week 1	+6.4 (18.85)	+0.7 (20.18)
To week 2	+5.5 (19.34)	-0.6 (20.28)
To week 4	+2.8 (20.23)	+3.0 (19.40)
To week 8	+5.0 (18.52)	+0.9 (18.38)

Overall Risk of Bias	High; most outcomes recorded measured for 1, 2 or 4 weeks, primary outcome altered after futility analysis for part a showed no impact for original primary outcome, no description of randomisation or blinding processes used in study
Other information	1. An appropriate method of randomization was used to allocate pts to treatment groups? method not described 2. There was adequate concealment of allocation - not described 3. The groups were comparable at baseline, including all major confounding and prognostic factors? Yes 4. Comparison groups received same care apart from interventions - pharmacological treatments kept comparable, non-pharmacological treatments not controlled 5. Pts receiving care were kept blind to tmt allocation - not described

Bibliographic reference	Hauser,R.A., Isaacson,S., Lisk,J.P., Hewitt,L.A., Rowse,G., Droxidopa for the Short-Term Treatment of Symptomatic Neurogenic Orthostatic Hypotension in Parkinson's Disease (nOH306B), Movement Disorders.30 (5) (pp 646-654), 2015.Date of Publication: 15 Apr 2015., 646-654, 2015
	6. Individuals administering care were kept blind to tmt allocation - not described 7. All groups followed up for an equal length of time - yes 8. Groups comparable for treatment completion? yes 9. Groups were comparable with respect to availability of outcome data? - yes 10. Study had appropriate length of follow up - 8 weeks from end of dosage titration, most primary and secondary outcomes reported only measured for 1, 2 and 4 weeks 11. Study used a precise definition of outcome - questionnaires as described above, plus blood pressure, number of falls and H&Y stage 12. Valid and reliable method was used to determine the outcome - yes 13. Investigators were kept blind to participants exposure to the intervention - not described 14. Investigators were kept blind to other important confounding and prognostic factors - not described

Bibliographic reference	Schoffer,K.L., Henderson,R.D., O'Maley,K., O'Sullivan,J.D., 20071128, Nonpharmacological treatment, fludrocortisone, and domperidone for orthostatic hypotension in Parkinson's disease, Movement Disorders, 22, 1543-1549, 2007
Country/ies where the study was carried out	Australia
Study type	RCT - Intervention
Aim of the study	Assess the efficacy of nonpharmological therapy, domperidone and fludrocortisone for Orthostatic Hypotension in Parkinson’s Disease
Study dates	January 2005 - November 2005
Source of funding	Not reported
Sample size	17
Inclusion criteria	• Diagnosis of IPD • Sustained response to medications, (held stable through study) • Symptomatic orthostasis
Exclusion criteria	• Acute coronary syndrome

<table>
<tr><th>Bibliographic reference</th><th>Schoffer,K.L., Henderson,R.D., O'Maley,K., O'Sullivan,J.D., 20071128, Nonpharmacological treatment, fludrocortisone, and domperidone for orthostatic hypotension in Parkinson's disease, Movement Disorders, 22, 1543-1549, 2007</th></tr>
<tr><td></td><td>• Inability to give consent
• Alternative etiology for autonomic failure
• SBP>200mg Hg or DBP>100mg Hg</td></tr>
<tr><td>Details</td><td>During first visit, clinical evaluation was performed, focusing on symptoms over 3 week period, including COMPASS-OD score and clinically measured BP after 15 min supine, and after 1 and 3 minutes standing. Patients were instructed to follow series of non-pharmacological treatments for 3 weeks, after which evaluation was repeated.
Patients were randomly allocated to receive one of 2 pharmacological treatments first; this treatment course was followed for 3 weeks, then, after a 1 week washout period, the alternative treatment course was followed for 3 weeks. After each treatment course, a clinical evaluation was performed, including tilt table testing with both a non-invasive finger BP measurement and an automatic sphygmomanometric method, in which the patient lay supine for 15 minutes, and then had heart rate and BP changes recorded over 5 minutes supine, 5 minutes with an 80 degree head up tilt, and a further 5 minutes supine. Non-pharmacological treatments were sustained over both courses of pharmacological treatment.
Patients were asked to choose which, if any, of the 3 treatments they found most beneficial</td></tr>
<tr><td>Interventions</td><td>Instruction sheet of 12 non-pharmacological treatments asked to be followed over entire period
2 treatment courses;
0.1mg fludrocortisone during morning, 2 placebo tablets at lunch and supper
10mg domperidone three times a day</td></tr>
<tr><td>Results</td><td>
<table>
<tr><td></td><td>baseline</td><td>fludrocortisone</td><td>domperidone</td></tr>
<tr><td>COMPASS-OD score (+/-)*</td><td>9 (3)</td><td>6 (3)</td><td>7 (2)</td></tr>
<tr><td>Average CGI score (+/-)</td><td>-</td><td>MC =+0.6 (1.2)</td><td>MC=+0.9 (1.2)</td></tr>
<tr><td>supine SBP/mm Hg</td><td>139</td><td>137 (134 ± 24; 100-165)</td><td>125 (138 ± 27; 107 - 189)</td></tr>
</table>
<table>
<tr><td></td><td>fludrocortisone</td><td>domperidone</td><td>both</td><td>neither</td></tr>
<tr><td>Preference/greater response</td><td>4</td><td>3</td><td>3</td><td>3</td></tr>
</table>
<table>
<tr><td></td><td>fludrocortisone</td><td>domperidone</td></tr>
</table>
</td></tr>
</table>

Bibliographic reference	Schoffer,K.L., Henderson,R.D., O'Maley,K., O'Sullivan,J.D., 20071128, Nonpharmacological treatment, fludrocortisone, and domperidone for orthostatic hypotension in Parkinson's disease, Movement Disorders, 22, 1543-1549, 2007
	<table><tr><td>Patients reporting AEs</td><td>6</td><td>5</td></tr><tr><td>Most common AE</td><td>Nausea</td><td>Nausea</td></tr></table> COMPASS OD = composite autonomic symptom scale -OT component Mean difference scores calculated from mean values and SD's presented in text Supine blood pressure (SBP mm/Hg): fludrocortisone v domperidone: MD= -4 (95%CI: -23.6 to 15.64) COMPASS-OD: fludrocortisone v domperidone: MD = -1 (-2.96 to 0.96)
Overall Risk of Bias	High; very small sample size, with noticeable difference between demographics of treatment groups
Other information	An appropriate method of randomization was used to allocate pts to treatment groups - patients allocated using computerised random number generator program - Research Randomizer There was adequate concealment of allocation - randomisation sequence performed, kept and administered by uninvolved staff member The groups were comparable at baseline, including all major confounding and prognostic factors - all women in trial received domperidone treatment before fludrocortisone, making up 4 of 5 such patients; two fludrocortisone first patients were on Entacapone during study; average UPDRS score seems much higher for fludrocortisone first patients than for domperidone first, though this may be mostly due to a typo in table 1; fludrocortisone first patients receiving 70% more levodopa on average Comparison groups received same care apart from interventions - yes Pts receiving care were kept blind to tmt allocation - yes Individuals administering care were kept blind to tmt allocation - medications identically encapsulated and delivered in unmarked packages All groups followed up for an equal length of time - yes Groups comparable for treatment completion? 3 patients assigned to domperidone and 1 assigned to fludrocortisone withdrawn in first week of pharmacological treatment Groups were comparable with respect to availability of outcome data? yes Study had appropriate length of follow up - 3 weeks on each drug Study used a precise definition of outcome - orthostatic domain of the Composite Autonomic Symptom Scale, clinical global impression of change, and postural blood pressure testing Valid and reliable method was used to determine the outcome - yes Investigators were kept blind to participants exposure to the intervention - not mentioned Investigators were kept blind to other important confounding and prognostic factors - not mentioned

D.3.4 Psychotic symptoms (hallucinations and delusions)

Bibliographic reference	**Fernandez,H.H., Okun,M.S., Rodriguez,R.L., Malaty,I.A., Romrell,J., Sun,A., Wu,S.S., Pillarisetty,S., Nyathappa,A., Eisenschenk,S., 20100128, Quetiapine improves visual hallucinations in Parkinson disease but not through normalization of sleep architecture: results from a double-blind clinical-polysomnography study, International Journal of Neuroscience, 119, 2196-2205, 2009**
Country/ies where the study was carried out	US
Study type	Pilot, double-blind, placebo-controlled parallel-group study
Aim of the study	To confirm quetiapine's efficacy in improving visual hallucinations (VH), and to determine whether the mechanism was due to its effect on rapid eye movement (REM) sleep architecture.
Study dates	Study dates: Not reported Study duration: ~6.5 - 14 weeks
Source of funding	AstraZeneca Pharmaceuticals LP
Sample size	In total n =16; Quetiapine n = 8, Placebo n = 8 Randomised in a 1:1 drug to placebo ratio
Inclusion criteria	Patients were included if they: • Had been diagnosed with idiopathic PD • Experienced consistent and persistent (i.e., greater than one month), predominantly nocturnal VH • Were on stable doses of PD medications
Exclusion criteria	Patients were excluded if they: • Had been diagnosed with having "brittle" PD • Required constant medication adjustments • With a previous "non-response" to any antipsychotic drug • With threatening psychosis or delusions that make it difficult to justify participation in a place-controlled study • Had significant cognitive impairment that prevented accurate assessment of drug efficacy or understanding or informed consent • Were taking clonazepam or other sleeping agents that could interfere with sleep architecture • Had known central sleep disorders
Interventions	Quetiapine: 25 mg, 50 mg, 75 mg, 100 mg, 125 mg, or 150 mg once a day at bedtime
Details	Quetiapine (or matching placebo) was initiated at dose 25 mg at bedtime. The dose was increased every 3 to 7 days by 25 mg

<table>
<tr><th>Bibliographic reference</th><th>Fernandez,H.H., Okun,M.S., Rodriguez,R.L., Malaty,I.A., Romrell,J., Sun,A., Wu,S.S., Pillarisetty,S., Nyathappa,A., Eisenschenk,S., 20100128, Quetiapine improves visual hallucinations in Parkinson disease but not through normalization of sleep architecture: results from a double-blind clinical-polysomnography study, International Journal of Neuroscience, 119, 2196-2205, 2009</th></tr>
<tr><td></td><td>until a final dose of 150 mg at bedtime of quetiapine was reached or a complete resolution of nocturnal hallucinations was experienced, whichever was achieved first. Patients also received a phone call twice per week during the titration phase to monitor for efficacy, tolerance, and side effects. Patients needed to be on their final, stable dose for at least one month prior to obtaining the repeat polysomnogram. One month after the repeat polysomnography, all subjects returned for their final visit.

All PD medications were kept stable throughout the study.

There were no differences in baseline characteristics between the treatment arms except that the placebo group had a longer stage REM (74.7 min vs 40.1 min; p<0.001) at baseline:
<table>
<tr><td>Variable</td><td>Overall (n=16)</td><td>Active arm (n=8</td><td>Placebo arm (n=8)</td><td>p-value</td></tr>
<tr><td>Age</td><td>68 (8.04)</td><td>64.6 (7.48)</td><td>71.5 (7.46)</td><td>.087</td></tr>
<tr><td>Stage REMa</td><td>56.2 (26.4)</td><td>40.1 (17.7</td><td>74.6 (22.8)</td><td>.006</td></tr>
<tr><td>BPRS Total</td><td>30.8 (8.25)</td><td>31.2 (9.43)</td><td>30.2 (7.49)</td><td>.818</td></tr>
<tr><td>BPRS item No. 12</td><td>3.25 (1.1)</td><td>3.5 (1.06)</td><td>3.3 (0.92)</td><td>.334</td></tr>
<tr><td>UPDRS motor</td><td>33.6 (10.58)</td><td>31.6 (9.72)</td><td>35.8 (11.83)</td><td>.460</td></tr>
</table>
[a]Measured in minutes.</td></tr>
<tr><td>Primary outcome measures</td><td>Changes in REM architecture, as demonstrated via polysomnography.</td></tr>
<tr><td>Secondary outcomes measures</td><td>• CGIS
• BPRS
• UPDRS motor</td></tr>
<tr><td>Results</td><td></td></tr>
<tr><td>BPRS Hallucination</td><td>
<table>
<tr><td></td><td>Mean</td><td>SD</td><td>Total</td></tr>
<tr><td>Experimental</td><td>-1.32</td><td>1.13</td><td>8</td></tr>
</table>
</td></tr>
</table>

Bibliographic reference	**Fernandez,H.H., Okun,M.S., Rodriguez,R.L., Malaty,I.A., Romrell,J., Sun,A., Wu,S.S., Pillarisetty,S., Nyathappa,A., Eisenschenk,S., 20100128, Quetiapine improves visual hallucinations in Parkinson disease but not through normalization of sleep architecture: results from a double-blind clinical-polysomnography study, International Journal of Neuroscience, 119, 2196-2205, 2009**
	Control -0.04 0.82 8
UPDRS Motor	<table><tr><td></td><td>Mean</td><td>SD</td><td>Total</td></tr><tr><td>Experimental</td><td>-5.74</td><td>6.84</td><td>8</td></tr><tr><td>Control</td><td>2.83</td><td>7.46</td><td>8</td></tr></table>
Mortality	<table><tr><td></td><td>Deaths</td><td>Total</td></tr><tr><td>Experimental</td><td>0</td><td>8</td></tr><tr><td>Control</td><td>0</td><td>8</td></tr></table>
Number of dropouts due to adverse events	<table><tr><td></td><td>Events</td><td>Total</td></tr><tr><td>Experimental</td><td>4</td><td>8</td></tr><tr><td>Control</td><td>1</td><td>8</td></tr></table>
Results	Average quetiapine dose was 58.3 mg/day (range: 25-100 mg/day). The worsening of Parkinsonism was noted to be mild in all cases, and no patients discontinued quetiapine because of Parkinsonism. However, 4 patients randomised to the quetiapine arm eventually dropped out: two due to the lack of efficacy in controlling the hallucinations, one was due to drowsiness, and one was lost to the follow-up. <table><tr><td>Adverse event</td><td>Quetiapine</td><td>Placebo</td></tr><tr><td>Bronchitis</td><td>0</td><td>1</td></tr><tr><td>Confusion</td><td>1</td><td>1</td></tr><tr><td>Drowsiness</td><td>3</td><td>1</td></tr><tr><td>Dry mouth</td><td>0</td><td>1</td></tr></table>

Bibliographic reference	**Fernandez,H.H., Okun,M.S., Rodriguez,R.L., Malaty,I.A., Romrell,J., Sun,A., Wu,S.S., Pillarisetty,S., Nyathappa,A., Eisenschenk,S., 20100128, Quetiapine improves visual hallucinations in Parkinson disease but not through normalization of sleep architecture: results from a double-blind clinical-polysomnography study, International Journal of Neuroscience, 119, 2196-2205, 2009**
	<table><tr><td>Dizziness/Syncope</td><td>0</td><td>4</td></tr><tr><td>Depression</td><td>0</td><td>1</td></tr><tr><td>Decreased appetite</td><td>0</td><td>1</td></tr><tr><td>Increased appetite</td><td>1</td><td>0</td></tr><tr><td>Loss of balance/increased</td><td>3</td><td>0</td></tr><tr><td>Nightmares</td><td>1</td><td>0</td></tr><tr><td>Sore throat</td><td>0</td><td>1</td></tr></table> Data extracted for BPRS hallucination and UPDRS motor are the mean change scores from baseline to end point.
Overall Risk of Bias	1. Has an appropriate method of randomisation been used? UNCLEAR 2. Was there adequate concealment of allocation? UNCLEAR 3. Were the groups comparable at baseline for all major confounding/prognostic factors? YES 4. Did the comparison groups receive the same care apart from interventions studied? YES 5. Were participants receiving care kept blind to treatment allocation? UNCLEAR* 6. Were the individuals administering care kept blind to treatment allocation? UNCLEAR* 7. Were groups comparable with respect to availability of outcome data and for how many participants were no outcome data available? NO. Dropout rate >20% 8. Did the study have an appropriate length of follow up? UNCLEAR (6.5 - 14 wks) 9. Did the study use a precise definition of outcome? YES 10. Was a valid and reliable method used to determine that outcome? UNCLEAR 11. Were investigators kept blind to participant’s exposure to the intervention? UNCLEAR* 12. Were investigators kept blind to other important confounding and prognostic factors? UNCLEAR* *Level of blinding unclear - no details beyond description of study as "randomized, double-blind, placebo-controlled trial".

Bibliographic reference	**Fernandez,H.H., Okun,M.S., Rodriguez,R.L., Malaty,I.A., Romrell,J., Sun,A., Wu,S.S., Pillarisetty,S., Nyathappa,A., Eisenschenk,S., 20100128, Quetiapine improves visual hallucinations in Parkinson disease but not through normalization of sleep architecture: results from a double-blind clinical-polysomnography study, International Journal of Neuroscience, 119, 2196-2205, 2009**
	Overall there is likely high risk of bias.

Bibliographic reference	**Ondo,W.G., Tintner,R., Voung,K.D., Lai,D., Ringholz,G., 20051019, Double-blind, placebo-controlled, unforced titration parallel trial of quetiapine for dopaminergic-induced hallucinations in Parkinson's disease, Movement Disorders, 20, 958-963, 2005**
Country/ies where the study was carried out	US
Study type	Randomised, double-blind, placebo-controlled, parallel study
Aim of the study	To test the effectiveness of quetiapine in PD-associated hallucinations.
Study dates	Study dates: Not reported Study duration: 12 weeks
Source of funding	AstraZeneca Pharmaceuticals
Sample size	In total n= 31; Quetiapine n= 21; Placebo n= 10 Randomised in a 2:1 drug to placebo ratio
Inclusion criteria	Patients were included if they: • Were between 30 - 80 years of age with subjectively problematic visual hallucinations while taking dopaminergic medications
Exclusion criteria	Patients were excluded if they had: • A Mini-Mental State Examination score of <21 • Previous treatment for hallucinations within the past 30 days • Current use of any dopamine antagonist for any reason • The presence of a psychiatric diagnosis not believed to be directly related to their PD
Interventions	Quetiapine: 50 mg or 100 mg twice daily (in the afternoon and at night)
Details	Drug or placebo was titrated up to 50 mg twice daily (in the afternoon and at night). After 3 weeks participants returned for a safety visit and UPDRS testing. They were then further titrated to 100 mg twice daily of quetiapine over 3 weeks, but were allowed to reduce to the dose if adverse events were problematic. Six weeks after this titration period, they returned for assessment.

Bibliographic reference	**Ondo,W.G., Tintner,R., Voung,K.D., Lai,D., Ringholz,G., 20051019, Double-blind, placebo-controlled, unforced titration parallel trial of quetiapine for dopaminergic-induced hallucinations in Parkinson's disease, Movement Disorders, 20, 958-963, 2005**
	There were no demographic or baseline differences between subjects randomised to drug vs. placebo, except that the drug group had a higher initial score on the Goetz Dyskinesia Rating scale (p <0.05): Variable / Quetiapine n=21 / Placebo n= 10 Age (yr): 74 ± 7 / 71 ± 5 Duration of PD (yr): 12 ± 7 / 9 ± 4 Fluctuating: 12/19 / 9/12 UPDRS (Part II): 34.2 ± 7.9 / 30.7 ± 11.9 UPDRS (Motor): 34 ± 8 / 31 ± 12 Goetz dyskinesia: 2.0 ± 3.3 / 5.6 ± 5.2 MMSE: 26.1 ± 2.5 / 27 ± 2.9 Initial BPRS: 11 ± 5 / 11 ± 5
Primary outcome measures	• Baylor PD Hallucination Questionnaire • UPDRS Motor • UPDRS Part II (in fluctuators only as a mean of their on and off scores) All primary outcome measures were display graphically only. Hence, no data could therefore be extracted.
Secondary outcomes measures	• BPRS Total • BPRS Hallucination • Goetz Dyskinesia rating Scale • HAM-D • Adverse events All secondary outcome measures apart from adverse events/ dropouts were displayed graphically only. Hence no data could be extracted.

Bibliographic reference	Ondo,W.G., Tintner,R., Voung,K.D., Lai,D., Ringholz,G., 20051019, Double-blind, placebo-controlled, unforced titration parallel trial of quetiapine for dopaminergic-induced hallucinations in Parkinson's disease, Movement Disorders, 20, 958-963, 2005
Results	
Mortality	<table><tr><td></td><td>Deaths</td><td>Total</td></tr><tr><td>Experimental</td><td>0</td><td>21</td></tr><tr><td>Control</td><td>2</td><td>10</td></tr></table>
Number of dropouts due to adverse events	<table><tr><td></td><td>Events</td><td>Total</td></tr><tr><td>Experimental</td><td>0</td><td>21</td></tr><tr><td>Control</td><td>0</td><td>10</td></tr></table>
Results	The final daily dose of active drug in completers was 200 mg (n=11), 150 mg (n= 2), 100 mg (n= 3), and 75 mg (n=1). All placebos were on the daily equivalent of 200mg. Of 31 recruited subjects, 26 completed the study. The medication was generally well tolerated. No patients dropped out secondary to a related AE, which included sedation (n=9; 43%) and subjective worsening in PD (n= 4; 19%). One other AE was reported by 10 different subjects while on drug, but none was believed to be serious. Sedation was reported in 4 (40%) of placebo subjects and a single different AE was reported in all 10 subjects. Of those randomly assigned to drug, 2 dropped out due to serious unrelated illness, and 2 dropped out due to lack of effect and poor compliance. On placebo, 2 patients dropped out due to unrelated serious illness, both resulting in deaths. Although no primary or secondary data apart from adverse events, dropouts and mortality were extracted for analysis due to results being presented graphically, the author did report that none of those outcomes reached statistical significance in comparison to placebo. Quetiapine at doses up to 200 mg/day therefore failed to significantly improve hallucinations compared to placebo. The medication was generally well tolerated. No patients on drug dropped out secondary to a related AE, which included

Bibliographic reference	Ondo,W.G., Tintner,R., Voung,K.D., Lai,D., Ringholz,G., 20051019, Double-blind, placebo-controlled, unforced titration parallel trial of quetiapine for dopaminergic-induced hallucinations in Parkinson's disease, Movement Disorders, 20, 958-963, 2005
	sedation (n=9; 43%) and subjective worsening in PD 9n=4; 19%). One other AE was reported by 10 different subjects while on drug, but none was believed to be serious. Sedation was reported by 4 (40%) of placebo subjects, and a single different AE was reported in all 10 subjects.
Overall Risk of Bias	1. Has an appropriate method of randomisation been used? UNCLEAR 2. Was there adequate concealment of allocation? UNCLEAR 3. Were the groups comparable at baseline for all major confounding/prognostic factors? NO (drug group had a significantly higher initial score on the Goetz Dyskinesia Rating Scale) 4. Did the comparison groups receive the same care apart from interventions studied? YES 5. Were participants receiving care kept blind to treatment allocation? UNCLEAR* 6. Were the individuals administering care kept blind to treatment allocation? UNCLEAR* 7. Were groups comparable with respect to availability of outcome data and for how many participants were no outcome data available? YES (number of dropouts similar across but >20%) 8. Did the study have an appropriate length of follow up? YES (12 wks) 9. Did the study use a precise definition of outcome? YES 10. Was a valid and reliable method used to determine that outcome? UNCLEAR 11. Were investigators kept blind to participant's exposure to the intervention? UNCLEAR* 12. Were investigators kept blind to other important confounding and prognostic factors? UNCLEAR* *Level of blinding unclear - no details beyond description of study as "randomized, double-blind, placebo-controlled trial". Overall there is likely high risk of bias.

Bibliographic reference	Nichols,M.J., Hartlein,J.M., Eicken,M.G., Racette,B.A., Black,K.J., 20140314, A fixed-dose randomized controlled trial of olanzapine for psychosis in Parkinson disease, F1000Research, 2, 150-, 2013
Country/ies where the study was carried out	US
Study type	Randomised, double-blind, placebo-controlled, parallel group study
Aim of the study	To discuss the findings of a double-blind, placebo-controlled study of fixed, low-dose olanzapine for treatment of drug-induced

Bibliographic reference	Nichols,M.J., Hartlein,J.M., Eicken,M.G., Racette,B.A., Black,K.J., 20140314, A fixed-dose randomized controlled trial of olanzapine for psychosis in Parkinson disease, F1000Research, 2, 150-, 2013
	psychosis (DIP) in the context of flexible dopaminomimetic dosing.
Study dates	Study dates: February 1998 - October 2003 Study duration: 4 weeks
Source of funding	Lilly Research Laboratories (Investigator-Initiated Trial F1D-MC-I012)
Sample size	In total n=23; Placebo n=9; Olanzapine 2.5 mg n=6; Olanzapine 5 mg n=8; Olanzapine 10 mg n=1. Randomised in a 1:1:1 to treatment with placebo or either of two doses (2.5 mg or 5 mg) of olanzapine. The one subject treated with 10 mg of olanzapine was excluded from analysis due to change in study randomisation.
Inclusion criteria	Patients were included if they: • Have been diagnosed with idiopathic PD • Have been treated with levodopa and were experiencing clinically significant hallucinations or delusions • >30 years old • Have a caregiver who could provide a reliable report • Were treated with the lowest clinically acceptable dose of dopaminomimetic at study entry
Exclusion criteria	Patients were excluded if they: • Were treated only with a dopamine agonist • Have a Folstein Mini-mental State Examination (MMSE) score < 22 • Were pregnant • Have concurrent diagnosis of delirium (unless clearly explained by dopaminomimetics) • Have catatonia or neuroleptic malignant syndrome (NMS)-like syndrome • Have other confounding central nervous system (CNS) illness or systematic illness with potential CNS effects • Used antipsychotic within the last month predating study enrolment (within the past six months for depot neuroleptics) • Have a history of olanzapine sensitivity • Have any expectation of significant medical or surgical intervention within six weeks after enrolment • Have psychosis warranted hospitalisation or if in the investigator's judgement, psychosis severity would have made randomisation to placebo inappropriate
Interventions	Olanzapine: 2.5 mg or 5mg once a day (night-time)
Details	All assessments were done at baseline, and on weeks 2 and 4 of treatment (end of trial).

<table>
<tr><th>Bibliographic reference</th><th>Nichols,M.J., Hartlein,J.M., Eicken,M.G., Racette,B.A., Black,K.J., 20140314, A fixed-dose randomized controlled trial of olanzapine for psychosis in Parkinson disease, F1000Research, 2, 150-, 2013</th></tr>
<tr><td></td><td>No significant differences were present at baseline between placebo and treatment groups on any demographic characteristic or any psychiatric or neurologic measure:
<table>
<tr><th></th><th></th><th colspan="2">Olanzapine</th><th></th></tr>
<tr><td>Measure</td><td>Placebo (n=9)</td><td>2.5 mg (n=6)</td><td>5 mg (n=8)</td><td>p value</td></tr>
<tr><td>Age</td><td>71.3 (6.5)</td><td>70.7 (8.1)</td><td>72.4 (4.8)</td><td>0.882</td></tr>
<tr><td>MMSE</td><td>26 (2.6)</td><td>27 (3.6)</td><td>27 (2.7)</td><td>0.976</td></tr>
<tr><td>BPRS-T</td><td>34.8 (5.9)</td><td>34.3 (5.4)</td><td>33.4 (3)</td><td>0.874</td></tr>
<tr><td>BPRS-P</td><td>7.9 (2)</td><td>9 (3)</td><td>7.8 (2.1)</td><td>0.633</td></tr>
<tr><td>UPDRS, motor score</td><td>30 (11)</td><td>27.5 (13.1)</td><td>31 (11.6)</td><td>0.855</td></tr>
<tr><td>PDQ-39</td><td>53 (25.7)</td><td>59 (15.9)</td><td>59 (27.3)</td><td>0.867</td></tr>
<tr><td>BDI</td><td>10.1 (6)</td><td>9.8 (6)</td><td>12.6 (9.2)</td><td>0.738</td></tr>
<tr><td>HAM-D</td><td>8.7 (6.1)</td><td>5.3 (1.6)</td><td>11.6 (7.6)</td><td>0.177</td></tr>
<tr><td>CGI</td><td>4.1 (0.9)</td><td>3.2 (1)</td><td>3.9 (0.8)</td><td>0.161</td></tr>
<tr><td>SEADL</td><td>76 (15)</td><td>72 (24)</td><td>75 (17)</td><td>0.918</td></tr>
</table></td></tr>
<tr><td>Primary outcome measures</td><td>• Clinical Global Impression (CGI) scores
• BPRS ratings of psychosis scored from videotaped interviews after study termination by an observer blinded to dose signment and to interview timing
• UPDRS motor ratings
• MMSE</td></tr>
<tr><td>Secondary outcomes measures</td><td>• PDQ-39
• ADL assessments
• BDI</td></tr>
<tr><td>Results</td><td></td></tr>
</table>

Bibliographic reference	Nichols,M.J., Hartlein,J.M., Eicken,M.G., Racette,B.A., Black,K.J., 20140314, A fixed-dose randomized controlled trial of olanzapine for psychosis in Parkinson disease, F1000Research, 2, 150-, 2013

BPRS Psychosis

	Mean	SD	Total
Experimental	7.75	4.97	9
Control	8.00	4.90	9

UPDRS Motor

	Mean	SD	Total
Experimental	30.30	13.39	9
Control	31.00	13.09	9

Mortality

	Deaths	Total
Experimental	0	14
Control	1	9

Number of dropouts due to adverse events

	Events	Total
Experimental	7	14
Control	0	9

Results

Data extracted for BPRS psychosis and UPDRS motor are the mean endpoint scores.

Subject retention and side effects	Placebo	Olanzapine 2.5 mg	Olanzapine 5 mg	All	p-value
# enrolled	9	6	8	23	
# withdrew	2	4	3	9	0.2232
# withdrew for motor SEs	0	2	1	3	0.1712
# w/motor SE complaint	1	2	1	4	0.4863

Bibliographic reference	Nichols,M.J., Hartlein,J.M., Eicken,M.G., Racette,B.A., Black,K.J., 20140314, A fixed-dose randomized controlled trial of olanzapine for psychosis in Parkinson disease, F1000Research, 2, 150-, 2013
	<table><tr><td># w/any mild SEs</td><td>2</td><td>5</td><td>2</td><td>9</td><td>0.0356</td></tr><tr><td># w/serious adverse events</td><td>1</td><td>0</td><td>2</td><td>3</td><td>0.3795</td></tr><tr><td># w/dopaminomimetic ↑</td><td>1</td><td>2</td><td>1</td><td>4</td><td>0.4863</td></tr></table> Side effects (SEs) were any complaint of drug spontaneously reported by the patient, independent of whether SE intensity was severe enough to prompt withdrawal from the study. Serious adverse events always prompted withdrawal. The extracted data for mortality and number of dropouts due to AEs for the experimental group are the total number of events combined from the two treatment groups (2.5 mg and 5 mg).
Overall Risk of Bias	1. Has an appropriate method of randomisation been used? YES 2. Was there adequate concealment of allocation? YES 3. Were the groups comparable at baseline for all major confounding/prognostic factors? YES 4. Did the comparison groups receive the same care apart from interventions studied? YES 5. Were participants receiving care kept blind to treatment allocation? YES 6. Were the individuals administering care kept blind to treatment allocation? YES 7. Were groups comparable with respect to availability of outcome data and for how many participants were no outcome data available? NO and number of dropouts >20% 8. Did the study have an appropriate length of follow up? UNCLEAR (4 wks) 9. Did the study use a precise definition of outcome? YES 10. Was a valid and reliable method used to determine that outcome? UNCLEAR 11. Were investigators kept blind to participant's exposure to the intervention? YES 12. Were investigators kept blind to other important confounding and prognostic factors? UNCLEAR Overall there is likely high risk of bias.

Bibliographic reference	Shotbolt,P., Samuel,M., Fox,C., David,A.S., 20110426, A randomized controlled trial of quetiapine for psychosis in Parkinson's disease, Neuropsychiatric Disease & Treatment, 5, 327-332, 2009

Bibliographic reference	Shotbolt,P., Samuel,M., Fox,C., David,A.S., 20110426, A randomized controlled trial of quetiapine for psychosis in Parkinson's disease, Neuropsychiatric Disease & Treatment, 5, 327-332, 2009
Country/ies where the study was carried out	UK
Study type	Randomised, double-blind, placebo-controlled study
Aim of the study	To provide further evidence on the efficacy of quetiapine in the management of PD psychosis
Study dates	Study dates: not reported Study duration: 12 weeks
Source of funding	Parkinson's Disease Society and Medication provided by AstraZeneca UK Ltd
Sample size	In total n=24; Quetiapine n=11; Placebo n=13
Inclusion criteria	Patients were included if: • Diagnosed with idiopathic PD • Suffered from either hallucinations, suspiciousness or unusual though content (delusions) of a severity >3/7, on the Brief Psychiatric Rating Scale (BPRS). Symptoms must have been present for over 2 weeks • They have a reliable caregiver • They have the ability to assent to treatment • Current antiparkinsonian treatment deemed to be optimal by the attending specialist consultants • Their communication ability were sufficient to enable main assessments
Exclusion criteria	Patients were excluded if: • They were under current treatment with cholinesterase inhibitors • They were on antipsychotic medication currently or in the preceding two weeks • There were any contraindication to quetiapine, important drug interactions, major concomitant medical illness, stroke or transient ischemic attack in the six months preceding assessment • They had uncontrolled diabetes or hypertension, uncontrolled atrial fibrillation or other cardiac arrhythmia • They had past drug/alcohol dependence • They have possible delirium • There has been a change in medication over the preceding two weeks (three weeks if cabergoline) • They had dementia with Lewy bodies
Interventions	Quetiapine: 25 mg, 50 mg, 100 mg or 150 mg once or twice a day.
Details	The starting dose was 25 mg for week 1, 25 mg twice a day for week 2, 50 mg twice a day for week 3, with an optional further

<table>
<tr><th>Bibliographic reference</th><th>Shotbolt,P., Samuel,M., Fox,C., David,A.S., 20110426, A randomized controlled trial of quetiapine for psychosis in Parkinson's disease, Neuropsychiatric Disease & Treatment, 5, 327-332, 2009</th></tr>
<tr><td></td><td>increase to 50 mg in the morning and 100 mg in the evening if clinically indicated. Clinicians were free to increase or maintain dose of trial medication and placebo up to the beginning of the 6th week (after which it could be reduced if considered necessary due to side effects).
Assessments were performed at 0, 2, 6, and 12 weeks.

Baseline data:
<table>
<tr><td>Variable</td><td>Quetiapine n=11</td><td>Placebo n=13</td></tr>
<tr><td>Age (yr)</td><td>74 ± 8</td><td>70 ± 8</td></tr>
<tr><td>PD duration (yr)</td><td>8 ± 4</td><td>9 ± 5</td></tr>
<tr><td>MMSE</td><td>24.6 ± 3.6</td><td>20.8 ± 5.7</td></tr>
<tr><td>UPDRS total</td><td>59.1 ± 21.0</td><td>59.3 ± 26.5</td></tr>
<tr><td>UPDRS motor</td><td>31.2 ± 14.4</td><td>29.0 ± 16.8</td></tr>
<tr><td>NPI</td><td>15.4 ± 7.4</td><td>21.5 ± 11.3</td></tr>
<tr><td>BPRS</td><td>39.2 ± 8.4</td><td>41.5 ± 6.5</td></tr>
<tr><td>Baylor PD hallucination</td><td>11.6 ± 2.7</td><td>11.9 ± 5.3</td></tr>
</table></td></tr>
<tr><td>Primary outcome measures</td><td>Time remaining in the trial.</td></tr>
<tr><td>Secondary outcomes measures</td><td>• Unified Parkinson's Disease Rating Scale (UPDRS)
• BPRS
• Neuropsychiatric Inventory (NPI)
• Baylor PD hallucination scale</td></tr>
<tr><td>Results</td><td></td></tr>
<tr><td>UPDRS Motor</td><td>
<table>
<tr><td></td><td>Mean</td><td>SD</td><td>Total</td></tr>
<tr><td>Experimental</td><td>28.20</td><td>12.30</td><td>11</td></tr>
<tr><td>Control</td><td>30.10</td><td>10.40</td><td>13</td></tr>
</table></td></tr>
</table>

Bibliographic reference	Shotbolt,P., Samuel,M., Fox,C., David,A.S., 20110426, A randomized controlled trial of quetiapine for psychosis in Parkinson's disease, Neuropsychiatric Disease & Treatment, 5, 327-332, 2009
Baylor PD Hallucination	<table><tr><td></td><td>Mean</td><td>SD</td><td>Total</td></tr><tr><td>Experimental</td><td>8.30</td><td>2.90</td><td>11</td></tr><tr><td>Control</td><td>9.40</td><td>4.90</td><td>13</td></tr></table>
Mortality	<table><tr><td></td><td>Deaths</td><td>Total</td></tr><tr><td>Experimental</td><td>0</td><td>11</td></tr><tr><td>Control</td><td>0</td><td>13</td></tr></table>
Number of dropouts due to adverse events	<table><tr><td></td><td>Events</td><td>Total</td></tr><tr><td>Experimental</td><td>3</td><td>11</td></tr><tr><td>Control</td><td>3</td><td>13</td></tr></table>
Results	Thirteen patients completed six weeks in the double-blind part of the study (four quetiapine patients and nine placebos). Only eight patients completed the 12 week double-blind (four from each group). The mean dose in the quetiapine group was 72.7 ± 26.1 mg; in the placebo group it was 96.2 ± 32 mg. Primary outcome: time remaining in the trial. Patients on quetiapine dropped out faster than patients on placebo. The log rank test was used to compare the survival distributions; they were not found to be significantly different (p=0.68). Quetiapine therefore did not have a significant effect on time to dropout. Secondary outcomes measures were analysed at six weeks due to the small numbers and high dropout rates. The data extracted are the follow-up results at 6 weeks. With regards to tolerability, three patients on quetiapine dropped out due to related adverse events (drowsiness). Three patients on placebo also dropped out due to related adverse events (two drowsiness, one confusion). Data extracted for Baylor PD Hallucination and UPDRS motor are the mean endpoint scores.
Overall Risk of Bias	Has an appropriate method of randomisation been used? UNCLEAR

Bibliographic reference	Shotbolt,P., Samuel,M., Fox,C., David,A.S., 20110426, A randomized controlled trial of quetiapine for psychosis in Parkinson's disease, Neuropsychiatric Disease & Treatment, 5, 327-332, 2009
	1. Was there adequate concealment of allocation? UNCLEAR 2. Were the groups comparable at baseline for all major confounding/prognostic factors? UNCLEAR 3. Did the comparison groups receive the same care apart from interventions studied? YES 4. Were participants receiving care kept blind to treatment allocation? UNCLEAR* 5. Were the individuals administering care kept blind to treatment allocation? UNCLEAR* 6. Were groups comparable with respect to availability of outcome data and for how many participants were no outcome data available? NO 7. Did the study have an appropriate length of follow up? UNCLEAR (12 wks trial but due to large no. of dropouts, data were only analysed at 6 wks) 8. Did the study use a precise definition of outcome? YES 9. Was a valid and reliable method used to determine that outcome? NO 10. Were investigators kept blind to participant's exposure to the intervention? UNCLEAR* 11. Were investigators kept blind to other important confounding and prognostic factors? UNCLEAR* *Level of blinding unclear - no details beyond description of study as "randomized, double-blind, placebo-controlled trial". Overall there is likely high risk of bias.

Bibliographic reference	Ondo,W.G., Levy,J.K., Vuong,K.D., Hunter,C., Jankovic,J., Olanzapine treatment for dopaminergic-induced hallucinations, Movement disorders, 17, 1031-1035, 2002
Country/ies where the study was carried out	US
Study type	Randomised, double-blind, placebo-controlled, parallel study
Aim of the study	To determine the effect of low dose olanzapine on hallucinations, motor performance, cognition, and mood in PD patients experiencing hallucinations.
Study dates	Study dates: not reported Study duration: 9 weeks
Source of funding	Eli-Lilly Corporation and National Parkinson's Foundation

<table>
<tr><th>Bibliographic reference</th><th>Ondo,W.G., Levy,J.K., Vuong,K.D., Hunter,C., Jankovic,J., Olanzapine treatment for dopaminergic-induced hallucinations, Movement disorders, 17, 1031-1035, 2002</th></tr>
<tr><td>Sample size</td><td>In total n= 30; Olanzapine n= 18; Placebo n= 12
Randomised in a 2:1 drug to placebo ratio</td></tr>
<tr><td>Inclusion criteria</td><td>Patients were included if they:
• Had been diagnosed with PD
• Had drug-induced hallucinations
• Had a Mini-Mental Status Examination (MMSE) scores ≥20/30</td></tr>
<tr><td>Exclusion criteria</td><td>Not reported</td></tr>
<tr><td>Interventions</td><td>Olanzapine: 2.5 mg 5 mg or 7.5 mg once a day at night-time.</td></tr>
<tr><td>Details</td><td>Both fluctuating and nonfluctuating patients were included. All patients started at 2.5 mg of olanzapine or placebo as a single night-time dose. At 3 weeks, all participants returned for a complete UPDRS and a hallucination survey. On the basis of clinical judgment it was decided whether or not to increase the drug, or placebo, to 5 mg. Patients were contacted by phone after 3 more weeks. At that time, it was again decided whether to increase, decrease or maintain the same dose. The medication was kept at a constant dose for the last 3 weeks of the study. Patients then returned for a complete evaluation identical to that of the baseline visit, which included an extensive battery of neuropsychological tests, the UPDRS, and assessments of on and off time in fluctuating patients.

There were no significant differences in baseline demographics (age, duration of PD, Hoehn and Yahr), hallucination severity, or MMSE between the two groups. The means of these variables of the 30 patients are described in the table below:
<table>
<tr><td>Variable</td><td>Olanzapine n= 18</td><td>Placebo n= 12</td></tr>
<tr><td>Age (yr)</td><td colspan="2">71 ± 7.1</td></tr>
<tr><td>Mean off Hoehn and Yahr</td><td colspan="2">3.2 ± 0.5</td></tr>
<tr><td>Duration of PD (yrs)</td><td colspan="2">9.6 ± 5.1</td></tr>
<tr><td>MMSE</td><td colspan="2">26.8 ± 3.3</td></tr>
</table></td></tr>
<tr><td>Primary outcome measures</td><td>• An extensive battery of neuropsychological tests (including MMSE, HAM-D and others)
• UPDRS Total (while on medications)
• UPDRS Part II (in fluctuating patients to represent the averages of on and off scores)</td></tr>
<tr><td>Secondary outcomes</td><td>Not reported.</td></tr>
</table>

<table>
<tr><th>Bibliographic reference</th><th>Ondo,W.G., Levy,J.K., Vuong,K.D., Hunter,C., Jankovic,J., Olanzapine treatment for dopaminergic-induced hallucinations, Movement disorders, 17, 1031-1035, 2002</th></tr>
<tr><td>measures</td><td></td></tr>
<tr><td>Results</td><td></td></tr>
<tr><td>Structured interview for hallucinations in PD</td><td>
<table>
<tr><td></td><td>Mean</td><td>SD</td><td>Total</td></tr>
<tr><td>Experimental</td><td>9.50</td><td>6.80</td><td>16</td></tr>
<tr><td>Control</td><td>11.10</td><td>4.70</td><td>11</td></tr>
</table>
</td></tr>
<tr><td>Mortality</td><td>
<table>
<tr><td></td><td>Deaths</td><td>Total</td></tr>
<tr><td>Experimental</td><td>0</td><td>18</td></tr>
<tr><td>Control</td><td>0</td><td>12</td></tr>
</table>
</td></tr>
<tr><td>Number of dropouts due to adverse events</td><td>
<table>
<tr><td></td><td>Events</td><td>Total</td></tr>
<tr><td>Experimental</td><td>0</td><td>18</td></tr>
<tr><td>Control</td><td>0</td><td>12</td></tr>
</table>
</td></tr>
<tr><td>Results</td><td>16 patients on olanzapine (mean dose, 4.6 mg/night) and 11 on placebo completed the study.

The final mean dose of olanzapine was 4.6 ± 2.2 mg, whereas the mean dose of placebo was the equivalent of 6.6 ± 2.0 mg.

A total of three patients discontinued before completion of the study. One patient randomly assigned to drug dropped out before taking any study medication. One patient in the drug and one in the placebo group dropped out after 3 weeks and 6 weeks, respectively, due to lack of improvement.

Subjective AEs on olanzapine included worsening movement (n=6), worse posture (n=3), dysarthria (n=2), edema (n=2), drooling (n=2), weight gain, dry mouth, nausea, insomnia, sedation, perspiration, and agitation.

AE on placebo included insomnia, sedation, leg cramps, light headedness, weakness, and tremor in one each.

Data extracted for structured interview for hallucinations in PD are the mean endpoint score at the final visit.</td></tr>
</table>

Bibliographic reference	Ondo,W.G., Levy,J.K., Vuong,K.D., Hunter,C., Jankovic,J., Olanzapine treatment for dopaminergic-induced hallucinations, Movement disorders, 17, 1031-1035, 2002
Overall Risk of Bias	1. Has an appropriate method of randomisation been used? YES 2. Was there adequate concealment of allocation? UNCLEAR 3. Were the groups comparable at baseline for all major confounding/prognostic factors? YES 4. Did the comparison groups receive the same care apart from interventions studied? YES 5. Were participants receiving care kept blind to treatment allocation? UNCLEAR* 6. Were the individuals administering care kept blind to treatment allocation? UNCLEAR* 7. Were groups comparable with respect to availability of outcome data and for how many participants were no outcome data available? YES and <20 % dropout rate. 8. Did the study have an appropriate length of follow up? YES (9 wks) 9. Did the study use a precise definition of outcome? YES 10. Was a valid and reliable method used to determine that outcome? UNCLEAR 11. Were investigators kept blind to participant's exposure to the intervention? UNCLEAR* 12. Were investigators kept blind to other important confounding and prognostic factors? UNCLEAR* *Level of blinding unclear - no details beyond description of study as "randomized, double-blind, placebo-controlled trial". Overall there is likely high risk of bias.

Bibliographic reference	Pollak,P., Tison,F., Rascol,O., Destee,A., Pere,J.J., Senard,J.M., Durif,F., Bourdeix,I., Clozapine in drug induced psychosis in Parkinson's disease: a randomised, placebo controlled study with open follow up, J.Neurol.Neurosurg.Psychiatry., 75, 689-695, 2004
Country/ies where the study was carried out	France
Study type	Prospective, randomised, double-blind, placebo-controlled study
Aim of the study	To assess the efficacy and tolerability of clozapine in drug-induced psychosis in Parkinson's disease
Study dates	Study dates: January 1996 and October 1997 Study duration: 4 weeks double-blind, followed by a 12-week clozapine open period, plus a one month period after drug withdrawal.

Bibliographic reference	**Pollak,P., Tison,F., Rascol,O., Destee,A., Pere,J.J., Senard,J.M., Durif,F., Bourdeix,I., Clozapine in drug induced psychosis in Parkinson's disease: a randomised, placebo controlled study with open follow up, J.Neurol.Neurosurg.Psychiatry., 75, 689-695, 2004**
Source of funding	Novartis Pharma France
Sample size	In total n=60; Clozapine n=32; Placebo n=28 Randomised in a 1:1 drug to placebo ratio
Inclusion criteria	Inclusion criteria were: • Idiopathic PD clinical diagnosis • PD patients experiencing a drug induced psychosis of at least two weeks' duration • Psychotic symptoms score ≥ 4 for at least one of the items P1 (hallucinations) or P3 (delusions) of the positive subscore of the "positive and negative syndrome scale" (PANSS). • >3 on the "clinical global impression scale" (CGI)
Exclusion criteria	Exclusion criteria were: • A history of medical conditions or drug treatment that might put them at special risk or bias the assessment of their clinical or mental status • Patients likely to require continuous treatment with drugs that can lower the white blood cell count, and those previously treated with clozapine • Women of childbearing potential who were not practising a medically approved form of birth control
Interventions	Clozapine: A starting dose of 6.25 mg, followed, if necessary, by progressive dose increases (maximum of three 12.5 mg steps each week) up to a maximum daily dose of 50 mg, which could not be reached within less than 10 days.
Details	This study consists of 4 periods. The first was a period of screening. The second period of four weeks (day 0 to day 28) involved clozapine dose titration according to the intervention schedule. The doses of antiparkinsonian drugs remained unchanged. The dose of clozapine could be reduced if adverse effects occurred by steps of 12.5 mg. All patients who completed period II and those experiencing no improvements after two weeks of treatment entered a 12 week unblinded open label period, where they all received clozapine. At the end of period III, patients demonstrating mental normalisation were subjected to clozapine withdrawal within one week and to a further three week follow up period (period IV). Only results from period II are of interests to this RQ. Baseline characteristics: Variable | Clozapine n=32 | Placebo n=28

Bibliographic reference	**Pollak,P., Tison,F., Rascol,O., Destee,A., Pere,J.J., Senard,J.M., Durif,F., Bourdeix,I., Clozapine in drug induced psychosis in Parkinson's disease: a randomised, placebo controlled study with open follow up, J.Neurol.Neurosurg.Psychiatry., 75, 689-695, 2004**
	Age (yr) 71.2 (7.4) 72.8 (8.2) Duration of PD (yrs) 12.1 (5.7) 11.3 (5.4) Hoehn and Yahr stage 3.3 (0.9) 3.1 (1.4) UPDRS total 52.6 (21.1) 52.7 (19.8) UPDRS motor 31.5 (14.2) 31.4 (13.2) Positive PANSS 17.8 (4.7) 15.3 (5.0) CGI 5.1 (0.8) 4.9 (0.9) MMSE 26.1 (3.0) 24.1 (2.8)
Primary outcome measures	CGI
Secondary outcomes measures	• PANSS • UPDRS • MMSE
Results	
UPDRS Motor	Experimental: Mean -3.50, SD 7.70, Total 32 Control: Mean -3.00, SD 8.10, Total 28
Positive PANSS	Experimental: Mean -5.60, SD 3.90, Total 32 Control: Mean -0.80, SD 2.80, Total 28
Mortality	Deaths, Total

Bibliographic reference	Pollak,P., Tison,F., Rascol,O., Destee,A., Pere,J.J., Senard,J.M., Durif,F., Bourdeix,I., Clozapine in drug induced psychosis in Parkinson's disease: a randomised, placebo controlled study with open follow up, J.Neurol.Neurosurg.Psychiatry., 75, 689-695, 2004

Experimental	0	32
Control	0	28

Number of dropouts due to adverse events

	Events	Total
Experimental	2	32
Control	2	28

Results

By the end of period II, patients were receiving a mean dose of 35.8 (range 12.5-50) mg/day of clozapine or 41.7 (range 6-50) mg/day of placebo.

Serious adverse events were reported in 4 of the 32 patients in the clozapine group and in 7 of the 28 patients in the placebo group during period II.

Table below summarises AEs occurring with a frequency >10% during period II:

Adverse events	Clozapine (n=32)	Placebo (n=28)
Worsening of PD	7 (21.8%)	1 (4%)
Sialorrhoea	3 (9%)	0
Confusion	0	2 (7%)
Somnolence	17 (53%)	5 (18%)
Nausea/vomiting	0	4 (15%)
Constipation	1 (3%)	1 (4%)
Postural hypotension	6 (19%)	4 (14%)
Respiratory infection	5 (16%)	3 (11%)
General condition aggravated	0	3 (11%)

Bibliographic reference	**Pollak,P., Tison,F., Rascol,O., Destee,A., Pere,J.J., Senard,J.M., Durif,F., Bourdeix,I., Clozapine in drug induced psychosis in Parkinson's disease: a randomised, placebo controlled study with open follow up, J.Neurol.Neurosurg.Psychiatry., 75, 689-695, 2004**
	<table><tr><td>Syncope/malaise</td><td>0</td><td>4 (15%)</td></tr></table> Withdrawals because of adverse events occurred in 4 patients, 2 from each group. The events leading to withdrawal were one neutropenia and one fracture in the clozapine group, and one hypotension and one syncope in the placebo group. Data extracted for UPDRS motor and Positive PANSS are the mean change scores from baseline to end point.
Overall Risk of Bias	1. Has an appropriate method of randomisation been used? YES 2. Was there adequate concealment of allocation? UNCLEAR 3. Were the groups comparable at baseline for all major confounding/prognostic factors? NO (MMSE score in clozapine group was higher) 4. Did the comparison groups receive the same care apart from interventions studied? YES 5. Were participants receiving care kept blind to treatment allocation? UNCLEAR* 6. Were the individuals administering care kept blind to treatment allocation? UNCLEAR* 7. Were groups comparable with respect to availability of outcome data and for how many participants were no outcome data available? YES and >20 % dropout rate. 8. Did the study have an appropriate length of follow up? UNCLEAR (4 wks) 9. Did the study use a precise definition of outcome? YES 10. Was a valid and reliable method used to determine that outcome? UNCLEAR 11. Were investigators kept blind to participant’s exposure to the intervention? UNCLEAR* 12. Were investigators kept blind to other important confounding and prognostic factors? UNCLEAR* *Level of blinding unclear - no details beyond description of study as "randomized, double-blind, placebo-controlled trial". Overall there is likely high risk of bias.

Bibliographic reference	**Morgante,L., Epifanio,A., Spina,E., Zappia,M., Di Rosa,A.E., Marconi,R., Basile,G., Di,Raimondo G., La,Spina P., Quattrone,A., Quetiapine and clozapine in parkinsonian patients with dopaminergic psychosis, Clin Neuropharmacol, 27, 153-156, 2004**

Bibliographic reference	Morgante,L., Epifanio,A., Spina,E., Zappia,M., Di Rosa,A.E., Marconi,R., Basile,G., Di,Raimondo G., La,Spina P., Quattrone,A., Quetiapine and clozapine in parkinsonian patients with dopaminergic psychosis, Clin Neuropharmacol, 27, 153-156, 2004
Country/ies where the study was carried out	Italy
Study type	Randomised, open-label, blinded-rater, parallel group study
Aim of the study	To investigate the efficacy and safety of quetiapine vs. clozapine in parkinsonian patients with dopaminergic psychosis
Study dates	Study dates: Not reported Study duration: 12 weeks
Source of funding	Not reported
Sample size	In total n=45; Clozapine n=23; Quetiapine n=22
Inclusion criteria	Patients were included if they had: • A diagnosis of idiopathic PD • A documented history of L-dopa or L-dopa plus dopamine agonist drug-induced psychosis of at least 4 weeks before study entry • A baseline score of ≥3 on the items hallucinations or unusual thought content (or delusions) of the BPRS
Exclusion criteria	Patients were excluded if they had: • A history of leukopenia, dementia (MMSE score <24) or any primary psychiatric illness including schizophrenia, psychotic depression, or bipolar disorder • A history of epilepsy • Presence of any underlying intermittent diseases causing psychosis • Presence of cardiovascular diseases or symptomatic orthostatic hypotension • Use of antipsychotic agents in the past 6 months
Interventions	Clozapine: Initial dose of 6.25 mg/day, administered orally once or twice daily. This dose was then titrated up to a maximum of 50 mg/day, according to the individual clinical response and tolerability. Quetiapine: Initial dose of 25 mg/day, administered orally once or twice daily. This dose was then titrated up to a maximum of 200 mg/day, according to the individual clinical response and tolerability.
Details	During the study, the dosage of antiparkinsonian drugs was kept constant. All patients were assessed at baseline and after 2, 4, 8, and 12 weeks. Baseline characteristics:

Bibliographic reference	**Morgante,L., Epifanio,A., Spina,E., Zappia,M., Di Rosa,A.E., Marconi,R., Basile,G., Di,Raimondo G., La,Spina P., Quattrone,A., Quetiapine and clozapine in parkinsonian patients with dopaminergic psychosis, Clin Neuropharmacol, 27, 153-156, 2004**

Variable	Clozapine n=20	Quetiapine n=20
Age (yr)	69 ± 10.7	70 ± 10.1
Duration of illness (months)	115 ± 45	100.5 ± 45
BPRS total	37.4 ± 5.4	37.1 ± 6.1
BPRS (5 items)	16.4 ± 2.6	15.5 ± 3.4
CGIS	3.8 ± 0.8	3.6 ± 0.7
UPDRS motor	58 ± 9.4	53 ± 11

Primary outcome measures

- BPRS
- CGIS
- UPDRS motor
- AIMS

Results

BPRS Psychosis

	Mean	SD	Total
Experimental	8.50	2.00	20
Control	8.40	1.50	20

UPDRS Motor

	Mean	SD	Total
Experimental	56.70	9.20	20
Control	54.00	11.00	20

Mortality

	Deaths	Total
Experimental	0	23

Bibliographic reference	Morgante,L., Epifanio,A., Spina,E., Zappia,M., Di Rosa,A.E., Marconi,R., Basile,G., Di,Raimondo G., La,Spina P., Quattrone,A., Quetiapine and clozapine in parkinsonian patients with dopaminergic psychosis, Clin Neuropharmacol, 27, 153-156, 2004
	Control | 0 | 22
Number of dropouts due to adverse events	| Events | Total Experimental | 3 | 23 Control | 2 | 22
Results	The experimental group represent the Clozapine group and the control group represent the Quetiapine group. Forty patients, 20 on clozapine and 20 on quetiapine, completed the study and were included in the clinical analysis. In the clozapine group, the final mean dose was 26 ± 12 mg/d, while in the quetiapine group, the final mean dose was 91 ± 47 mg/d. Side effects were mild in both groups. Subjective adverse side effects included worsening movement (n=3), sedation (n=1), and dizziness (n=1) in the quetiapine group and drooling (n=1), weight gain (n=1), and sedation (n=1) in the clozapine group. The BPRS psychosis data is the cluster subscores of the items hallucinations, suspiciousness, unusual thought content, hostility, and conceptual disorganisation. Data extracted for BPRS psychosis (five items) and UPDRS motor are the mean endpoint scores at 12 weeks.
Overall Risk of Bias	1. Has an appropriate method of randomisation been used? UNCLEAR 2. Was there adequate concealment of allocation? NO 3. Were the groups comparable at baseline for all major confounding/prognostic factors? YES 4. Did the comparison groups receive the same care apart from interventions studied? YES 5. Were participants receiving care kept blind to treatment allocation? NO 6. Were the individuals administering care kept blind to treatment allocation? NO 7. Were groups comparable with respect to availability of outcome data and for how many participants were no outcome data available? YES and <20% dropout rate 8. Did the study have an appropriate length of follow up? YES (12 wks) 9. Did the study use a precise definition of outcome? YES 10. Was a valid and reliable method used to determine that outcome? UNCLEAR

Bibliographic reference	Morgante,L., Epifanio,A., Spina,E., Zappia,M., Di Rosa,A.E., Marconi,R., Basile,G., Di,Raimondo G., La,Spina P., Quattrone,A., Quetiapine and clozapine in parkinsonian patients with dopaminergic psychosis, Clin Neuropharmacol, 27, 153-156, 2004
	11. Were investigators kept blind to participant's exposure to the intervention? YES 12. Were investigators kept blind to other important confounding and prognostic factors? UNCLEAR Overall there is likely high risk of bias.

Bibliographic reference	Friedman J, Lannon M, Cornelia C, Factor S, Kurlan R, Richard I et al. Low-dose clozapine for the treatment of drug-induced psychosis in Parkinson's disease. New England Journal of Medicine 1999;340:757-63.
Country/ies where the study was carried out	Not reported
Study type	Randomised, double-blinded, placebo-controlled study
Aim of the study	To determine whether clozapine, administered at low doses, is an effective treatment for drug-induced psychosis in patients with Parkinson's disease and to determine its effect on motor function in such patients.
Study dates	Study dates: April 1995 - October 1996 Study duration: 4 weeks
Source of funding	Orphan Drug Division of the Food and Drug Administration and Parkinson Study Group
Sample size	In total n=60 (9 to 12 patients per site (6 sites in total)); Clozapine n=30; Placebo n=30
Inclusion criteria	Patients were included if: • They were diagnosed with idiopathic PD • They had documented history of psychosis of at least 4 weeks' duration before enrolment • They had a reliable caregiver who could accurately report the patient's daily level of function, accompany the patient to each visit and administer the study drug
Exclusion criteria	Criteria for exclusion were: • A history of leukopenia • The presence of any systemic factor that might contribute to a behavioural disorder • Therapy with any dopamine-blocking drug within the three months before this study began • Therapy with neuroleptic drugs administered in depot form within the year before the study

Bibliographic reference	**Friedman J, Lannon M, Cornelia C, Factor S, Kurlan R, Richard I et al. Low-dose clozapine for the treatment of drug-induced psychosis in Parkinson's disease. New England Journal of Medicine 1999;340:757-63.**
	• A change in antidepressants or anxiolytic drugs within the month before the study • Previous therapy with clozapine for the treatment of psychosis • The presence of symptomatic orthostatic hypotension, uncontrolled seizures, uncontrolled angina, the acquired immunodeficiency syndrome or another illness that would make the use of clozapine potentially hazardous, or narrow-angle glaucoma • Myocardial infarction during the three months before the study • Treatment with chemotherapeutic drugs that lower white-cell counts • An inability to tolerate a fixed dose of antiparkinsonian drugs for one month • The presence of dementia severe enough to preclude assessment on the psychiatric-test battery • Women of childbearing potential who were not using reliable forms of contraception
Interventions	Clozapine: 6.25 mg, 12.5 mg, 18.75 mg, 25 mg, 37.5 mg, or 50 mg daily
Details	All daily doses started at 6.25 mg and could be raised one level depending on the patient's clinical response; if the patient's daily dose had been increased from the initial 6.25 mg level, it could also be lowered one level. The dosage reached at the beginning of the final week was the maximal dose, it could not be increase further but could be decreased, if necessary, because of side effects. Thus, at the final assessment, when all base-line measures were repeated, the patient had been receiving a stable dose or declining dose of study medicine for at least seven days. There were some significant imbalances at baseline between the groups in the intention-to-treat analysis (the patients receiving clozapine had slightly less severe psychosis than those receiving placebo), but not between the groups in the analysis based on the treatment the patient actually received:

Variable	Placebo n=30	Clozapine n=30	p value
Age (yr)	71.9 ± 8.1	70.8 ± 8.6	0.62
Duration of Parkinson's disease (yr)	10.4 ± 7.5	10.8 ± 6.1	0.84
Hoehn-Yahr stage of disease	2.8 ± 0.8	2.6 ± 0.9	0.33
UPDRS Motor	37.1 ± 13	32.8 ± 11.3	0.19
UPDRS Total	61.3 ± 20.3	52.0 ± 17.3	0.07
MMSE	21.7 ± 5.2	23.8 ± 4.8	0.11

<table>
<tr><th>Bibliographic reference</th><th>Friedman J, Lannon M, Cornelia C, Factor S, Kurlan R, Richard I et al. Low-dose clozapine for the treatment of drug-induced psychosis in Parkinson's disease. New England Journal of Medicine 1999;340:757-63.</th></tr>
<tr><td></td><td>
<table>
<tr><td>BPRS</td><td>35.0 ± 10.7</td><td>33.1 ± 9.9</td><td>0.47</td></tr>
<tr><td>CGIS</td><td>4.4 ± 1.0</td><td>4.4 ± 0.8</td><td>0.89</td></tr>
</table>
There were no significant differences in the use of antiparkinsonian or psychotropic drugs between the two groups. All 60 patients were taking levodopa.
</td></tr>
<tr><td>Primary outcome measures</td><td>• CGIS for psychosis
• UPDRS</td></tr>
<tr><td>Secondary outcomes measures</td><td>Not reported.</td></tr>
<tr><td>Results</td><td></td></tr>
<tr><td>UPDRS Motor</td><td>
<table>
<tr><td></td><td>Mean</td><td>SD</td><td>Total</td></tr>
<tr><td>Experimental</td><td>-3.60</td><td>9.50</td><td>25</td></tr>
<tr><td>Control</td><td>-1.80</td><td>6.00</td><td>25</td></tr>
</table>
</td></tr>
<tr><td>SAPS</td><td>SAPS
<table>
<tr><td></td><td>Mean</td><td>SD</td><td>Total</td></tr>
<tr><td>Experimental</td><td>-11.80</td><td>10.39</td><td>27</td></tr>
<tr><td>Control</td><td>-3.80</td><td>9.87</td><td>27</td></tr>
</table>
</td></tr>
<tr><td>Mortality</td><td>
<table>
<tr><td></td><td>Deaths</td><td>Total</td></tr>
<tr><td>Experimental</td><td>0</td><td>30</td></tr>
<tr><td>Control</td><td>0</td><td>30</td></tr>
</table>
</td></tr>
<tr><td>Number of dropouts due to adverse events</td><td>
<table>
<tr><td></td><td>Events</td><td>Total</td></tr>
<tr><td>Experimental</td><td>3</td><td>30</td></tr>
<tr><td>Control</td><td>3</td><td>30</td></tr>
</table>
</td></tr>
</table>

Bibliographic reference	Friedman J, Lannon M, Cornelia C, Factor S, Kurlan R, Richard I et al. Low-dose clozapine for the treatment of drug-induced psychosis in Parkinson's disease. New England Journal of Medicine 1999;340:757-63.
Results	Fifty-four patients completed the trial. The mean daily dose of clozapine prescribed at the end of the study was 24.7 mg (range 6.25 to 50). The mean daily dose of placebo was equivalent to 35.2 mg (range 6.25 to 50). Three patients receiving placebo and three receiving clozapine withdrew from the study. The psychiatric condition of two of the three patients receiving placebo worsened. One patient required psychiatric hospitalization, and the other discarded her medications, declaring herself "cured". The third patient was hospitalized for pneumonia. Of the three patients in the clozapine group who withdrew from the study, one discontinued the drug because of leukopenia, one because of myocardial infarction, and one because of sedation. Data extracted for UPDRS motor and SAPS are the mean change scores from baseline to end point.
Overall Risk of Bias	1. Has an appropriate method of randomisation been used? UNCLEAR 2. Was there adequate concealment of allocation? UNCLEAR 3. Were the groups comparable at baseline for all major confounding/prognostic factors? NO (some significant imbalances in psychosis at baseline between the groups) 4. Did the comparison groups receive the same care apart from interventions studied? YES 5. Were participants receiving care kept blind to treatment allocation? UNCLEAR* 6. Were the individuals administering care kept blind to treatment allocation? UNCLEAR* 7. Were groups comparable with respect to availability of outcome data and for how many participants were no outcome data available? YES and <20% dropout rate. 8. Did the study have an appropriate length of follow up? UNCLEAR (4 weeks) 9. Did the study use a precise definition of outcome? YES 10. Was a valid and reliable method used to determine that outcome? UNCLEAR 11. Were investigators kept blind to participant's exposure to the intervention? UNCLEAR* 12. Were investigators kept blind to other important confounding and prognostic factors? UNCLEAR* *Level of blinding unclear - no details beyond description of study as "randomized, double-blind, placebo-controlled trial". Overall there is likely high risk of bias.

Bibliographic reference	Breier,A., Sutton,V.K., Feldman,P.D., Kadam,D.L., Ferchland,I., Wright,P., Friedman,J.H., Olanzapine in the treatment of dopamimetic-induced psychosis in patients with Parkinson's disease (European Study Results), Biological Psychiatry.52 (5) (pp 438-445), 2002.Date of Publication: 01 Sep 2002., 438-445, 2002
Country/ies where the study was carried out	Europe
Study type	Randomised, double-blind, placebo-controlled trials (2 multi-centre trials)
Aim of the study	To report the findings from two placebo-controlled, double-blind studies of the use of olanzapine for control of dopamimetic psychosis when added to a fixed dose of dopamimetic agent
Study dates	Study date: Not reported Study duration: 4 weeks
Source of funding	Eli Lilly and Company
Sample size	77 in the European study; Olanzapine n = 49, Placebo n = 28
Inclusion criteria	Patients were included if they: • Had a diagnosis of idiopathic PD • Had been responsive to dopamimetics for motor symptoms • Experienced hallucinations, delusions, or both in the 2-week period before entry (Visit 1) • Had an individual Hallucinations or Delusions item score of ≥2 on the Neuropsychiatric Inventory (NPI; Cummings et al 1994) at both study entry (Visit 1) and randomisation (Visit 2). • Had a full-time (7 days/week) caregiver who was familiar with the patient's medical history and accompanied the patient to all office visits. • Were on stable doses of PD medications, defined as the lowest level of anti-PD medications required to control motor symptoms in the judgement of the investigator and consisting of L-DOPA, L-DOPA with decarboxylase inhibitor, dopamimergic receptor agonist therapy, or a combination of these, for at least 1 week immediately before study entry.
Exclusion criteria	Patients were excluded if they had: • Any prior treatment with olanzapine, treatment with clozapine or risperidone within 3 months before Visit 1 • Treatment with any other antipsychotic within 1 month before Visit 1 • Any other concomitant medication that had central nervous system activity
Interventions	Olanzapine: 2.5 mg, 5 mg, 7.5 mg, 10 mg, 12.5 mg or 15 mg once a day.
Details	Enrolled patients were assigned by random allocation to a 4-week, double-blind treatment with either olanzapine or placebo. Doses of dopamimetic therapy were held constant throughout the study. Olanzapine was initiated at 2.5 mg/day (one tablet), with 2.5mg/day increases allowed every 3 to 4 days up to the maximum dose of 15 mg/day (6 tablets), according to the clinical

Bibliographic reference	**Breier,A., Sutton,V.K., Feldman,P.D., Kadam,D.L., Ferchland,I., Wright,P., Friedman,J.H., Olanzapine in the treatment of dopamimetic-induced psychosis in patients with Parkinson's disease (European Study Results), Biological Psychiatry.52 (5) (pp 438-445), 2002.Date of Publication: 01 Sep 2002., 438-445, 2002**
	response of psychotic symptoms. Dosage decreases could occur at any time by any number of decrements. Patients who were unable to tolerate the lowest dose of olanzapine were released from the study. Baseline demographic and clinical data did not differ between treatment groups.

European study

Variable	Olanzapine n= 49	Placebo n= 28	p-value
Age: years (SD)	70.9 (6.3)	70.5 (8.2)	
Age at onset: years (SD)	60.8 (8.0)	55.4 (16.1)	
Hoehn and Yahr staging: No.			0.703
Stage 1	0 (0.0)	0 (0.0)	-
Stage 1.5	1 (2.0)	0 (0.0)	-
Stage 2	6 (12.2)	3 (10.7)	-
Stage 2.5	5 (10.2)	4 (14.3)	-
Stage 3	24 (49.0)	10 (35.7)	-
Stage 4	13 (26.5)	11 (39.3)	-
Dementia: No. (%)			0.623
Demented	17 (34.7)	8 (28.6)	-
Nondemented	32 (65.3)	20 (71.4)	-

Primary outcome measures	Positive symptom cluster subscore of the Brief Psychiatric Rating Scale (BPRS; Guy 1976), comprising the sum score of the item scores for Conceptual Disorganization, Suspiciousness, Hallucinatory Behavior, and Unusual Thought Content.
Secondary outcomes measures	• BPRS total and negative symptom cluster scores • Clinical Global Impressions - Severity (CGI-S; Guy 1976) score for psychosis

<table>
<tr><th>Bibliographic reference</th><th>Breier,A., Sutton,V.K., Feldman,P.D., Kadam,D.L., Ferchland,I., Wright,P., Friedman,J.H., Olanzapine in the treatment of dopamimetic-induced psychosis in patients with Parkinson's disease (European Study Results), Biological Psychiatry.52 (5) (pp 438-445), 2002.Date of Publication: 01 Sep 2002., 438-445, 2002</th></tr>
<tr><td></td><td>• NPI total score and individual item subscores.

A subgroup analysis was also performed to examine efficacy scores among patients characterised at baseline as demented (MMSE score < 4) vs. those without dementia (MMSE ≥ 24).</td></tr>
<tr><td>Results</td><td></td></tr>
<tr><td>BPRS Positive</td><td><table><tr><td></td><td>Mean</td><td>SD</td><td>Total</td></tr><tr><td>Experimental</td><td>-2.30</td><td>4.10</td><td>49</td></tr><tr><td>Control</td><td>-2.90</td><td>3.40</td><td>28</td></tr></table></td></tr>
<tr><td>BPRS Hallucination</td><td><table><tr><td></td><td>Mean</td><td>SD</td><td>Total</td></tr><tr><td>Experimental</td><td>-1.00</td><td>1.50</td><td>49</td></tr><tr><td>Control</td><td>-1.40</td><td>1.50</td><td>28</td></tr></table></td></tr>
<tr><td>UPDRS Motor</td><td><table><tr><td></td><td>Mean</td><td>SD</td><td>Total</td></tr><tr><td>Experimental</td><td>2.70</td><td>6.00</td><td>49</td></tr><tr><td>Control</td><td>-0.30</td><td>5.00</td><td>28</td></tr></table></td></tr>
<tr><td>NPI Delusions</td><td><table><tr><td></td><td>Mean</td><td>SD</td><td>Total</td></tr><tr><td>Experimental</td><td>-1.10</td><td>3.40</td><td>49</td></tr><tr><td>Control</td><td>-2.00</td><td>2.60</td><td>28</td></tr></table></td></tr>
<tr><td>NPI hallucination</td><td><table><tr><td></td><td>Mean</td><td>SD</td><td>Total</td></tr><tr><td>Experimental</td><td>-2.70</td><td>3.30</td><td>49</td></tr><tr><td>Control</td><td>-2.70</td><td>3.60</td><td>28</td></tr></table></td></tr>
</table>

Bibliographic reference	**Breier,A., Sutton,V.K., Feldman,P.D., Kadam,D.L., Ferchland,I., Wright,P., Friedman,J.H., Olanzapine in the treatment of dopamimetic-induced psychosis in patients with Parkinson's disease (European Study Results), Biological Psychiatry.52 (5) (pp 438-445), 2002.Date of Publication: 01 Sep 2002., 438-445, 2002**
Number of dropouts due to adverse events	<table><tr><td></td><td>Events</td><td>Total</td></tr><tr><td>Experimental</td><td>8</td><td>49</td></tr><tr><td>Control</td><td>1</td><td>28</td></tr></table>
Results	Data extracted for all BPRS subscales and UPDRS motor scale are the mean change scores from baseline to end point. <table><tr><td rowspan="2">Completion Rates</td><td colspan="2">European Study</td></tr><tr><td>%</td><td>p value vs. Placebo</td></tr><tr><td colspan="3">Completion rates (4 weeks):</td></tr><tr><td>Olanzapine</td><td>75.5</td><td rowspan="2">0.386</td></tr><tr><td>Placebo</td><td>85.7</td></tr><tr><td colspan="3">Discontinued due to adverse event:</td></tr><tr><td>Olanzapine</td><td>16.3</td><td rowspan="2">0.144</td></tr><tr><td>Placebo</td><td>3.6</td></tr></table> Treatment-related adverse events not reported.
Overall Risk of Bias	1. Has an appropriate method of randomisation been used? UNCLEAR 2. Was there adequate concealment of allocation? UNCLEAR 3. Were the groups comparable at baseline for all major confounding/prognostic factors? YES 4. Did the comparison groups receive the same care apart from interventions studied? YES 5. Were participants receiving care kept blind to treatment allocation? UNCLEAR* 6. Were the individuals administering care kept blind to treatment allocation? UNCLEAR* 7. Were groups comparable with respect to availability of outcome data and for how many participants were no outcome data available? YES but dropout rate >20%

Bibliographic reference	Breier,A., Sutton,V.K., Feldman,P.D., Kadam,D.L., Ferchland,I., Wright,P., Friedman,J.H., Olanzapine in the treatment of dopamimetic-induced psychosis in patients with Parkinson's disease (European Study Results), Biological Psychiatry.52 (5) (pp 438-445), 2002.Date of Publication: 01 Sep 2002., 438-445, 2002
	8. Did the study have an appropriate length of follow up? UNCLEAR (4 wks) 9. Did the study use a precise definition of outcome? YES 10. Was a valid and reliable method used to determine that outcome? UNCLEAR 11. Were investigators kept blind to participant's exposure to the intervention? UNCLEAR* 12. Were investigators kept blind to other important confounding and prognostic factors? UNCLEAR* 13. *Level of blinding unclear - no details beyond description of study as "randomized, double-blind, placebo-controlled trial". 14. Overall there is likely high risk of bias.

Bibliographic reference	Breier,A., Sutton,V.K., Feldman,P.D., Kadam,D.L., Ferchland,I., Wright,P., Friedman,J.H., Olanzapine in the treatment of dopamimetic-induced psychosis in patients with Parkinson's disease (USA Study Results), Biological Psychiatry.52 (5) (pp 438-445), 2002.Date of Publication: 01 Sep 2002., 438-445, 2002
Country/ies where the study was carried out	US
Study type	Randomised, double-blind, placebo-controlled trials (2 multi-centre trials)
Aim of the study	To report the findings from two placebo-controlled, double-blind studies of the use of olanzapine for control of dopamimetic psychosis when added to a fixed dose of dopamimetic agent
Study dates	Study date: Not reported Study duration: 4 weeks
Source of funding	Eli Lilly and Company
Sample size	83 in the US study; Olanzapine n = 41, Placebo n= 42 Randomised in a 1:1 drug to placebo ratio
Inclusion criteria	Patients were included if they: • Had a diagnosis of idiopathic PD • Had been responsive to dopamimetics for motor symptoms

Bibliographic reference	**Breier,A., Sutton,V.K., Feldman,P.D., Kadam,D.L., Ferchland,I., Wright,P., Friedman,J.H., Olanzapine in the treatment of dopamimetic-induced psychosis in patients with Parkinson's disease (USA Study Results), Biological Psychiatry.52 (5) (pp 438-445), 2002.Date of Publication: 01 Sep 2002., 438-445, 2002**
	• Experienced hallucinations, delusions, or both in the 2-week period before entry (Visit 1) • Had an individual Hallucinations or Delusions item score of ≥2 on the Neuropsychiatric Inventory (NPI; Cummings et al 1994) at both study entry (Visit 1) and randomisation (Visit 2). • Had a full-time (7 days/week) caregiver who was familiar with the patient's medical history and accompanied the patient to all office visits. • Were on stable doses of PD medications, defined as the lowest level of anti-PD medications required to control motor symptoms in the judgement of the investigator and consisting of L-DOPA, L-DOPA with decarboxylase inhibitor, dopamimergic receptor agonist therapy, or a combination of these, for at least 1 week immediately before study entry.
Exclusion criteria	Patients were excluded if they had: • Any prior treatment with olanzapine, treatment with clozapine or risperidone within 3 months before Visit 1 • Treatment with any other antipsychotic within 1 month before Visit 1 • Any other concomitant medication that had central nervous system activity
Interventions	Olanzapine: 2.5 mg, 5 mg, 7.5 mg, 10 mg, 12.5 mg or 15 mg once a day.
Details	Enrolled patients were assigned by random allocation to a 4-week, double-blind treatment with either olanzapine or placebo. Doses of dopamimetic therapy were held constant throughout the study. Olanzapine was initiated at 2.5 mg/day (one tablet), with 2.5mg/day increases allowed every 3 to 4 days up to the maximum dose of 15 mg/day (6 tablets), according to the clinical response of psychotic symptoms. Dosage decreases could occur at any time by any number of decrements. Patients who were unable to tolerate the lowest dose of olanzapine were released from the study. Baseline demographic and clinical data did not differ between treatment groups in either study and were roughly equivalent between the two studies, although there was a trend toward younger age onset of PD among placebo patients in the European study (55.4(16.1) vs 61.1(10.3) years).

Variable	United States Study		
	Olanzapine	Placebo	p-value
Age: years (SD)	73.5 (8.7)	71.7 (6.8)	.419
Age at onset: years (SD)	60.6 (14.1)	61.1 (10.3)	.705

Bibliographic reference	**Breier,A., Sutton,V.K., Feldman,P.D., Kadam,D.L., Ferchland,I., Wright,P., Friedman,J.H., Olanzapine in the treatment of dopamimetic-induced psychosis in patients with Parkinson's disease (USA Study Results), Biological Psychiatry.52 (5) (pp 438-445), 2002.Date of Publication: 01 Sep 2002., 438-445, 2002**

Hoehn and Yahr staging: No. (%)			0.843
Stage 1	1 (2.4)	0 (0.0)	-
Stage 1.5	0 (0.0)	1 (2.4)	-
Stage 2	8 (19.5)	8 (19.0)	-
Stage 2.5	3 (7.3)	1 (2.4)	-
Stage 3	19 (46.3)	20 (47.6)	-
Stage 4	10 (24.4)	12 (28.6)	-
Dementia: No. (%)			0.266
Demented	19 (46.3)	14 (33.3)	-
Nondemented	22 (53.7)	28 (66.7)	-

Primary outcome measures

Positive symptom cluster subscore of the Brief Psychiatric Rating Scale (BPRS; Guy 1976), comprising the sum score of the item scores for Conceptual Disorganization, Suspiciousness, Hallucinatory Behaviour, and Unusual Thought Content.

Secondary outcomes measures

- BPRS total and negative symptom cluster scores
- Clinical Global Impressions - Severity (CGI-S; Guy 1976) score for psychosis
- NPI total score and individual item subscores.

A subgroup analysis was also performed to examine efficacy scores among patients characterised at baseline as demented (MMSE score < 4) vs. those without dementia (MMSE ≥ 24).

Results

BPRS Positive

	Mean	SD	Total
Experimental	-1.70	3.50	41
Control	-1.60	3.90	42

<table>
<tr><th>Bibliographic reference</th><th>Breier,A., Sutton,V.K., Feldman,P.D., Kadam,D.L., Ferchland,I., Wright,P., Friedman,J.H., Olanzapine in the treatment of dopamimetic-induced psychosis in patients with Parkinson's disease (USA Study Results), Biological Psychiatry.52 (5) (pp 438-445), 2002.Date of Publication: 01 Sep 2002., 438-445, 2002</th></tr>
<tr><td>BPRS Hallucination</td><td>
<table>
<tr><td></td><td>Mean</td><td>SD</td><td>Total</td></tr>
<tr><td>Experimental</td><td>-0.70</td><td>1.60</td><td>41</td></tr>
<tr><td>Control</td><td>-0.90</td><td>1.40</td><td>42</td></tr>
</table>
</td></tr>
<tr><td>UPDRS Motor</td><td>
<table>
<tr><td></td><td>Mean</td><td>SD</td><td>Total</td></tr>
<tr><td>Experimental</td><td>2.60</td><td>6.00</td><td>41</td></tr>
<tr><td>Control</td><td>-0.20</td><td>4.30</td><td>42</td></tr>
</table>
</td></tr>
<tr><td>NPI Delusions</td><td>
<table>
<tr><td></td><td>Mean</td><td>SD</td><td>Total</td></tr>
<tr><td>Experimental</td><td>-0.70</td><td>3.30</td><td>41</td></tr>
<tr><td>Control</td><td>-1.70</td><td>3.90</td><td>42</td></tr>
</table>
</td></tr>
<tr><td>NPI hallucination</td><td>
<table>
<tr><td></td><td>Mean</td><td>SD</td><td>Total</td></tr>
<tr><td>Experimental</td><td>-2.10</td><td>4.30</td><td>41</td></tr>
<tr><td>Control</td><td>-2.50</td><td>2.70</td><td>42</td></tr>
</table>
</td></tr>
<tr><td>Number of dropouts due to adverse events</td><td>
<table>
<tr><td></td><td>Events</td><td>Total</td></tr>
<tr><td>Experimental</td><td>10</td><td>41</td></tr>
<tr><td>Control</td><td>1</td><td>42</td></tr>
</table>
</td></tr>
<tr><td>Results</td><td>Data extracted for all BPRS subscales and UPDRS motor scale are the mean change scores from baseline to end point.

<table>
<tr><td rowspan="2">Completion Rates and Adverse Events</td><td>United States Study</td></tr>
<tr><td>% p value vs. Placebo</td></tr>
</table>
</td></tr>
</table>

Bibliographic reference	Breier,A., Sutton,V.K., Feldman,P.D., Kadam,D.L., Ferchland,I., Wright,P., Friedman,J.H., Olanzapine in the treatment of dopamimetic-induced psychosis in patients with Parkinson's disease (USA Study Results), Biological Psychiatry.52 (5) (pp 438-445), 2002.Date of Publication: 01 Sep 2002., 438-445, 2002		
	Completion rates (4 weeks):		
	Olanzapine	61	0.029
	Placebo	83.3	
	Discontinued due to adverse event:		
	Olanzapine	24.4	0.003
	Placebo	2.4	
	Treatment-emergent adverse events		
	- Extrapyramidal syndrome:		
	Olanzapine	24.4	0.003
	Placebo	2.4	
	- Hallucinations:		
	Olanzapine	24.4	0.013
	Placebo	4.8	
	- Increased salivation:		
	Olanzapine	22	0.026
	Placebo	4.8	
Overall Risk of Bias	1. Has an appropriate method of randomisation been used? UNCLEAR 2. Was there adequate concealment of allocation? UNCLEAR 3. Were the groups comparable at baseline for all major confounding/prognostic factors? YES 4. Did the comparison groups receive the same care apart from interventions studied? YES 5. Were participants receiving care kept blind to treatment allocation? UNCLEAR* 6. Were the individuals administering care kept blind to treatment allocation? UNCLEAR*		

Bibliographic reference	Breier,A., Sutton,V.K., Feldman,P.D., Kadam,D.L., Ferchland,I., Wright,P., Friedman,J.H., Olanzapine in the treatment of dopamimetic-induced psychosis in patients with Parkinson's disease (USA Study Results), Biological Psychiatry.52 (5) (pp 438-445), 2002.Date of Publication: 01 Sep 2002., 438-445, 2002
	7. Were groups comparable with respect to availability of outcome data and for how many participants were no outcome data available? YES but dropout rate >20% 8. Did the study have an appropriate length of follow up? UNCLEAR (4 weeks) 9. Did the study use a precise definition of outcome? YES 10. Was a valid and reliable method used to determine that outcome? UNCLEAR 11. Were investigators kept blind to participant's exposure to the intervention? UNCLEAR* 12. Were investigators kept blind to other important confounding and prognostic factors? UNCLEAR* *Level of blinding unclear - no details beyond description of study as "randomized, double-blind, placebo-controlled trial". Overall there is likely high risk of bias.

D.3.5 REM sleep disorder behaviour

Bibliographic reference	Di,Giacopo R., Fasano,A., Quaranta,D., Della,Marca G., Bove,F., Bentivoglio,A.R., 20120808, Rivastigmine as alternative treatment for refractory REM behaviour disorder in Parkinson's disease, Movement Disorders, 27, 559-561, 2012
Country/ies where the study was carried out	Italy
Study type	RCT
Aim of the study	To assess the efficacy of rivastigmine to treat RBD in whom conventional therapy has failed (melatonin or clonazepam)
Study dates	July 2011 received. Published Dec 2011
Source of funding	None reported.
Sample size	n = 12
Inclusion criteria	Consecutive patients with idiopathic PD and RBD refractory to melatonin (up to 5mg per day) and clonazepam (up to 2 mg per day). RBD confirmed by polysomnography without atonia (RSWA) features
Exclusion criteria	Dementia, orthostatic hypotension, chronic obstructive pulmonary diseases, active peptic ulcer epilepsy, urinary obstruction, cardiac arrhythmias, treatment with anticholinergics or antidepressants, and DBS
Details	Before randomization all patients underwent clinical interview, neuro exam, neuropsychological examination, psychiatric assessment, blood pressure measured, and electrocardiogram. RBD frequency at baseline assessed on basis of 1 month diary of patients RBD episodes filled in by the bed partners Patients considered affected by severe RBD if suffered> 5 episodes a week. Each patient randomized to receive either rivastigmine patch 4.6mg per day or a placebo patch for 3 weeks washout period of 7 days, each group shifted to other treatment for an additional 3 weeks antiparkinsonian therapy maintained unaltered for the duration of study
Interventions	Each patient randomized to receive either rivastigmine patch 4.6mg per day or a placebo patch for 3 weeks washout period of 7 days, each group shifted to other treatment for an additional 3 weeks
Results	11 men, 1 female Mean age 67.7 (7.3); disease duration 9.2 (3.2) Mean LDD = 445.8 mg Adverse events 2 patients dropped out because of orthostatic hypotension and asthenia, both occurring during active treatment arm RBD episodes RBD episodes significantly less frequent in rivastigmine treatment compared to baseline (Z = -2.524, p = 0.012); not the case

Bibliographic reference	Di,Giacopo R., Fasano,A., Quaranta,D., Della,Marca G., Bove,F., Bentivoglio,A.R., 20120808, Rivastigmine as alternative treatment for refractory REM behaviour disorder in Parkinson's disease, Movement Disorders, 27, 559-561, 2012
	in placebo (Z= -1.289, p=.197) Mean frequency of RBD episode significantly lower in rivastigmine compared with placebo (Z=-2.207, p=0.027). Median *(25th - 75th percentiles)= 2.5 (0.0 to 4.5) Reduction in frequency of RBD episodes was more consistent in patients with severe RBD.
Overall Risk of Bias	NICE RCT checklist: 1. An appropriate method of randomization was used to allocate pts to treatment groups? Unclear - details on randomization method not given 2. There was adequate concealment of allocation: details for allocation concealment details not given 3. The groups were comparable at baseline, including all major confounding and prognostic factors? cross over trial. Random allocated treatment order groups were comparable 4. Comparison groups received same care apart from interventions: yes 5. Pts receiving care were kept blind to tmt allocation: No details given on blinding 6. Individuals administering care were kept blind to tmt allocation: No details given on blinding 7. All groups followed up for an equal length of time: yes - equal time follow-up 8. Groups comparable for treatment completion? No - 2 patients dropped out of rivastigmine group, no drop out from placebo 9. Groups were comparable with respect to availability of outcome data? Data for 2 patients was not available for the placebo trial. 10. Study had appropriate length of follow up? Unclear whether 3 weeks is adequate 11. Study used a precise definition of outcome: No; primary outcome was measured by bedpartner diary on RBD episodes. No other measure used i.e. polysomnography 12. Valid and reliable method was used to determine the outcome: No; primary outcome was measured by bedpartner diary on RBD episodes. 13. Investigators were kept blind to participants' exposure to the intervention: unclear - details for blinding were not given 14. Investigators were kept blind to other important confounding and prognostic factors: Unclear - details for blinding of prognostic factors were not given. overall quality = LOW (risk of bias = high)
Other information	None

D.3.6 Thermoregulatory dysfunction

No evidence found for this question

D.4 Pharmacological management of dementia associated with Parkinson's disease

<table>
<tr><th>Bibliographic reference</th><th>Aarsland,D., Laake,K., Larsen,J.P., Janvin, C., Donepezil for cognitive impairment in Parkinson's disease: a randomised controlled study, J Neurol Neurosurg Psychiatry, 72, 708-712, 2002</th></tr>
<tr><td>Study type</td><td>Double-blind randomised controlled trial</td></tr>
<tr><td>Aim of the study</td><td>To assess the safety and efficacy of donepezil in people with PD and cognitive impairment</td></tr>
<tr><td>Country/ies where the study was carried out</td><td>Norway</td></tr>
<tr><td>Study dates</td><td>Not stated, study published in 2002</td></tr>
<tr><td>Source of funding</td><td>Pfizer Norway</td></tr>
<tr><td>Sample size</td><td>N=14 randomised</td></tr>
<tr><td>Inclusion criteria</td><td>People aged 45-95 years with cognitive impairment associated with PD (MMSE score 16 to 26 inclusive) with caregiver support</td></tr>
<tr><td>Exclusion criteria</td><td>Brain disease other than PD, severe medical disorders, concomitant anticholinergics or psychotropic drugs with anticholinergic effects</td></tr>
<tr><td>Details</td><td>20-week double blind, placebo-controlled crossover RCT. Participants were randomised to either donepezil or placebo for 10 weeks, followed by crossover treatment for a further 10 weeks. There was no wash-out period.</td></tr>
<tr><td>Intervention(s)</td><td>Donepezil 5mg daily, increased to 10mg daily after 6 weeks if well tolerated</td></tr>
<tr><td>Comparator(s)</td><td>Placebo</td></tr>
<tr><td>Results</td><td>Efficacy results after 10 weeks treatment:
<table>
<tr><th>Outcome</th><th>Donepezil (n=12)</th><th>Placebo (n=12)</th></tr>
<tr><td>MMSE</td><td>22.8 (3.7)*</td><td>21.0 (5.0)</td></tr>
<tr><td>CIBIC+</td><td>3.3 (0.9)*</td><td>4.1 (0.8)</td></tr>
<tr><td>NPI</td><td colspan="2">Results not presented (no significant difference)</td></tr>
<tr><td>UPDRS III</td><td>31.8 (15.4)</td><td>35.1 (8.1)</td></tr>
<tr><td colspan="3">Values are mean (SD). * P<0.05 compared with placebo</td></tr>
</table>

Adverse events
2 people receiving donepezil withdrew due to adverse events, 0 people withdrew due to adverse events on placebo
Number of adverse events (any) was 12 (SD 11) for donepezil and 9 (SD 7) for placebo</td></tr>
</table>

Bibliographic reference	Aarsland,D., Laake,K., Larsen,J.P., Janvin, C., Donepezil for cognitive impairment in Parkinson's disease: a randomised controlled study, J Neurol Neurosurg Psychiatry, 72, 708-712, 2002
	Number of adverse events per person, mean (SD) 4.2 (3.2) for donepezil and 2.8 (1.0) for placebo
Overall Risk of Bias	1. Has an appropriate method of randomisation been used? YES 2. Was there adequate concealment of allocation? YES 3. Were the groups comparable at baseline for all major confounding/prognostic factors? UNCLEAR 4. Did the comparison groups receive the same care apart from interventions studied? YES 5. Were participants receiving care kept blind to treatment allocation? YES 6. Were the individuals administering care kept blind to treatment allocation? YES 7. Were groups comparable with respect to availability of outcome data and for how many participants were no outcome data available? NO 8. Did the study have an appropriate length of follow up? YES 9. Did the study use a precise definition of outcome? YES 10. Was a valid and reliable method used to determine that outcome? YES 11. Were investigators kept blind to participant's exposure to the intervention? YES 12. Were investigators kept blind to other important confounding and prognostic factors? UNCLEAR
Other information	Included in NICE CG35

Bibliographic reference	Aarsland,D., Ballard,C., Walker,Z., Bostrom,F., Alves,G., Kossakowski,K., Leroi,I., Pozo-Rodriguez,F., Minthon,L., Londos,E., 20090814, Memantine in patients with Parkinson's disease dementia or dementia with Lewy bodies: a double-blind, placebo-controlled, multicentre trial, Lancet Neurology, 8, 613-618, 2009
Study type	Double-blind randomised controlled trial
Aim of the study	To assess the safety and efficacy of memantine in people with PDD and DLB
Country/ies where the study was carried out	Norway, Sweden and UK
Study dates	2005-2008, study published 2009
Source of funding	The Western Norway Regional Health Authority and Lundbeck
Sample size	N=72 randomised
Inclusion criteria	People with PDD or DLB (MMSE score 12 or above). 47% of people in the memantine group and 63% of people in the placebo

Bibliographic reference	**Aarsland,D., Ballard,C., Walker,Z., Bostrom,F., Alves,G., Kossakowski,K., Leroi,I., Pozo-Rodriguez,F., Minthon,L., Londos,E., 20090814, Memantine in patients with Parkinson's disease dementia or dementia with Lewy bodies: a double-blind, placebo-controlled, multicentre trial, Lancet Neurology, 8, 613-618, 2009**
	group were taking a cholinesterase inhibitor at baseline.
Exclusion criteria	Other brain disease, recent major changes in health status, major depression, moderate to severe renal impairment, heart disease, pulmonary disease, hepatic impairment, abnormal laboratory results, allergy to memantine
Details	Parallel group, 24-week double-blind, placebo-controlled RCT
Intervention(s)	Memantine 5mg daily, increasing to a maintenance dose of 10mg twice daily
Comparator(s)	Placebo
Results	Efficacy results at week 24

	n	Baseline	24 weeks (LOCF)	Change at 24 weeks	Between-group difference
Primary outcome					
CGIC score					
Memantine	30	—	3·5 (1.5)	—	
Placebo	33	—	4·2 (1.5)	—	0·7 (0·04 to 1·39)†
Secondary outcomes					
MMSE					
Memantine	30	20·1 (3·7)	21·5 (4·2)	–1·4 (3·2)‡	
Placebo	33	20·6 (4·2)	20·0 (6·2)	0·5 (4·2)	1·9 (0·06 to 3·8)
NPI					
Memantine	29	15·2 (14·2)	13·7 (12·8)	1·5 (10·8)	
Placebo	33	13·0 (9·9)	11·6 (11·7)	1·4 (10·6)	–0·1 (-1·2 to 4·3)
DAD					
Memantine	30	21·6 (10·8)	20·6 (12·6)	1·0 (6·4)	
Placebo	33	23·8 (8·2)	21·2 (9·5)	2·5 (4·6)§	1·5 (-1·2 to 4·3)
Modified UPDRS III					
Memantine	28	11·1 (5·7)	11·3 (6·1)	0·3(3·1)	
Placebo	30	11·6 (4·1)	11·6 (4·6)	0·0 (4·3)	–0·3 (-2·4 to 1·8)
Numbers are mean (SD), mean (95% CI), or mean seconds taken to complete the test (SD)					

Bibliographic reference	Aarsland,D., Ballard,C., Walker,Z., Bostrom,F., Alves,G., Kossakowski,K., Leroi,I., Pozo-Rodriguez,F., Minthon,L., Londos,E., 20090814, Memantine in patients with Parkinson's disease dementia or dementia with Lewy bodies: a double-blind, placebo-controlled, multicentre trial, Lancet Neurology, 8, 613-618, 2009
	*Mann–Whitney test †P=0.03; ‡Wilcoxon Z test P=0.02; §Wilcoxon Z test P=0·004; ¶P=0.045
Overall Risk of Bias	1. Has an appropriate method of randomisation been used? YES 2. Was there adequate concealment of allocation? YES 3. Were the groups comparable at baseline for all major confounding/prognostic factors? YES 4. Did the comparison groups receive the same care apart from interventions studied? YES 5. Were participants receiving care kept blind to treatment allocation? YES 6. Were the individuals administering care kept blind to treatment allocation? YES 7. Were groups comparable with respect to availability of outcome data and for how many participants were no outcome data available? YES 8. Did the study have an appropriate length of follow up? YES 9. Did the study use a precise definition of outcome? YES 10. Was a valid and reliable method used to determine that outcome? YES 11. Were investigators kept blind to participant's exposure to the intervention? YES 12. Were investigators kept blind to other important confounding and prognostic factors? UNCLEAR
Other information	None

Bibliographic reference	Dubois,B., Tolosa,E., Katzenschlager,R., Emre,M., Lees,A.J., Schumann,G., Pourcher,E., Gray,J., Thomas,G., Swartz,J., Hsu,T., Moline,M.L., 20130214, Donepezil in Parkinson's disease dementia: a randomized, double-blind efficacy and safety study, Movement Disorders, 27, 1230-1238, 2012
Study type	Double-blind randomised controlled trial
Aim of the study	To assess the efficacy and safety of donepezil in people with PDD
Country/ies where the study was carried out	Multicentre (UK, Germany, Austria, Spain, Russia, France, Australia, New Zealand, South Africa, Canada, Italy, Belgium, Portugal)
Study dates	2002-2005, study published 2012
Source of funding	Eisai
Sample size	N=550 randomised
Inclusion criteria	People aged 40 years and older with PDD (MMSE score 10 to 26 inclusive) with a reliable caregiver

<table>
<tr><th>Bibliographic reference</th><th>Dubois,B., Tolosa,E., Katzenschlager,R., Emre,M., Lees,A.J., Schumann,G., Pourcher,E., Gray,J., Thomas,G., Swartz,J., Hsu,T., Moline,M.L., 20130214, Donepezil in Parkinson's disease dementia: a randomized, double-blind efficacy and safety study, Movement Disorders, 27, 1230-1238, 2012</th></tr>
<tr><td>Exclusion criteria</td><td>Other causes of dementia (including DLB), recurrent major depression, previous treatment with cholinesterase inhibitor, allergy to donepezil, concomitant anticholinergics</td></tr>
<tr><td>Details</td><td>Parallel group, 24-week double-blind, placebo-controlled RCT</td></tr>
<tr><td>Intervention(s)</td><td>Donepezil 5mg or 10mg daily</td></tr>
<tr><td>Comparator(s)</td><td>Placebo</td></tr>
<tr><td>Results</td><td>Efficacy results at week 24 (LOCF)
<table>
<tr><th></th><th>Donepezil 5mg vs placebo</th><th>Donepezil 10mg vs placebo</th></tr>
<tr><td colspan="3">Co-primary outcomes</td></tr>
<tr><td>ADAS-cog</td><td>MD –1.45, 95%CI –2.9 to 0.00, P=0.05</td><td>MD –1.45, 95%CI –3.04 to 0.15, P=0.076</td></tr>
<tr><td>CIBIC+ overall change score</td><td>3.7 (SD 1.12) vs. 3.9 (SD 1.27), P=0.113</td><td>3.6 (SD 1.29) vs. 3.9 (SD 1.27), P=0.04</td></tr>
<tr><td colspan="3">Secondary outcomes</td></tr>
<tr><td>MMSE</td><td>MD 1.44, 95%CI 0.81 to 2.07, P<0.001</td><td>MD 1.66, 95%CI 1.02 to 2.29, P<0.001</td></tr>
<tr><td>D-KEFS:
Letter fluency
Category fluency
Category switching</td><td>
MD 2.56, 95%CI 0.99 to 4.14, P=0.001
MD 3.67, 95%CI 2.26 to 5.09, P<0.001
MD 1.14, 95%CI 0.46 to 1.82, P=0.001</td><td>
MD 3.12, 95%CI 1.52 to 4.72, P<0.001
MD 4.22, 95%CI 2.78 to 5.65, P=0.001
MD 1.21, 95%CI 0.52 to 1.90, P<0.001</td></tr>
<tr><td>BTA</td><td>MD 0.78, 95%CI 0.22 to 1.34, P=0.007</td><td>MD 1.00, 95%CI 0.42 to 1.57, P<0.001</td></tr>
<tr><td>DAD</td><td>MD 2.27, 95%CI –0.74 to 5.28, P=0.138</td><td>MD 2.24, 95%CI –0.82 to 5.30, P=0.15</td></tr>
<tr><td>SE scale</td><td>MD –0.68, 95%CI –3.19 to 1.84, P=0.598</td><td>MD –0.33, 95%CI –2.90 to 2.23, P=0.797</td></tr>
<tr><td>NPI</td><td>MD –1.52, 95%CI –3.68 to 0.63, P=0.166</td><td>MD –1.15, 95%CI –3.34 to 1.04, P=0.303</td></tr>
</table>
Adverse events
<table>
<tr><th></th><th>Donepezil 5mg (n=195)</th><th>Donepezil 10mg (n=182)</th><th>Placebo (n=173)</th></tr>
<tr><td>All adverse events (%)</td><td>76.9</td><td>73.1</td><td>71.1</td></tr>
</table></td></tr>
</table>

Bibliographic reference	**Dubois,B., Tolosa,E., Katzenschlager,R., Emre,M., Lees,A.J., Schumann,G., Pourcher,E., Gray,J., Thomas,G., Swartz,J., Hsu,T., Moline,M.L., 20130214, Donepezil in Parkinson's disease dementia: a randomized, double-blind efficacy and safety study, Movement Disorders, 27, 1230-1238, 2012**
	<table><tr><td>Adverse events leading to discontinuation (%)</td><td>13.8</td><td>17</td><td>11</td></tr><tr><td>Severe adverse events (%)</td><td>19</td><td>16.5</td><td>12.7</td></tr><tr><td>Visual hallucinations</td><td>5.1</td><td>0.5</td><td>1.2</td></tr></table>
Overall Risk of Bias	1. Has an appropriate method of randomisation been used? YES 2. Was there adequate concealment of allocation? UNCLEAR 3. Were the groups comparable at baseline for all major confounding/prognostic factors? YES 4. Did the comparison groups receive the same care apart from interventions studied? YES 5. Were participants receiving care kept blind to treatment allocation? YES 6. Were the individuals administering care kept blind to treatment allocation? YES 7. Were groups comparable with respect to availability of outcome data and for how many participants were no outcome data available? YES 8. Did the study have an appropriate length of follow up? YES 9. Did the study use a precise definition of outcome? YES 10. Was a valid and reliable method used to determine that outcome? YES 11. Were investigators kept blind to participant's exposure to the intervention? UNCLEAR 12. Were investigators kept blind to other important confounding and prognostic factors? UNCLEAR
Other information	None

Bibliographic reference	**Emre,M., Aarsland,D., Albanese,A., Byrne,E., Deuschl,G., De Deyn,P., Durif,F., Kulisevsky,J., van Laar,T., Lees,A., Poewe,W., Robillard,A., Rosa,M., Wolters,E., Quarg,P., Tekin,S., Lane,S., Rivastigmine for dementia associated with Parkinson's disease, N Engl J Med, 351, 2509-2518, 2004**
Full citation	Emre,M., Aarsland,D., Albanese,A., Byrne,E., Deuschl,G., De Deyn,P., Durif,F., Kulisevsky,J., van Laar,T., Lees,A., Poewe,W., Robillard,A., Rosa,M., Wolters,E., Quarg,P., Tekin,S., Lane,S., Rivastigmine for dementia associated with Parkinson's disease, N Engl J Med, 351, 2509-2518, 2004
Ref Id	Study not identified in literature search
Study type	Double-blind randomised controlled trial
Aim of the study	To assess the efficacy and safety of rivastigmine in people with PDD

Bibliographic reference	**Emre,M., Aarsland,D., Albanese,A., Byrne,E., Deuschl,G., De Deyn,P., Durif,F., Kulisevsky,J., van Laar,T., Lees,A., Poewe,W., Robillard,A., Rosa,M., Wolters,E., Quarg,P., Tekin,S., Lane,S., Rivastigmine for dementia associated with Parkinson's disease, N Engl J Med, 351, 2509-2518, 2004**
Country/ies where the study was carried out	Multicentre (Europe and Canada)
Study dates	Recruitment 2002-2003, study published 2004
Source of funding	Not stated in paper
Sample size	N=541 randomised
Inclusion criteria	People aged at least 50 years old with PDD (MMSE 10 to 24)
Exclusion criteria	Any primary neurodegenerative disorder other than PD or other causes of dementia, history of a major depressive episode, presence of an active, uncontrolled seizure disorder, presence of any disability or unstable disease unrelated to PD, known hypersensitivity to drugs similar to rivastigmine, use of a cholinesterase inhibitor or anticholinergic drugs during the 4 weeks before randomisation. No changes were permitted in the dose of current dopaminergic medicines within 4 weeks before and throughout the study, nor was the start of treatment with new psychotropic medications (except atypical neuroleptic agents for acute psychosis) permitted during this period
Details	Parallel group, 24-week double-blind, placebo-controlled RCT
Intervention(s)	Rivastigmine 1.5mg twice daily, increasing to a maximum well tolerated dose (up to 6mg twice daily)
Comparator(s)	Placebo
Results	Efficacy results at week 24

	n	Baseline (mean ± SD)	Change at 24 weeks (mean ± SD)	Between-group difference (value)	P value
Primary outcome					
ADAS-cog Rivastigmine Placebo	 329 161	 23.8±10.2 24.3±10.5	 –2.1±8.2 0.7±7.5	 2.90† 	 <0.001
ADCS-CGIC Rivastigmine Placebo	 329 165	 — —	 3.8±1.4 4.3±1.5	 0.5 	 0.007
Secondary outcomes					
MMSE					

Bibliographic reference	Emre,M., Aarsland,D., Albanese,A., Byrne,E., Deuschl,G., De Deyn,P., Durif,F., Kulisevsky,J., van Laar,T., Lees,A., Poewe,W., Robillard,A., Rosa,M., Wolters,E., Quarg,P., Tekin,S., Lane,S., Rivastigmine for dementia associated with Parkinson's disease, N Engl J Med, 351, 2509-2518, 2004

Rivastigmine Placebo	335 166	19.5±3.8 19.2±4.0	0.8±3.8 –0.2±3.5	1.00	 0.03
D-KEFS Rivastigmine Placebo	 258 144	 13.9±9.5 14.5±9.4	 1.7±6.8 –1.1±6.4	 2.80	 <0.001‡
CDR Rivastigmine Placebo	 328 158	 2197.0±1170.2 2490.5±2314.8	 –31.0±989.8 142.7±1780.2	 294.84†	 0.009
Clock drawing test Rivastigmine Placebo	 49 30	 3.4±3.7 2.9±3.8	 0.5±2.5 –0.6±2.4	 1.10	 0.02‡
ADCS-ADL Rivastigmine Placebo	 333 165	 41.6±18.6 41.2±17.7	 –1.1±12.6 –3.6±10.3	 2.50	 0.02
NPI Rivastigmine Placebo	 334 166	 12.7±11.7 13.2±13.0	 –2.0±10.0 0.0±10.4	 2.15†	 0.02
† The value is the modelled treatment difference (difference of least-square means) ‡ Because executive-function tests were not performed at all sites, analyses involving these tests included only patients who actually took these tests					

Adverse events

	Rivastigmine (n=362) No. (%)	Placebo (n=179) No. (%)	P value
All adverse events	303 (83.7)	127 (70.9)	<0.001
Serious adverse events	(13)	(14.5)	0.69
Hallucinations	17 (4.7)	17 (9.5)	0.04

Bibliographic reference	Emre,M., Aarsland,D., Albanese,A., Byrne,E., Deuschl,G., De Deyn,P., Durif,F., Kulisevsky,J., van Laar,T., Lees,A., Poewe,W., Robillard,A., Rosa,M., Wolters,E., Quarg,P., Tekin,S., Lane,S., Rivastigmine for dementia associated with Parkinson's disease, N Engl J Med, 351, 2509-2518, 2004
Overall Risk of Bias	1. Has an appropriate method of randomisation been used? YES 2. Was there adequate concealment of allocation? UNCLEAR 3. Were the groups comparable at baseline for all major confounding/prognostic factors? YES 4. Did the comparison groups receive the same care apart from interventions studied? YES 5. Were participants receiving care kept blind to treatment allocation? YES 6. Were the individuals administering care kept blind to treatment allocation? YES 7. Were groups comparable with respect to availability of outcome data and for how many participants were no outcome data available? YES 8. Did the study have an appropriate length of follow up? YES 9. Did the study use a precise definition of outcome? YES 10. Was a valid and reliable method used to determine that outcome? YES 11. Were investigators kept blind to participant's exposure to the intervention? YES 12. Were investigators kept blind to other important confounding and prognostic factors? UNCLEAR
Other information	Included in NICE CG35

Bibliographic reference	Emre,M., Tsolaki,M., Bonuccelli,U., Destee,A., Tolosa,E., Kutzelnigg,A., Ceballos-Baumann,A., Zdravkovic,S., Bladstrom,A., Jones,R., Study,Investigators, 20101018, Memantine for patients with Parkinson's disease dementia or dementia with Lewy bodies: a randomised, double-blind, placebo-controlled trial, Lancet Neurology, 9, 969-977, 2010
Full citation	Emre,M., Tsolaki,M., Bonuccelli,U., Destee,A., Tolosa,E., Kutzelnigg,A., Ceballos-Baumann,A., Zdravkovic,S., Bladstrom,A., Jones,R., Study,Investigators, 20101018, Memantine for patients with Parkinson's disease dementia or dementia with Lewy bodies: a randomised, double-blind, placebo-controlled trial. [Review], Lancet Neurology, 9, 969-977, 2010
Ref Id	298618
Study type	Double-blind randomised controlled trial
Aim of the study	To assess the efficacy and safety of memantine in in people with mild to moderate PDD or DLB
Country/ies where the study was carried out	Multicentre (UK, Germany, Austria, France, Greece, Italy, Spain, Turkey)
Study dates	Recruitment 2007-2008, study published 2010
Source of funding	Lundbeck

Bibliographic reference	**Emre,M., Tsolaki,M., Bonuccelli,U., Destee,A., Tolosa,E., Kutzelnigg,A., Ceballos-Baumann,A., Zdravkovic,S., Bladstrom,A., Jones,R., Study,Investigators, 20101018, Memantine for patients with Parkinson's disease dementia or dementia with Lewy bodies: a randomised, double-blind, placebo-controlled trial, Lancet Neurology, 9, 969-977, 2010**
Sample size	N=199 randomised
Inclusion criteria	People aged 50 years and older with PDD or DLB (MMSE score 10 to 24 inclusive) with a caregiver
Exclusion criteria	Cholinesterase inhibitors within 6 weeks before screening or memantine in the last 6 months, or any investigational drug within 30 days of screening. Psychiatric disorders, clinically significant or unstable systemic disease. Use of cholinesterase inhibitors, antipsychotic, antidepressant or benzodiazepine drugs were not allowed
Details	Parallel group, 24-week double-blind placebo-controlled RCT
Intervention(s)	Memantine 5mg daily, increasing to a maintenance dose of 20mg daily
Comparator(s)	Placebo
Results	Efficacy results at week 24 – people with PDD

Outcome	n	Change from baseline at 24 weeks Mean value (95%CI)	Between-group difference Mean value (95%CI)	P value
ADCS-CGIC				
Memantine	62	3.6 (3.3 to 4.0)	–0.1 (–0.6 to 0.3)	
Placebo	58	3.8 (3.4 to 4.1)		0.576
ADCS-ADL23				
Memantine	62	0.5 (–2.3 to 3.3)	0.7 (–3.0 to 4.5)	
Placebo	58	–0.3 (–3.3 to 2.8)		0.703
NPI				
Memantine	62	–1.6 (–4.9 to 1.8)	–1.4 (–5.9 to 3.0)	
Placebo	58	0.1 (–3.8 to 3.5)		0.522
UPDRS III				
Memantine	62	1.5 (–1.0 to 4.1)	0.6 (–2.6 to 3.8)	
Placebo	58	1.0 (–1.7 to 3.6)		0.719
ZBI				
Rivastigmine	62	–0.5 (–3.6 to 2.7)	–2.9 (–6.9 to 1.1)	
Placebo	58	2.4 (–0.8 to 5.7)		0.153

Bibliographic reference	**Emre,M., Tsolaki,M., Bonuccelli,U., Destee,A., Tolosa,E., Kutzelnigg,A., Ceballos-Baumann,A., Zdravkovic,S., Bladstrom,A., Jones,R., Study,Investigators, 20101018, Memantine for patients with Parkinson's disease dementia or dementia with Lewy bodies: a randomised, double-blind, placebo-controlled trial, Lancet Neurology, 9, 969-977, 2010**

Efficacy results at week 24 – people with DLB

Outcome	n	Change from baseline at 24 weeks Mean value (95%CI)	Between-group difference Mean value (95%CI)	P value
ADCS-CGIC				
Memantine	34	3.3 (2.8 to 3.8)	–0.6 (–1.2 to –0.1)	
Placebo	41	3.9 (3.5 to 4.3)		0.023
ADCS-ADL23				
Memantine	34	–0.1 (–5.2 to 5.1)	1.7 (–4.2 to 7.6)	
Placebo	41	–1.7 (–6.1 to 2.7)		0.569
NPI				
Memantine	34	–4.3 (–9.2 to 0.7)	–5.9 (–11.6 to –0.2)	
Placebo	41	1.7 (–2.5 to 5.9)		0.041
UPDRS III				
Memantine	34	1.5 (–1.0 to 4.1)	0.6 (–2.6 to 3.8)	
Placebo	41	1.0 (–1.7 to 3.6)		0.719
ZBI				
Rivastigmine	34	–0.5 (–3.6 to 2.7)	–2.9 (–6.9 to 1.1)	
Placebo	41	2.4 (–0.8 to 5.7)		0.153

Adverse events – people with PDD

	Memantine (n=62) No. (%)	Placebo (n=58) No. (%)
All adverse events	28 (45)	26 (45)
Serious adverse events	8 (13)	7 (12)
Adverse events leading to study withdrawal	6 (10)	5 (9)

Bibliographic reference	**Emre,M., Tsolaki,M., Bonuccelli,U., Destee,A., Tolosa,E., Kutzelnigg,A., Ceballos-Baumann,A., Zdravkovic,S., Bladstrom,A., Jones,R., Study,Investigators, 20101018, Memantine for patients with Parkinson's disease dementia or dementia with Lewy bodies: a randomised, double-blind, placebo-controlled trial, Lancet Neurology, 9, 969-977, 2010**
	Adverse events – people with DLB <table><tr><th></th><th>Memantine (n=34) No. (%)</th><th>Placebo (n=41) No. (%)</th></tr><tr><td>All adverse events</td><td>18 (53)</td><td>17 (41)</td></tr><tr><td>Serious adverse events</td><td>6 (18)</td><td>3 (7)</td></tr><tr><td>Adverse events leading to study withdrawal</td><td>5 (15)</td><td>7 (17)</td></tr></table>
Overall Risk of Bias	1. Has an appropriate method of randomisation been used? YES 2. Was there adequate concealment of allocation? YES 3. Were the groups comparable at baseline for all major confounding/prognostic factors? YES 4. Did the comparison groups receive the same care apart from interventions studied? YES 5. Were participants receiving care kept blind to treatment allocation? YES 6. Were the individuals administering care kept blind to treatment allocation? YES 7. Were groups comparable with respect to availability of outcome data and for how many participants were no outcome data available? YES 8. Did the study have an appropriate length of follow up? YES 9. Did the study use a precise definition of outcome? YES 10. Was a valid and reliable method used to determine that outcome? YES 11. Were investigators kept blind to participant's exposure to the intervention? YES 12. Were investigators kept blind to other important confounding and prognostic factors? YES
Other information	None

Bibliographic reference	**Emre,M., Poewe,W., De Deyn,P.P., Barone,P., Kulisevsky,J., Pourcher,E., van,Laar T., Storch,A., Micheli,F., Burn,D., Durif,F., Pahwa,R., Callegari,F., Tenenbaum,N., Strohmaier,C., 20140911, Long-term safety of rivastigmine in Parkinson's disease dementia: an open-label, randomized study, Clinical Neuropharmacology, 37, 9-16, 2014**
Study type	Open-label randomised controlled trial
Aim of the study	To assess the safety of rivastigmine and effects on motor symptoms in people with mild to moderately severe PDD
Country/ies where the study	Multicentre (Europe, USA, Argentina Canada and Australia)

Bibliographic reference	**Emre,M., Poewe,W., De Deyn,P.P., Barone,P., Kulisevsky,J., Pourcher,E., van,Laar T., Storch,A., Micheli,F., Burn,D., Durif,F., Pahwa,R., Callegari,F., Tenenbaum,N., Strohmaier,C., 20140911, Long-term safety of rivastigmine in Parkinson's disease dementia: an open-label, randomized study, Clinical Neuropharmacology, 37, 9-16, 2014**
was carried out	
Study dates	Recruitment 2008-2010, study published 2014
Source of funding	Novartis
Sample size	N=583 randomised
Inclusion criteria	People aged 50 to 85 years with PDD (MMSE score 10 to 26 inclusive) with caregiver support
Exclusion criteria	Other causes of dementia, Hoehn and Yahr stage of 5 in on-state, use of cholinesterase inhibitors or cholinergic drugs within 4 weeks before randomisation
Details	76-week prospective open-label RCT
Intervention(s)	Rivastigmine 4.6mg/24h patch, increasing to 9.5mg/24h patch
Comparator(s)	Rivastigmine 1.5mg twice daily, increasing to a maximum well tolerated dose (up to 6mg twice daily)
Results	Efficacy results

Outcome	Rivastigmine caps		Rivastigmine patch		Least squares means difference (95%CI)	P value
	n	Mean (SD)	n	Mean (SD)		
MDRS						
Baseline	273	109.5 (19.3)	273	109.4 (19.6)		
Change from baseline at week 24	273	6.5 (13.0)	273	4.4 (12.9)	2.3 (0.2 to 4.4)	0.035
Change from baseline at week 76	273	3.9 (16.8)	273	–1.4 (17.4)	5.5 (2.6 to 8.4)	<0.001
ADCS-ADL						
Baseline	273	49.2	270	50.1		
Change from baseline at week 24	273	–0.6 (10.1)	270	–1.5 (10.9)	0.8 (–0.9 to 2.6)	0.355
Change from baseline at week 76	273	–4.4 (13.3)	270	–7.8 (15.6)	3.4 (1.0 to 5.7)	0.006
NPI						
Baseline	273	11.3 (11.8)	273	11.4 (11.9)		

Bibliographic reference	Emre,M., Poewe,W., De Deyn,P.P., Barone,P., Kulisevsky,J., Pourcher,E., van,Laar T., Storch,A., Micheli,F., Burn,D., Durif,F., Pahwa,R., Callegari,F., Tenenbaum,N., Strohmaier,C., 20140911, Long-term safety of rivastigmine in Parkinson's disease dementia: an open-label, randomized study, Clinical Neuropharmacology, 37, 9-16, 2014

Change from baseline at week 24 Change from baseline at week 76	273 273	–2.6 (10.3) –1.6 (11.2)	273 273	–1.0 (10.3) 0.7 (12.6)	–1.7 (–3.2 to –0.1) –2.4 (–4.1 to –0.7)	0.032 0.007
Note: Results for change from baseline at week 52 also reported in paper						

Adverse events

	Rivastigmine patch (n=288)	Rivastigmine capsules (n=294)
All adverse events (%)	91.3	93.2
Serious adverse events	28.8	29.6
Adverse events leading to study withdrawal (including deaths)	24.7	27.2
Deaths	24.7	27.2
Visual hallucinations	6.6	5.1

Overall Risk of Bias

1. Has an appropriate method of randomisation been used? UNCLEAR
2. Was there adequate concealment of allocation? NO
3. Were the groups comparable at baseline for all major confounding/prognostic factors? YES
4. Did the comparison groups receive the same care apart from interventions studied? YES
5. Were participants receiving care kept blind to treatment allocation? NO
6. Were the individuals administering care kept blind to treatment allocation? NO
7. Were groups comparable with respect to availability of outcome data and for how many participants were no outcome data available? YES
8. Did the study have an appropriate length of follow up? YES
9. Did the study use a precise definition of outcome? YES
10. Was a valid and reliable method used to determine that outcome? YES
11. Were investigators kept blind to participant's exposure to the intervention? NO
12. Were investigators kept blind to other important confounding and prognostic factors? NO

Bibliographic reference	**Emre,M., Poewe,W., De Deyn,P.P., Barone,P., Kulisevsky,J., Pourcher,E., van,Laar T., Storch,A., Micheli,F., Burn,D., Durif,F., Pahwa,R., Callegari,F., Tenenbaum,N., Strohmaier,C., 20140911, Long-term safety of rivastigmine in Parkinson's disease dementia: an open-label, randomized study, Clinical Neuropharmacology, 37, 9-16, 2014**
Other information	None

Bibliographic reference	**Ikeda,M., Mori,E., Matsuo,K., Nakagawa,M., Kosaka,K., 20150225, Donepezil for dementia with Lewy bodies: a randomized, placebo-controlled, confirmatory phase III trial, Alzheimer's Research & Therapy, 7, 4-, 2015**
Study type	Double-blind randomised controlled trial
Aim of the study	To assess the efficacy of donepezil in people with DLB to confirm superiority over placebo
Country/ies where the study was carried out	Not stated in paper
Study dates	Not stated in paper, study published 2015
Source of funding	Eisai
Sample size	N=142 randomised
Inclusion criteria	People aged 50 years and older with DLB (MMSE score 10 to 26 inclusive) with caregiver support
Exclusion criteria	PD that was diagnosed at least 1 year prior to the onset of dementia; focal vascular lesions, other neurological or psychiatric diseases, clinically significant systemic disease, complications or a history of severe gastrointestinal ulcer, severe asthma or COPD, systolic hypotension, bradycardia, other significant cardiac problems, hypersensitivity to donepezil or piperidine derivatives, severe PD, treatment with cholinesterase inhibitors or any investigational drug within 3 months prior to screening. Cholinesterase inhibitors, antipsychotics and anti-Parkinson's drugs other than levodopa or dopamine agonists were not allowed during the study
Details	Parallel group, 12-week double-blind placebo-controlled RCT
Intervention(s)	Donepezil 5mg or 10mg daily
Comparator(s)	Placebo
Results	Efficacy results at week 12

Co-primary outcomes				
	n	Baseline Mean value ± SD	Change at week 12 (LOCF) Mean value ± SD	P value
MMSE Placebo	44	20.3 ± 4.2	0.6 ± 3.0	

Bibliographic reference	Ikeda,M., Mori,E., Matsuo,K., Nakagawa,M., Kosaka,K., 20150225, Donepezil for dementia with Lewy bodies: a randomized, placebo-controlled, confirmatory phase III trial, Alzheimer's Research & Therapy, 7, 4-, 2015

Donepezil 5mg	45	20.6 ± 4.1	1.4 ± 3.4	0.232
Donepezil 10mg	49	20.3 ± 4.8	2.2 ± 2.9	0.016
NPI-2				
Placebo	44	6.9 ± 4.5	–2.0 ± 4.2	
Donepezil 5mg	45	6.9 ± 4.5	–1.7 ± 4.3	0.661
Donepezil 10mg	49	7.3 ± 4.7	–2.9 ± 4.7	0.391
Secondary outcomes				
	n	Baseline Mean value ± SE	Change at week 12 (LOCF) Mean value ± SE	P value
NPI				
Placebo	44	–20.5 ± 15.0	–6.4 ± 1.5	
Donepezil 5mg	45	–18.9 ± 15.3	–3.3 ± 1.4	0.143
Donepezil 10mg	49	–16.6 ± 11.7	–5.5 ± 1.4	0.660
UPDRS III				
Placebo	44	Data not reported	–0.9 ± 0.9	
Donepezil 5mg	45		–1.7 ± 0.9	0.525
Donepezil 10mg	49		–0.4 ± 0.9	0.306
ZBI				
Placebo	44	28.4 ± 16.2	–0.1 ± 1.8	
Donepezil 5mg	45	28.3 ± 18.5	–5.0 ± 1.8	NS
Donepezil 10mg	49	31.4 ± 17.8	–0.8 ± 1.7	NS
NPI-2; 2 domains of NPI - hallucinations and cognitive fluctuations NS; No significant difference between groups, but P value not reported in paper				

Adverse events

	Donepezil 5mg (n=47) No. (%)	Donepezil 10mg (n=49) No. (%)	Placebo (n=46) No. (%)
All adverse events	30 (63.8)	34 (69.4)	31 (67.4)

Bibliographic reference	Ikeda,M., Mori,E., Matsuo,K., Nakagawa,M., Kosaka,K., 20150225, Donepezil for dementia with Lewy bodies: a randomized, placebo-controlled, confirmatory phase III trial, Alzheimer's Research & Therapy, 7, 4-, 2015
	Treatment-related adverse events: 12 (25.5) | 14 (28.6) | 11 (23.9) Serious adverse events: 4 (8.5) | 1 (2.0) | 5 (10.9) Withdrawal due to adverse events: 10 (21.3) | 1 (2.0) | 5 (10.9)
Overall Risk of Bias	1. Has an appropriate method of randomisation been used? YES 2. Was there adequate concealment of allocation? NO 3. Were the groups comparable at baseline for all major confounding/prognostic factors? YES 4. Did the comparison groups receive the same care apart from interventions studied? YES 5. Were participants receiving care kept blind to treatment allocation? YES 6. Were the individuals administering care kept blind to treatment allocation? YES 7. Were groups comparable with respect to availability of outcome data and for how many participants were no outcome data available? YES 8. Did the study have an appropriate length of follow up? YES 9. Did the study use a precise definition of outcome? YES 10. Was a valid and reliable method used to determine that outcome? YES 11. Were investigators kept blind to participant's exposure to the intervention? YES 12. Were investigators kept blind to other important confounding and prognostic factors? UNCLEAR
Other information	None

Bibliographic reference	Leroi,I., Overshott,R., Byrne,E.J., Daniel,E., Burns,A., 20090917, Randomized controlled trial of memantine in dementia associated with Parkinson's disease, Movement Disorders, 24, 1217-1221, 2009
Study type	Double-blind randomised controlled trial
Aim of the study	To assess the safety and tolerability of memantine in people with PDD
Country/ies where the study was carried out	UK
Study dates	Not stated in paper, study published 2009
Source of funding	Lundbeck
Sample size	N=25 randomised
Inclusion criteria	People with PDD (MMSE score 10 to 27). Those taking cholinesterase inhibitors (2 people in each group) had to have been

Bibliographic reference	Leroi,I., Overshott,R., Byrne,E.J., Daniel,E., Burns,A., 20090917, Randomized controlled trial of memantine in dementia associated with Parkinson's disease, Movement Disorders, 24, 1217-1221, 2009
	stable on the medication for at least 6 months prior to study entry with no recorded improvement in cognitive and behavioural symptoms for at least 4 weeks prior to randomisation.
Exclusion criteria	Known sensitivity to NMDA receptor antagonists, current use of amantadine, ranitidine or cimetidine, brain disease other than PD, history of neurosurgery, meeting criteria for probable DLB
Details	Parallel group, 22-week double-blind, placebo-controlled RCT. Memantine was discontinued at week 16 with final evaluation (off-drug) at week 22
Intervention(s)	Memantine 20mg daily
Comparator(s)	Placebo
Results	Efficacy results

	Placebo mean (SD)			Memantine mean (SD)			Difference in mean scores between baseline and end of drug treatment		
Outcome	Baseline	Week 16a	Week 22b	Baseline	Week 16a	Week 22b	Deltac	Delta 95%CI	P value
MMSE	18.9 (6.2)	20.9 (6.0)	18.5 (6.7)	19.3 (5.9)	19.9 (6.3)	16.9 (7.2)	–1.5	–4.9 to 1.3	0.2
DRS	94.1 (38.5)	100.3 (33.9)	101.2 (37.5)	88.4 (31.7)	94.7 (32.8)	92.0 (28.4)	0.1	–19.3 to 19.6	1.0
NPI	14.3 (10.6)	13.5 (12.4)	19.6 (11.0)	14.9 (10.9)	11.5 (11.5)	18.2 (14.6)	–2.6	–15.6 to 10.3	0.7
UPDRS III	23.8 (10.1)	21.9 (9.1)	48.8 (15.1)	24.6 (10.0)	24.3 (8.8)	46.3 (19.9)	1.6	–1.4 to 4.7	0.3

a Week 16 was the end of drug treatment

b Week 22 was the end of the 6-week drug withdrawal phase

c Delta value = (end of study drug memantine – baseline memantine) – (end of study drug placebo – baseline placebo)

At week16, in mean CIBIC+ in the memantine group was 60% vs. 43% in the placebo group ($\chi 2$= 5.4, df 2, P=0.07). After 6 weeks off the study drug (week 22), 70% of the memantine treated participants deteriorated compared with 29% of people treated with placebo ($\chi 2$=4.0, df1, P =0.04). The magnitude of this deterioration was significantly greater in the memantine group vs. placebo (mean CIBIC+ score 5.4 (SD 1.2) vs. 4.4 (SD 0.5), respectively) (t=3.2, df22, P=0.004)

Adverse events

Bibliographic reference	**Leroi,I., Overshott,R., Byrne,E.J., Daniel,E., Burns,A., 20090917, Randomized controlled trial of memantine in dementia associated with Parkinson's disease, Movement Disorders, 24, 1217-1221, 2009**
	There were 2 serious adverse events (1 in each group), which were considered unlikely to have been related to study medication. | | Placebo | Memantine | | Minor adverse events (%) | 54.5 | 64.3 |
Overall Risk of Bias	1. Has an appropriate method of randomisation been used? UNCLEAR 2. Was there adequate concealment of allocation? UNCLEAR 3. Were the groups comparable at baseline for all major confounding/prognostic factors? YES 4. Did the comparison groups receive the same care apart from interventions studied? YES 5. Were participants receiving care kept blind to treatment allocation? YES 6. Were the individuals administering care kept blind to treatment allocation? YES 7. Were groups comparable with respect to availability of outcome data and for how many participants were no outcome data available? YES 8. Did the study have an appropriate length of follow up? YES 9. Did the study use a precise definition of outcome? YES 10. Was a valid and reliable method used to determine that outcome? YES 11. Were investigators kept blind to participant's exposure to the intervention? UNCLEAR 12. Were investigators kept blind to other important confounding and prognostic factors? UNCLEAR
Other information	None

Bibliographic reference	**McKeith,I., Del,Ser T., Spano,P., Emre,M., Wesnes,K., Anand,R., Cicin-Sain,A., Ferrara,R., Spiegel,R., Efficacy of rivastigmine in dementia with Lewy bodies: A randomised, double-blind, placebo-controlled international study, Lancet.356 (9247) (pp 2031-2036), 2000.Date of Publication: 16 Dec 2000., 2031-2036, 2000**
Study type	Double-blind randomised controlled trial
Aim of the study	To assess the efficacy, tolerability and safety of rivastigmine in people with DLB
Country/ies where the study was carried out	Spain, UK and Italy
Study dates	Not stated in paper, study published 2000
Source of funding	Not stated in paper

Bibliographic reference	**McKeith,I., Del,Ser T., Spano,P., Emre,M., Wesnes,K., Anand,R., Cicin-Sain,A., Ferrara,R., Spiegel,R., Efficacy of rivastigmine in dementia with Lewy bodies: A randomised, double-blind, placebo-controlled international study, Lancet.356 (9247) (pp 2031-2036), 2000.Date of Publication: 16 Dec 2000., 2031-2036, 2000**
Sample size	N=120 randomised
Inclusion criteria	People with DLB (MMSE score over 9) with caregiver support
Exclusion criteria	Severe extrapyramidal symptoms, asthma, known hypersensitivity to rivastigmine or similar drugs. Neuroleptics, anticholinergics, selegiline or similar drugs were not allowed
Details	Parallel group, 20-week double-blind, placebo-controlled RCT
Intervention(s)	Rivastigmine 1.5mg twice daily, increasing to a maximum well tolerated dose (up to 6mg twice daily)
Comparator(s)	Placebo
Results	Efficacy results at week 20

	n	Baseline mean (SD)	Change from baseline at 20 weeks (SD)	Between-group difference (95%CI)	P value
Primary outcome – NPI-4					
ITT Rivastigmine Placebo	 59 61	 12.2 (8.2) 11.7 (8.6)	 2.5 (8.4) 0.8 (7.3)	 1.7 (–1.1 to 4.6)	 0.088
LOCF Rivastigmine Placebo	 47 53	 12.1 (7.9) 11.2 (8.4)	 3.1 (9.1) 0.8 (7.4)	 2.3 (–0.9 to 5.7)	 0.045
OC Rivastigmine Placebo	 41 51	 12.0 (7.9) 11.3 (8.6)	 4.1 (8.3) 0.7 (7.4)	 3.4 (0.06 to 6.6)	 0.010
NPI-10					
LOCF Rivastigmine Placebo	 47 53	 23.2 (15.0) 20.2 (14.2)	 5.0 (16.2) 1.2 (10.7)	 3.8 (–1.6 to 9.2)	 0.048
OC Rivastigmine Placebo	 41 51	 22.7 (15.0) 20.1 (14.4)	 7.3 (13.7) 0.9 (10.4)	 6.4 (1.4 to 11.5)	 0.005

Bibliographic reference	**McKeith,I., Del,Ser T., Spano,P., Emre,M., Wesnes,K., Anand,R., Cicin-Sain,A., Ferrara,R., Spiegel,R., Efficacy of rivastigmine in dementia with Lewy bodies: A randomised, double-blind, placebo-controlled international study, Lancet.356 (9247) (pp 2031-2036), 2000.Date of Publication: 16 Dec 2000., 2031-2036, 2000**
	ITT; Intention to treat dataset, LOCF; Last observation carried forward dataset, OC; Observed cases dataset There were no significant differences between groups in MMSE, CGC+ score and UPDRS III (data not reported in paper) | | Placebo (n=61) | Rivastigmine (n=59) | | Adverse events (%) | 46 (75%) | 54 (92%) | | Severe adverse events | 8 (13%) | 10 (17%) |
Overall Risk of Bias	1. Has an appropriate method of randomisation been used? YES 2. Was there adequate concealment of allocation? UNCLEAR 3. Were the groups comparable at baseline for all major confounding/prognostic factors? YES 4. Did the comparison groups receive the same care apart from interventions studied? YES 5. Were participants receiving care kept blind to treatment allocation? YES 6. Were the individuals administering care kept blind to treatment allocation? YES 7. Were groups comparable with respect to availability of outcome data and for how many participants were no outcome data available? YES 8. Did the study have an appropriate length of follow up? YES 9. Did the study use a precise definition of outcome? YES 10. Was a valid and reliable method used to determine that outcome? YES 11. Were investigators kept blind to participant's exposure to the intervention? YES 12. Were investigators kept blind to other important confounding and prognostic factors? UNCLEAR
Other information	Included in CG42

Bibliographic reference	**Mori,E., Ikeda,M., Kosaka,K., Donepezil-DLB,Study,I, 20121024, Donepezil for dementia with Lewy bodies: a randomized, placebo-controlled trial, Annals of Neurology, 72, 41-52, 2012**
Study type	Double-blind randomised controlled trial
Aim of the study	To assess the efficacy and safety of donepezil in 3 different doses compared with placebo, in people with DLB
Country/ies where the study was carried out	Japan

Bibliographic reference	**Mori,E., Ikeda,M., Kosaka,K., Donepezil-DLB,Study,I, 20121024, Donepezil for dementia with Lewy bodies: a randomized, placebo-controlled trial, Annals of Neurology, 72, 41-52, 2012**
Study dates	Recruitment 2007-2010, study published 2012
Source of funding	Not stated in paper
Sample size	N=140 randomised
Inclusion criteria	People aged 50 years and older with DLB (MMSE score 10 to 26 inclusive) with caregiver support
Exclusion criteria	PD diagnosed at least 1 year prior to the onset of dementia, focal vascular lesions that might cause cognitive impairment, other neurological or psychiatric diseases, clinically significant systemic disease, complications or history of severe gastrointestinal ulcer, severe asthma or COPD, systolic hypotension and other significant CV problems (e.g. QT interval prolongation), hypersensitivity to donepezil or piperidine derivatives, severe PD, treatment with cholinesterase inhibitors or any investigational drug within 3 months prior to screening. Cholinesterase inhibitors, antipsychotics, and antiparkinsonian drugs other than levodopa or dopamine agonists were not allowed.
Details	Parallel group, 12-week double blind, placebo controlled RCT
Intervention(s)	Donepezil 3mg, 5mg or 10mg daily
Comparator(s)	Placebo
Results	Efficacy results for donepezil

	Baseline			Change				
Outcome	n	Mean (SD)	P (ANOVA)	n	Mean (SD)	Difference (95%CI)	P value (t test)	P value (ANCOVA)
MMSE								
Placebo	32	18.3 (4.7)	0.271	31	–0.4 (2.7)			
3mg	35	20.4 (4.1)		35	1.6 (3.8)	2.0 (0.4 to 3.7)	0.017	0.013
5mg	32	19.8 (4.4)		32	3.4 (3.2)	3.8 (2.3 to 5.3)	<0.001	<0.001
10mg	36	19.8 (4.4)		36	2.0 (3.3)	2.4 (0.9 to 3.9)	0.001	<0.001
NPI								
Placebo	32	18.3 (8.9)	0.079	32	0.3 (17.5)			
3mg	35	20.7 (12.8)		35	–3.9 (22.0)	–4.2 (–13.9 to 5.6)	0.396	0.602
5mg	32	14.0 (8.3)		32	–5.5 (6.7)	–5.8 (–12.4 to 0.8)	0.086	0.047
10mg	36	19.5 (12.8)		35	–8.0 (12.8)	–8.3 (–15.8 to –0.9)	0.029	0.019
NPI-2								

Bibliographic reference	Mori,E., Ikeda,M., Kosaka,K., Donepezil-DLB,Study,I, 20121024, Donepezil for dementia with Lewy bodies: a randomized, placebo-controlled trial, Annals of Neurology, 72, 41-52, 2012

Placebo	32	6.3 (4.0)	0.443	32	1.1 (5.7)			
3mg	35	7.1 (4.1)		35	–2.1 (6.3)	–3.2 (–6.1 to –0.3)	0.032	0.025
5mg	32	6.3 (4.8)		32	–3.3 (3.8)	–4.4 (–6.8 to –2.0)	<0.001	<0.001
10mg	36	7.9 (5.4)		35	–4.6 (4.5)	–5.8 (–8.2 to –3.3)	<0.001	<0.001
NPI-4								
Placebo	32	12.1 (6.3)	0.269	32	–0.3 (8.5)			
3mg	35	11.5 (7.0)		35	–2.4 (10.8)	–2.1 (–6.9 to 2.6)	0.377	0.261
5mg	32	9.0 (5.3)		32	–4.2 (4.9)	–3.9 (–7.3 to –0.4)	0.028	0.008
10mg	36	11.9 (8.8)		35	–5.1 (7.4)	–4.8 (–8.7 to –1.0)	0.015	0.006
ZBI								
Placebo	32	21.8 (10.1)	0.197	31	4.2 (10.4)			
3mg	35	27.9 (13.9)		33	–1.3 (13.2)	–5.5 (–11.5 to 0.5)	0.069	0.301
5mg	32	22.9 (11.5)		31	–0.7 (15.7)	–4.9 (–11.7 to 1.8)	0.149	0.172
10mg	36	26.5 (16.1)		31	–5.0 (13.6)	–9.2 (–15.3 to –3.0)	0.004	0.035
UPDRS III								
Placebo	33	20.8 (10.6)	0.702	31	0.7 (3.8)			
3mg	35	17.9 (9.0)		34	–0.5 (7.4)	–1.3 (–4.2 to 1.7)	0.393	0.397
5mg	33	19.1 (10.7)		32	–0.5 (5.4)	–1.3 (–3.6 to 1.1)	0.281	0.358
10mg	37	18.9 (11.6)		33	–1.0 (6.7)	–1.8 (–4.5 to 1.0)	0.200	0.258

NPI-2; 2 domains of NPI – hallucinations + cognitive fluctuation
NPI-4; 4 domains of NPI – delusions + hallucinations + dysphoria + apathy

	Mean CIBIC+ score (range 1-7)	P value (difference from placebo)
Placebo	3.73	—
Donepezil 3mg	4.78	0.010
Donepezil 5mg	5.03	0.004
Donepezil 10mg	4.86	0.034

Bibliographic reference	**Mori,E., Ikeda,M., Kosaka,K., Donepezil-DLB,Study,I, 20121024, Donepezil for dementia with Lewy bodies: a randomized, placebo-controlled trial, Annals of Neurology, 72, 41-52, 2012**
	Adverse events See table below
Overall Risk of Bias	1. Has an appropriate method of randomisation been used? YES 2. Was there adequate concealment of allocation? UNCLEAR 3. Were the groups comparable at baseline for all major confounding/prognostic factors? YES 4. Did the comparison groups receive the same care apart from interventions studied? YES 5. Were participants receiving care kept blind to treatment allocation? YES 6. Were the individuals administering care kept blind to treatment allocation? YES 7. Were groups comparable with respect to availability of outcome data and for how many participants were no outcome data available? YES 8. Did the study have an appropriate length of follow up? YES 9. Did the study use a precise definition of outcome? YES 10. Was a valid and reliable method used to determine that outcome? YES 11. Were investigators kept blind to participant's exposure to the intervention? YES 12. Were investigators kept blind to other important confounding and prognostic factors? UNCLEAR
Other information	None

	Placebo (n=34)	3mg (n=35)	5mg (n=33)	10mg (n=37)
All adverse events (%)	24 (71)	24 (69)	27 (82)	32 (87)
Serious adverse events (%)	2 (5.9)	2 (5.7)	2 (6.1)	4 (10.8)
Adverse events leading to study withdrawal (%)	4 (11.8)	3 (8.6)	1 (3.0)	3 (8.1)
No statistically significant differences between placebo and each active group				

Bibliographic reference	**Ravina,B., Putt,M., Siderowf,A., Farrar,J.T., Gillespie,M., Crawley,A., Fernandez,H.H., Trieschmann,M.M., Reichwein,S., Simuni,T., 20050719, Donepezil for dementia in Parkinson's disease: a randomised, double blind, placebo controlled, crossover study, Journal of Neurology, Neurosurgery & Psychiatry, 76, 934-939, 2005**
Study type	Double-blind randomised controlled trial
Aim of the study	To assess the safety and efficacy of donepezil in people with PDD

Bibliographic reference	**Ravina,B., Putt,M., Siderowf,A., Farrar,J.T., Gillespie,M., Crawley,A., Fernandez,H.H., Trieschmann,M.M., Reichwein,S., Simuni,T., 20050719, Donepezil for dementia in Parkinson's disease: a randomised, double blind, placebo controlled, crossover study, Journal of Neurology, Neurosurgery & Psychiatry, 76, 934-939, 2005**
Country/ies where the study was carried out	USA
Study dates	Not stated in paper, study published 2005
Source of funding	National Institutes of Neurological Disorders and Stroke, National Institute on Aging
Sample size	N=22 randomised
Inclusion criteria	People aged 40 years and older with PDD (MMSE score 17 to 26 inclusive)
Exclusion criteria	Other causes of dementia, pregnancy or lactation, use of cholinergic or anticholinergic drugs (except amantadine or tolterodine within 2 weeks prior to screening), medical conditions or uncontrolled psychosis that would interfere with the safe conduct of the study
Details	26-week double blind, placebo-controlled crossover RCT. Participants were randomised to either donepezil or placebo for 10 weeks, with a 6-week washout period prior to crossover treatment for a further 10 weeks
Intervention(s)	Donepezil 5mg daily or 5mg twice daily
Comparator(s)	Placebo
Results	Efficacy results after 10 weeks treatment

Outcome	Donepezil Mean score (SD)	Placebo Mean score (SD)	Treatment effect (SE)	P value	Adjusted P valuea
ADAS-cog	22.5 (6.9)	24.4 (9.4)	–1.9 (1.4)	0.18	0.54
MMSE	24.5 (3.2)	22.5 (4.7)	2.0 (0.61)	0.0044	0.018
MDRS	108.3 (17.1)	108.5 (18.2)	–0.2 (1.9)	0.98	0.98
CGI	3.58 (0.77)	3.95 (0.85)	–0.37 (N/A)	0.0056	0.022
UPDRS III	40.3 (13.6)	40.5 (13.7)	—	0.76	—
a Adjusted for multiple comparisons using Hommel method					

Adverse events

	Donepezil (n=21)	Placebo (n=20)	P value
Tolerability (%)	17 (81)	18 (90)	0.41

Bibliographic reference	**Ravina,B., Putt,M., Siderowf,A., Farrar,J.T., Gillespie,M., Crawley,A., Fernandez,H.H., Trieschmann,M.M., Reichwein,S., Simuni,T., 20050719, Donepezil for dementia in Parkinson's disease: a randomised, double blind, placebo controlled, crossover study, Journal of Neurology, Neurosurgery & Psychiatry, 76, 934-939, 2005**
	All adverse events (%) | 11 (52) | 9 (45) | 0.64 Tolerability was defined as the proportion of study participants remaining on study drug for the full period
Overall Risk of Bias	1. Has an appropriate method of randomisation been used? YES 2. Was there adequate concealment of allocation? UNCLEAR 3. Were the groups comparable at baseline for all major confounding/prognostic factors? YES 4. Did the comparison groups receive the same care apart from interventions studied? YES 5. Were participants receiving care kept blind to treatment allocation? YES 6. Were the individuals administering care kept blind to treatment allocation? YES 7. Were groups comparable with respect to availability of outcome data and for how many participants were no outcome data available? YES 8. Did the study have an appropriate length of follow up? YES 9. Did the study use a precise definition of outcome? YES 10. Was a valid and reliable method used to determine that outcome? YES 11. Were investigators kept blind to participant's exposure to the intervention? UNCLEAR 12. Were investigators kept blind to other important confounding and prognostic factors? UNCLEAR
Other information	Included in NICE CG35

D.5 Non-pharmacological management of motor and non-motor symptoms

D.5.1 Physiotherapy and physical activity

Study details	Participants	Methods	Results	Comments
Full citation Tomlinson,C.L., Patel,S., Meek,C., Clarke,C.E., Stowe,R., Shah,L., Sackley,C.M., Deane,K.H., Herd,C.P., Wheatley,K., Ives,N., 20120926, Physiotherapy versus placebo or no intervention in Parkinson's disease. [Review][Update of Cochrane Database Syst Rev. 2012;7:CD002817; PMID: 22786482], Cochrane Database of Systematic Reviews, 8, CD002817-,	Sample size 39 trials with 1827 participants Inclusion criteria RCT studies in patients with PD that examined the effectiveness of a physiotherapy intervention in comparison to placebo or best supportive care Exclusion criteria Reasons for exclusion: study design not an RCT outcomes	Details participants with a diagnosis of PD as defined by any duration of disease, all ages, any drug therapy, any duration of physiotherapy treatment methods 4 review authors independently identified and discussed papers inclusion criteria of papers validated by discussion Cochrane RCT assessment	Results for raw data results - please see Cochrane http://onlinelibrary.wiley.com/doi/10.1002/14651858.CD002817.pub4/abstract summary: Freezing of gait questionnaire (FOG) Four trials for three physiotherapy interventions (exercise, cueing, and dance). Two hundred ninety-eight participants were included in this analysis. A borderline significant benefit was noted, with freezing of gait questionnaire score improved by 1.4 points with a physiotherapy intervention compared with no intervention (-1.41, 95% CI -2.63 to -0.19; P = 0.02) Step length Six trials for seven comparisons within five physiotherapy interventions (general physiotherapy, exercise, treadmill, tai chi, and cueing). (Note: Fisher 2008 contributed data to both the general physiotherapy and treadmill comparisons.) four hundred and seven participants were included in this analysis. No difference in step length was noted between the two treatment arms (0.02 m, 95% CI - 0.01 to 0.04; P = 0.14). Timed up and go test: Nine trials for ten comparisons within four physiotherapy interventions (exercise, cueing, dance, and martial arts). (Note: Hackney 2009 contributed data to both the dance and martial arts comparisons.) Six hundred thirty-nine participants were included in this analysis. Overall, the time taken to complete the Timed Up & Go test was significantly improved (i.e. reduced) with physiotherapy intervention compared with no intervention (-0.63 s, 95% CI -1.05 to -0.21; P = 0.003) Berg Balance Score Data on the Berg Balance Scale were available from five trials for six comparisons within four physiotherapy interventions (exercise, treadmill, dance, and martial arts). (Note: Hackney 2009 contributed data to both the dance and martial arts comparisons.) Three hundred eighty-five participants were included in this analysis. The Berg	Overall Risk of Bias Overall improvement in trial methodological quality reporting since last Cochrane review (Deane 2001 - included in CG35) Only 18/39 trials provided info on method of randomisation 24 used blinded assessors and 9 reported using intention to treat analyses. 14/39 trials discussed participant compliance Follow-up period in the trials was relatively short - no indication if it is a long term benefit

Study details	Participants	Methods	Results	Comments
2012 Ref Id 227347 Country/ies where the study was carried out UK Study type systematic review Aim of the study To assess effectiveness of physiotherapy intervention compared with no intervention in patients with PD Study dates Any trial (that met inclusion criteria) published before Oct 2012 was included in the review Source of funding	not relevant intervention not delivered by a physiotherapist occupational therapy inclusion of other neurological conditions crossover with data not presented for first treatment period multidisciplinary therapy rehab excessive number of withdrawals insufficient information	of bias tool used for each study all results combined and synthesized using meta-analysis methods to estimate overall effect of physiotherapy v no physiotherapy subgroup analyses also carried out to examine individual interventions effect on PD outcomes Interventions types of interventions - wide range of techniques: definition used was inclusive, including	Balance Scale was significantly better after physiotherapy intervention (3.71 points, 95% CI 2.30 to 5.11; P <0.00001) Falls efficacy scale (FES) Data on the Falls Efficacy Scale were available from four trials for four comparisons within two physiotherapy interventions (exercise and cueing). Three hundred fifty-three participants were included in this analysis. No difference in the Falls Efficacy Scale was found between the two treatment arms (-1.91 points, 95% CI -4.76 to 0.94; P = 0.19) Speed of gait Two or 6 minute walk test Data on the two- or six-minute walk test were available from six trials for seven comparisons within four physiotherapy interventions (exercise, treadmill, dance, and martial arts). (Note: Hackney 2009 contributed data to both the dance and martial arts comparisons.) Two hundred forty-two participants were included in this analysis. A benefit of borderline significance was identified, along with a greater increase in the distance walked in two or six minutes with physiotherapy intervention compared with no intervention (mean difference 13.37 m, 95% confidence interval (CI) 0.55 to 26.20; P = 0.04) Ten or 20 min walk test Data on the 10- or 20-metre walk test were available from four trials for two physiotherapy interventions (exercise and treadmill). One hundred sixty-nine participants were included in the analysis. Borderline significance was reported in favour of no intervention for the time taken to walk 10 or 20 metres (0.40 s, CI 0.00 to 0.80; P = 0.05) Speed Data on speed were available from 15 trials for 19 comparisons within all six physiotherapy interventions. (Note: Fisher 2008;Hackney 2009; Mak 2008; and Thaut 1996 all contributed data to two physiotherapy comparisons.) Eight hundred fourteen participants were included in this analysis. A significant benefit was reported for physiotherapy, with speed increased by 4 cm/s with a physiotherapy intervention compared with no intervention (0.04 m/s, CI 0.02 to 0.06; P = 0.0002) Depression UPDRS mental component Data on the mental sub-scale of the UPDRS were available from two trials for three comparisons within two physiotherapy interventions (general physiotherapy and treadmill). (Note: Fisher 2008 contributed data to both the general physiotherapy and treadmill comparisons.) One hundred five participants were included in this analysis. No difference in UPDRS mental score was reported between the	

Study details	Participants	Methods	Results	Comments
Cochrane collaboration		interventions not delivered by a physiotherapist, with trials of general physio, exercise, treadmill training, cueing, dance, martial arts	two treatment arms (-0.44, 95% CI -0.98 to 0.09; P = 0.10). UPDRS - total score Data on the total UPDRS score were available from three trials for three comparisons within four physiotherapy interventions (general physiotherapy, exercise, and treadmill). (Note: Fisher 2008 contributed data to both the general physiotherapy and treadmill comparisons.) Two hundred seven participants were included in this analysis. Overall, the UPDRS total score was significantly improved with physiotherapy intervention compared with no intervention (-6.15 points, 95% CI -8.57 to -3.73; P =< 0.00001). UPDRS - motor component Data on the motor sub-scale of the UPDRS were available from 13 trials for 15 comparisons within all six physiotherapy interventions.(Note: Fisher 2008 and Hackney 2009 contributed data to two physiotherapy interventions.) Six hundred and seventeen participants were included in this analysis. Overall, the UPDRS motor score was significantly improved with physiotherapy intervention compared with no intervention (-4.50 points, CI -5.73 to -3.26; P < 0.00001) (PDQ39) Summary index Data on the Summary Index of the PDQ-39 were available from seven trials for eight comparisons within all six physiotherapy interventions. (Note: Hackney 2009 contributed data to both the dance and martial arts comparisons.) Four hundred five participants were included in this analysis. No difference between treatment arms was observed in patient-rated quality of life after physiotherapy intervention (-0.38 points, 95% CI -2.58 to 1.81; P =0.73). Mobility Data on the mobility domain of the PDQ-39 were available from two trials for three comparisons within three physiotherapy interventions (general physiotherapy, dance, and martial arts). (Note: Hackney 2009 contributed data to both the dance and martial arts comparisons.) One hundred five participants were included in this analysis. No difference in the PDQ-39 mobility score was observed between the two treatment arms (-1.43, 95% CI -8.03 to 5.18; P = 0.67).	
Full citation Amano,S., Nocera,J.R., Vallabhajosula, S., Juncos,J.L.,	Sample size N= 45 patients with idiopathic PD across 2	Details All pts in both projects visited the laboratory	Results No baseline differences between groups in any score No statistically significant differences between groups in any measure of: GI, gait, UPDRS	Overall Risk of Bias **Author's judgement** / **Description**

Study details	Participants	Methods	Results	Comments
Gregor,R.J., Waddell,D.E., Wolf,S.L., Hass,C.J., The effect of Tai Chi exercise on gait initiation and gait performance in persons with Parkinson's disease, Parkinsonism and Related Disorders.19 (11) (pp 955-960), 2013.Date of Publication: November 2013., 955-960, 2013 Ref Id 230423 Country/ies where the study was carried out USA Study type RCT Aim of the study To investigate the effect of tai	centres project a: 21 PD patients ; Tai chi n = 12, Qi-Gong n=9 project b: 24 PD patients ; Tai chi n=15, non-contact control N=9 Inclusion criteria all participants were diagnosed with idiopathic PD by a fellowship trained movement disorders neurologist using standard criteria Exclusion criteria Participants were excluded if they had:	both before and after the assigned intervention period for evaluations of their gait initiation (GI), gait performance, parkinsonian disabilities all pts tested at same time of day for both pre and post intervention evaluations at a time when they reported they were full responding to their antiparkinsonian medication evaluators were blind to group assignment in both trials pts performed at least 5 GI	<table><tr><td>test</td><td>intervention</td><td>pts</td><td>pre train</td><td>post train</td></tr><tr><td>GI S1 DisAP (cm)</td><td>Tai chi</td><td>15</td><td>2.03 (1.53)</td><td>1.55 (1.40)</td></tr><tr><td>GI S1 DisMl (cm)</td><td>control</td><td>9</td><td>2.02 (1.24)</td><td>2.12 (1.32)</td></tr><tr><td>GI S1 DisAP (cm)</td><td>Tai chi</td><td>15</td><td>2.16 (1.15)</td><td>1.63 (1.13)</td></tr><tr><td>GI S1 DisMl (cm)</td><td>control</td><td>9</td><td>1.42 (1.33)</td><td>1.97 (1.41)</td></tr><tr><td>Gait step length (m)</td><td>Tai chi</td><td>15</td><td>0.54 (0.13)</td><td>0.55 (0.11)</td></tr><tr><td>Gait step length (m)</td><td>control</td><td>9</td><td>0.58 (0.06)</td><td>0.59 (0.06)</td></tr><tr><td>UPDRS</td><td>Tai chi</td><td>15</td><td>23.1 (6.0)</td><td>23.4 (4.7)</td></tr><tr><td>UPDRS</td><td>control</td><td>9</td><td>23.1 (4.8)</td><td>22.0 (5.6)</td></tr></table>	<table><tr><td>Adequate sequence generation ?</td><td>Yes</td><td>Randomised</td></tr><tr><td>Allocation concealment?</td><td>N/A</td><td>N/A</td></tr><tr><td>Blinding? All outcomes</td><td>Yes</td><td>Assessor-blinded</td></tr></table>

Study details	Participants	Methods	Results	Comments
chi exercise on dynamic postural control during gait initiation and gait performance in persons with idiopathic PD , and to determine if benefits could be replicated in 2 different environments, as complementary projects Study dates First received Oct 2012, accepted June 2013. No further information on when data was collected. Source of funding This study was supported by a National institutes of health grant	any history or evidence of neurological deficit other than PD dementia - determined by MMSe < 26 inability to walk independently previous training in tai chi (TC) or current participation in other movement exercise training for >20min per week. inability to understand the protocol	trials at a self-selected pace in both projects pts performed a minimum of 8 gait trials at self-selected speed in response to verbal signal Interventions Tai Chi (TC) individuals who were randomly assigned to TC participated in 60min TC sessions for 16 consecutive weeks TC group 1 - practiced TC forms 2 x per week TC group 2 - practiced TC moved 3x per		

Study details	Participants	Methods	Results	Comments
		week exercise groups kept small (<5pts) to promote intensive TC master/student interaction TC intervention consisted of 1st 8 movements of Yang-style short forms progression of exercises involved a gradual reduction of the base of standing support until a single limb is achieved, increased body and trunk rotation, and reciprocal arm movements that incorporate controlled breathing		

Study details	Participants	Methods	Results	Comments
		Qui Gong control group 1 practiced 60min Qui Gong meditation in stillness - involves a series of exercises in energy discipline involving deep, long, periods of intense meditation non-contact control group 2 individuals assigned to nc control did not participate in any intervention		

Physiotherapy vs usual care n=19 (reruns)

Full citation	Methods	Participants	Interventions	Outcomes	Risk of bias
Canning,C.G.,	Randomi		Intervention: semi-	Primary	

<table>
<tr><th>Full citation</th><th>Methods</th><th>Participants</th><th>Interventions</th><th>Outcomes</th><th>Risk of bias</th></tr>
<tr>
<td>Allen,N.E., Dean,C.M., Goh,L., Fung,V.S., Home-based treadmill training for individuals with Parkinson's disease: a randomized controlled pilot trial, Clinical Rehabilitation, 26, 817-826, 2012</td>
<td>sed controlled pilot trial (6 weeks)</td>
<td>
<table>
<tr><td></td><td>Intervention</td><td>Control</td></tr>
<tr><td>Participants</td><td colspan="2">Idiopathic PD patients</td></tr>
<tr><td>Number randomised</td><td>10</td><td>10</td></tr>
<tr><td>Mean (SD) age (years)</td><td>60.7(5.9)</td><td>62.9(9.9)</td></tr>
<tr><td>Number of males (n (%))</td><td>5(50)</td><td>6(60)</td></tr>
<tr><td>Mean (SD) duration of PD (years)</td><td>6.1(4.0)</td><td>5.2(4.1)</td></tr>
</table>
</td>
<td>supervised home-based programme of treadmill walking for 20-40 minutes, four time a week.
Control: Usual care.</td>
<td>outcome: Walking capacity (6-minute walk test distance).
Secondary outcomes: exercise heart rate, PDQ-39, walking speed, walking speed while performing a concurrent task(s), walking consistency during the 6 minute walk test, UPDRS III, and fatigue.</td>
<td>
<table>
<tr><td></td><td>Author's judgement</td><td>Description</td></tr>
<tr><td>Adequate sequence generation?</td><td>Yes</td><td>Randomised</td></tr>
<tr><td>Allocation concealment?</td><td>N/A</td><td>N/A</td></tr>
<tr><td>Blinding? All outcomes</td><td>Yes</td><td>Assessor-blinded</td></tr>
</table>
</td>
</tr>
<tr>
<td>Canning,C.G., Sherrington,C., Lord,S.R., Close,J.C., Heritier,S., Heller,G.Z., Howard,K., Allen,N.E., Latt,M.D., Murray,S.M.,</td>
<td>Randomised controlled trial (6 months)</td>
<td>
<table>
<tr><td></td><td>Intervention</td><td>Control</td></tr>
<tr><td>Participants</td><td colspan="2">Community-dwelling people with PD</td></tr>
<tr><td>Number randomised</td><td>115</td><td>116</td></tr>
</table>
</td>
<td>Intervention: 40 to 60 minutes of progressive balance and lower limb strengthening exercises 3 times a week and cueing strategies to reduce freezing</td>
<td>Primary outcome: Fall rates and proportion of fallers during the intervention period.
Secondary</td>
<td>
<table>
<tr><td></td><td>Author's judgement</td><td>Description</td></tr>
<tr><td>Adequate sequence generation</td><td>Yes</td><td>Randomised</td></tr>
</table>
</td>
</tr>
</table>

<table>
<tr><th>Full citation</th><th>Methods</th><th>Participants</th><th>Interventions</th><th>Outcomes</th><th>Risk of bias</th></tr>
<tr>
<td>O'Rourke,S.D., Paul,S.S., Song,J., Fung,V.S., Exercise for falls prevention in Parkinson disease: a randomized controlled trial, Neurology, 84, 304-312, 2015</td>
<td></td>
<td>
<table>
<tr><td>Mean (SD) age (years)</td><td>71.4(8.1)</td><td>69.9(9.3)</td></tr>
<tr><td>Number of males (n (%))</td><td>69(60)</td><td>66(57)</td></tr>
<tr><td>Mean (SD) duration of PD (years)</td><td>7.5(5.8)</td><td>8.3(6.0)</td></tr>
</table>
</td>
<td>of gait for participants reporting freezing.
Control: Usual care from their medical practitioner and community services.</td>
<td>outcome: Physical (balance, mobility, freezing of gait, habitual physical activity), psychological (fear of falling, affect), and quality of life measures.</td>
<td>
<table>
<tr><td>?</td><td></td><td></td></tr>
<tr><td>Allocation concealment?</td><td>N/A</td><td>N/A</td></tr>
<tr><td>Blinding? All outcomes</td><td>Yes</td><td>Assessor-blinded</td></tr>
</table>
</td>
</tr>
<tr>
<td>Choi,H.J., Garber,C.E., Jun,T.W., Jin,Y.S., Chung,S.J., Kang,H.J., Therapeutic effects of Tai Chi in patients with Parkinson's disease, ISRN Neurology, 1, -, 2013</td>
<td>Randomised controlled trial (12 weeks)</td>
<td>
<table>
<tr><td></td><td>Intervention</td><td>Control</td></tr>
<tr><td>Participants</td><td colspan="2">Idiopathic PD patients</td></tr>
<tr><td>Number randomised</td><td>11</td><td>9</td></tr>
<tr><td>Mean (SD) age (years)</td><td>60.81(7.6)</td><td>65.54(6.8)</td></tr>
<tr><td>Mean (SD) duration of PD (years)</td><td>5.2(2.7)</td><td>5.2(2.7)</td></tr>
</table>
</td>
<td>Intervention: Therapeutic Tai Chi
Control: No exercise</td>
<td>Physical function (lateral stance, agility, tandem gait, timed up and go, and 6 minute walk) and UPDRS I-III</td>
<td>
<table>
<tr><td></td><td>Author's judgement</td><td>Description</td></tr>
<tr><td>Adequate sequence generation?</td><td>Yes</td><td>Randomised</td></tr>
<tr><td>Allocation concealment?</td><td>N/A</td><td>N/A</td></tr>
<tr><td>Blinding? All outcomes</td><td>Yes</td><td>Assessor-blinded</td></tr>
</table>
</td>
</tr>
<tr>
<td>Cholewa,J., Boczarska-Jedynak,M.FAU,</td>
<td>Randomised controlled</td>
<td>
<table>
<tr><td></td><td>Intervention</td><td>Control</td></tr>
</table>
</td>
<td>Intervention: Rehabilitation exercises twice a</td>
<td>UPDRS I-III
Schwab-England</td>
<td></td>
</tr>
</table>

<table>
<tr><th>Full citation</th><th>Methods</th><th>Participants</th><th>Interventions</th><th>Outcomes</th><th>Risk of bias</th></tr>
<tr>
<td>Opala,G., Influence of physiotherapy on severity of motor symptoms and quality of life in patients with Parkinson disease, Neurol Neurochir Pol., 47, 256-262, 2013</td>
<td>trial (12 weeks)</td>
<td>
<table>
<tr><td>Participants</td><td colspan="2">Idiopathic PD patients</td></tr>
<tr><td>Number randomised</td><td>40</td><td>30</td></tr>
<tr><td>Mean (SD) age (years)</td><td>70.2(5.75)</td><td>70.17(5.38)</td></tr>
<tr><td>Number of males (n)</td><td>27</td><td>19</td></tr>
<tr><td>Mean (SD) duration of PD (years)</td><td>8.03(3.41)</td><td>7.33(2.2)</td></tr>
</table>
</td>
<td>week for 60 minutes.
Control: No exercise.</td>
<td>scale
PDQ-39</td>
<td>
<table>
<tr><td></td><td>Author's judgement</td><td>Description</td></tr>
<tr><td>Adequate sequence generation?</td><td>Yes</td><td>Randomised</td></tr>
<tr><td>Allocation concealment?</td><td>N/A</td><td>N/A</td></tr>
<tr><td>Blinding? All outcomes</td><td>Not reported</td><td>Not reported</td></tr>
</table>
</td>
</tr>
<tr>
<td>Clarke,C.E., Patel,S., Ives,N., Rick,C.E., Dowling,F., Woolley,R., Wheatley,K., Walker,M.F., Sackley,C.M., Physiotherapy and Occupational Therapy vs No Therapy in Mild to Moderate Parkinson Disease: A Randomized Clinical Trial, JAMA Neurol, 73, 291-299, 2016</td>
<td>Multicenter, randomised, open-label, parallel group, controlled trial (15 months).</td>
<td>
<table>
<tr><td></td><td>Intervention</td><td>Control</td></tr>
<tr><td>Participants</td><td colspan="2">Idiopathic PD patients with limitations in ADL</td></tr>
<tr><td>Number randomised</td><td>381</td><td>381</td></tr>
<tr><td>Mean (SD) age (years)</td><td>70(9.1)</td><td>70(9.3)</td></tr>
<tr><td>Number of males (n (%))</td><td>240(63)</td><td>258(68)</td></tr>
<tr><td>Mean (SD) duration of PD (years)</td><td>4.5(4.9)</td><td>4.6(4.5)</td></tr>
</table>
</td>
<td>Intervention: Individualised combined physiotherapy and occupational therapy.
Control: No therapy.</td>
<td>Primary outcome: Total NEADL score at 3 months after randomisation.
Secondary outcomes: HrQoL measures (PDQ-39 and EuroQoL-5D), adverse events and caregiver QoL.</td>
<td>
<table>
<tr><td></td><td>Author's judgement</td><td>Description</td></tr>
<tr><td>Adequate sequence generation?</td><td>Yes</td><td>Randomised (computer generated)</td></tr>
<tr><td>Allocation concealment?</td><td>N/A</td><td>N/A</td></tr>
<tr><td>Blinding? All outcomes</td><td>Unclear</td><td>Not reported</td></tr>
</table>
</td>
</tr>
<tr>
<td>Conradsson,D.,</td>
<td>Randomi</td>
<td></td>
<td>Intervention:</td>
<td>Primary</td>
<td></td>
</tr>
</table>

<table>
<tr><th>Full citation</th><th>Methods</th><th>Participants</th><th>Interventions</th><th>Outcomes</th><th>Risk of bias</th></tr>
<tr>
<td>Lofgren,N., Nero,H., Hagstromer,M., Stahle,A., Lokk,J., Franzen,E., The Effects of Highly Challenging Balance Training in Elderly With Parkinson's Disease: A Randomized Controlled Trial, Neurorehabil.Neural Repair, 29, 827-836, 2015</td>
<td>sed controlled trial (10 weeks)</td>
<td>
<table>
<tr><td></td><td>Intervention</td><td>Control</td></tr>
<tr><td>Participants</td><td colspan="2">Community-dwelling idiopathic PD patients</td></tr>
<tr><td>Number randomised</td><td>51</td><td>49</td></tr>
<tr><td>Mean (SD) age (years)</td><td>72.9(6.0)</td><td>73.6(5.3)</td></tr>
<tr><td>Number of males (n (%))</td><td>28(60)</td><td>23(51)</td></tr>
<tr><td>Mean (SD) duration of PD (years)</td><td>6.0(5.1)</td><td>5.6(5.0)</td></tr>
</table>
</td>
<td>HiBalance program, a highly challenging balance training regimen that incorporates both dual-tasking and PD-specific balance components.
Control: Usual care</td>
<td>outcomes: Balance performance (Mini-BESTest), gait velocity (during normal and dual-task gait) and concerns about falling (Falls Efficacy Scale-International).
Secondary outcomes: Performance of a cognitive task while walking, physical activity level (average steps per day), and ADL.</td>
<td>
<table>
<tr><td></td><td>Author's judgement</td><td>Description</td></tr>
<tr><td>Adequate sequence generation?</td><td>Yes</td><td>Randomised</td></tr>
<tr><td>Allocation concealment?</td><td>N/A</td><td>N/A</td></tr>
<tr><td>Blinding? All outcomes</td><td>Unclear</td><td>Not reported</td></tr>
</table>
</td>
</tr>
<tr>
<td>Cugusi,L., Solla,P., Serpe,R., Carzedda,T., Piras,L., Oggianu,M., Gabba,S., Di,Blasio A., Bergamin,M.,</td>
<td>Randomised controlled trial (12 weeks)</td>
<td>
<table>
<tr><td></td><td>Intervention</td><td>Control</td></tr>
<tr><td>Participants</td><td colspan="2">Idiopathic PD patients</td></tr>
</table>
</td>
<td>Intervention: Nordic walking program consisting of exercise group sessions</td>
<td>Motor and non-motor symptoms, functional performances and body</td>
<td>
<table>
<tr><td></td><td>Author's judgement</td><td>Description</td></tr>
<tr><td>Adequate</td><td>Yes</td><td>Randomis</td></tr>
</table>
</td>
</tr>
</table>

<table>
<tr><th>Full citation</th><th>Methods</th><th>Participants</th><th>Interventions</th><th>Outcomes</th><th>Risk of bias</th></tr>
<tr>
<td>Cannas,A., Marrosu,F., Mercuro,G., Effects of a Nordic Walking program on motor and non-motor symptoms, functional performance and body composition in patients with Parkinson's disease, Neurorehabilitation, 37, 245-254, 2015</td>
<td></td>
<td>
<table>
<tr><td>Number randomised</td><td>10</td><td>10</td></tr>
<tr><td>Mean (SD) age (years)</td><td>68.1(8.7)</td><td>66.6(7.3)</td></tr>
<tr><td>Number of males (n (%))</td><td>8(80)</td><td>8(80)</td></tr>
<tr><td>Mean (SD) duration of PD (years)</td><td>7(2)</td><td>7(4)</td></tr>
</table>
</td>
<td>Control: Conventional care</td>
<td>composition</td>
<td>
<table>
<tr><td>sequence generation?</td><td></td><td>ed</td></tr>
<tr><td>Allocation concealment?</td><td>N/A</td><td>N/A</td></tr>
<tr><td>Blinding? All outcomes</td><td>Unclear</td><td>Not reported</td></tr>
</table>
</td>
</tr>
<tr>
<td>Frazzitta,G., Maestri,R., Bertotti,G., Riboldazzi,G., Boveri,N., Perini,M., Uccellini,D., Turla,M., Comi,C., Pezzoli,G., Ghilardi,M.F., Intensive rehabilitation treatment in early Parkinson's disease: A randomized pilot study with a 2-year follow-up, Neurorehabilitation and Neural Repair.29 (2) (pp 123-131), 2015.Date of Publication: 02 Mar 2015., 123-131, 2015</td>
<td>Randomised control pilot study (2 years)</td>
<td>
<table>
<tr><td></td><td>Intervention</td><td>Control</td></tr>
<tr><td>Participants</td><td colspan="2">Newly diagnosed PD patients on rasagiline</td></tr>
<tr><td>Number randomised</td><td>20</td><td>20</td></tr>
<tr><td>Mean (SD) age (years)</td><td>69(6)</td><td>68(8)</td></tr>
<tr><td>Number of males (%)</td><td>45%</td><td>45%</td></tr>
</table>
</td>
<td>Intervention: MIRT - two 28 days multidisciplinary intensive rehabilitation treatments, at 1 year interval.
Control: No exercise therapy.</td>
<td>UPDRS II and III
6-minute walking test
Timed Up-and-Go test
PD disability scale (PDDS)
L-dopa equivalents</td>
<td>
<table>
<tr><td></td><td>Author's judgement</td><td>Description</td></tr>
<tr><td>Adequate sequence generation?</td><td>Yes</td><td>Randomised (computer-generated)</td></tr>
<tr><td>Allocation concealment?</td><td>N/A</td><td>N/A</td></tr>
<tr><td>Blinding? All outcomes</td><td>Yes</td><td>Assessor-blinded</td></tr>
</table>
</td>
</tr>
<tr>
<td>Ganesan, M.,</td>
<td>Randomi</td>
<td></td>
<td>Intervention 1:</td>
<td>Outcomes</td>
<td></td>
</tr>
</table>

<table>
<tr><th>Full citation</th><th>Methods</th><th>Participants</th><th>Interventions</th><th>Outcomes</th><th>Risk of bias</th></tr>
<tr>
<td>Sathyaprabha, T. N., Pal, P. K., Gupta, A., Partial Body Weight-Supported Treadmill Training in Patients With Parkinson Disease: Impact on Gait and Clinical Manifestation, 96, 1557-65, 2015</td>
<td>sed trial (4 weeks)</td>
<td>
<table>
<tr><td></td><td>Intervention</td><td>Control</td></tr>
<tr><td>Participants</td><td colspan="2">Idiopathic PD patients</td></tr>
<tr><td>Number randomised</td><td>20</td><td>20</td></tr>
<tr><td>Mean (SD) age (years)</td><td>58.15(8.7)</td><td></td></tr>
</table>
</td>
<td>20% weight-supported treadmill training for 30mins/day, 4 days/week
Intervention 2: Conventional gait training for 30 mins/day, 4 days/week
Placebo: No exercise</td>
<td>were evaluated in their best on status:
UPDRS and its subscores
Gait was measured by 2 minutes of treadmill walking and the 10-m walk test</td>
<td>
<table>
<tr><td></td><td>Author's judgement</td><td>Description</td></tr>
<tr><td>Adequate sequence generation?</td><td>Yes</td><td>Randomised</td></tr>
<tr><td>Allocation concealment?</td><td>N/A</td><td>N/A</td></tr>
<tr><td>Blinding? All outcomes</td><td>Unclear</td><td>Not reported</td></tr>
</table>
</td>
</tr>
<tr>
<td>Gao,Q., Leung,A., Yang,Y., Wei,Q., Guan,M., Jia,C., He,C., Effects of Tai Chi on balance and fall prevention in Parkinson's disease: a randomized controlled trial, Clin Rehabil, 28, 748-753, 2014</td>
<td>Randomised control trial (6 months)</td>
<td>
<table>
<tr><td></td><td>Intervention</td><td>Control</td></tr>
<tr><td>Participants</td><td colspan="2">Idiopathic PD patients</td></tr>
<tr><td>Number randomised</td><td>37</td><td>39</td></tr>
<tr><td>Mean (SD) age (years)</td><td>69.54(7.32</td><td>68.28(8.53)</td></tr>
<tr><td>Number of males (n (%))</td><td>23(62.16)</td><td>27(69.23)</td></tr>
<tr><td>Mean (SD) duration of PD (years)</td><td>9.15(8.58)</td><td>8.37(8.24)</td></tr>
</table>
</td>
<td>Intervention: 24-form Yang style Tai Chi exercise for 60 minutes, 3 times a week and lasted 12 weeks
Control:
No intervention</td>
<td>Berg Balance Scale
UPDRS III
Timed Up-and-Go
Occurrences of falls</td>
<td>
<table>
<tr><td></td><td>Author's judgement</td><td>Description</td></tr>
<tr><td>Adequate sequence generation?</td><td>Yes</td><td>Randomised (random number table)</td></tr>
<tr><td>Allocation concealment?</td><td>N/A</td><td>N/A</td></tr>
<tr><td>Blinding? All outcomes</td><td>Yes</td><td>Assessor-blinded</td></tr>
</table>
</td>
</tr>
<tr>
<td>Hashimoto,H.,</td>
<td>Quasi-</td>
<td></td>
<td>Intervention 1:</td>
<td>Motor</td>
<td></td>
</tr>
</table>

<table>
<tr><th>Full citation</th><th>Methods</th><th>Participants</th><th>Interventions</th><th>Outcomes</th><th>Risk of bias</th></tr>
<tr>
<td>Takabatake,S., Miyaguchi,H., Nakanishi,H., Naitou,Y., Effects of dance on motor functions, cognitive functions, and mental symptoms of Parkinson's disease: a quasi-randomized pilot trial, Complement.Ther Med, 23, 210-219, 2015</td>
<td>randomised pilot trial (12 weeks)</td>
<td>
<table>
<tr><td></td><td>Intervention 1</td><td>Intervention 2</td><td>Control</td></tr>
<tr><td>Participants</td><td colspan="3">Mild-moderate PD patients</td></tr>
<tr><td>Number randomised</td><td>15</td><td>17</td><td>14</td></tr>
<tr><td>Mean (SD) age (years)</td><td>67.9(7.0)</td><td>62.7(14.9)</td><td>69.7(4.0)</td></tr>
<tr><td>Number of males (n)</td><td>3</td><td>2</td><td>7</td></tr>
<tr><td>Mean (SD) duration of PD (years)</td><td>6.3(4.6)</td><td>7.8(6.2)</td><td>6.9(4.0)</td></tr>
</table>
</td>
<td>Dance group - one 60mins session/week
Intervention 2: PD exercise group - one 60mins session/week
Control: No intervention</td>
<td>function (Timed-up-and-Go test and Berg Balance Scale)
Cognitive function (Frontal Assessment Battery at bedside and Mental Rotation Task)
Mental symptoms (Apathy Scale and Self-rating Depression Scale)
General PD assessment (UPDRS)</td>
<td>
<table>
<tr><td></td><td>Author's judgement</td><td>Description</td></tr>
<tr><td>Adequate sequence generation?</td><td>Yes</td><td>Randomised (using a coin)</td></tr>
<tr><td>Allocation concealment?</td><td>N/A</td><td>N/A</td></tr>
<tr><td>Blinding? All outcomes</td><td>Yes</td><td>Assessor-blinded</td></tr>
</table>
</td>
</tr>
<tr>
<td>Landers,M.R., Hatlevig,R.M., Davis,A.D., Richards,A.R., Rosenlof,L.E., Does attentional focus during balance training in people with Parkinson's</td>
<td>Randomised controlled trial (12 weeks)</td>
<td>
<table>
<tr><td></td><td>Intervention 1</td><td>Intervention 2</td><td>Intervention 3</td><td>Control</td></tr>
<tr><td>Participants</td><td colspan="4">Idiopathic PD patients</td></tr>
<tr><td>Number randomi</td><td>10</td><td>11</td><td>10</td><td>10</td></tr>
</table>
</td>
<td>Intervention 1: Balance training + external focus instructions, three times per week, approximately 45 minutes per day, for 4 weeks.
Intervention 2:</td>
<td>Sensory Organisation Test
Berg Balance Scale
Self-Selected Gait Velocity
Dynamic Gait</td>
<td>
<table>
<tr><td></td><td>Author's judgement</td><td>Description</td></tr>
<tr><td>Adequate sequence generation</td><td>Yes</td><td>Randomised (random</td></tr>
</table>
</td>
</tr>
</table>

<table>
<tr><th>Full citation</th><th>Methods</th><th>Participants</th><th>Interventions</th><th>Outcomes</th><th>Risk of bias</th></tr>
<tr>
<td>disease affect outcome? A randomised controlled clinical trial, Clin Rehabil, 30, 53-63, 2016</td>
<td></td>
<td>
<table>
<tr><td>sed</td><td></td><td></td><td></td><td></td></tr>
<tr><td>Mean (SD) age (years)</td><td>72.2(4.4)</td><td>70.2(4.4)</td><td>70.1(9.5)</td><td>74.3(8.8)</td></tr>
<tr><td>Number of males (n)</td><td>4</td><td>8</td><td>7</td><td>6</td></tr>
</table>
</td>
<td>Balance training + internal focus instructions, three times per week, approximately 45 minutes per day, for 4 weeks.
Intervention 3: Balance training + no attentional focus instructions, three times per week, approximately 45 minutes per day, for 4 weeks.
Control: No balance training</td>
<td>Index Activities-Specific Balance Confidence Scale
Obstacle course completion time</td>
<td>
<table>
<tr><td>?</td><td></td><td>numbers table)</td></tr>
<tr><td>Allocation concealment?</td><td>N/A</td><td>N/A</td></tr>
<tr><td>Blinding? All outcomes</td><td>No</td><td></td></tr>
</table>
</td>
</tr>
<tr>
<td>Liao,Y.Y., Yang,Y.R., Cheng,S.J., Wu,Y.R., Fuh,J.L., Wang,R.Y., Virtual Reality-Based Training to Improve Obstacle-Crossing Performance and Dynamic Balance in Patients With Parkinson's Disease, Neurorehabil.Neural Repair, 29, 658-667, 2015</td>
<td>Randomised controlled trial (6 weeks)</td>
<td>
<table>
<tr><td></td><td>Intervention 1</td><td>Intervention 2</td><td>Control</td></tr>
<tr><td>Participants</td><td colspan="3">Idiopathic PD patients</td></tr>
<tr><td>Number randomised</td><td>12</td><td>12</td><td>12</td></tr>
<tr><td>Mean (SD) age (years)</td><td>67.3(7.1)</td><td>65.1(6.7)</td><td>64.6(8.6)</td></tr>
<tr><td>Number of males (n)</td><td>6</td><td>6</td><td>5</td></tr>
</table>
</td>
<td>Intervention 1: Virtual reality-based Wii Fit exercise (45 mins) using both the Wii Fit Plus gaming system and Wii Fit balance board + additional treadmill training (15 mins) - 12 sessions (2 sessions per week)
Intervention 2: Traditional</td>
<td>Primary outcomes: Obstacle crossing performance (crossing velocity, stride length, and vertical toe obstacle clearance) and dynamic balance (maximal excursion, movement</td>
<td>
<table>
<tr><td></td><td>Author's judgement</td><td>Description</td></tr>
<tr><td>Adequate sequence generation?</td><td>Yes</td><td>Randomised</td></tr>
<tr><td>Allocation concealment?</td><td>N/A</td><td>N/A</td></tr>
<tr><td>Blinding? All</td><td>Yes</td><td>Assessor-blinded</td></tr>
</table>
</td>
</tr>
</table>

<table>
<tr><th>Full citation</th><th>Methods</th><th>Participants</th><th>Interventions</th><th>Outcomes</th><th>Risk of bias</th></tr>
<tr>
<td></td>
<td></td>
<td>
<table>
<tr><td>Mean (SD) duration of PD (years)</td><td>7.9(2.7)</td><td>6.9(2.8)</td><td>6.4(3.0)</td></tr>
</table>
</td>
<td>exercise involving 10 mins of stretching exercises, 15 mins of strengthening exercises,
20 mins of balance exercises + additional treadmill training (15 mins) - 12 sessions (2 sessions per week)
Control: Only fall prevention education</td>
<td>velocity, and directional control measured by the limits-of-stability test).
Secondary outcomes: Sensory organisation test, PDQ-39, fall efficacy scale (FES-I), and Timed Up-and-Go test.</td>
<td>
<table>
<tr><td>outcomes</td><td></td><td></td></tr>
</table>
</td>
</tr>
<tr>
<td>Ni,M., Signorile,J.F., Balachandran,A., Potiaumpai,M., Power training induced change in bradykinesia and muscle power in Parkinson's disease, Parkinsonism.Relat.Disord., 23, 37-44, 2016</td>
<td>Randomised controlled trial (3 months)</td>
<td>
<table>
<tr><td></td><td>Intervention</td><td>Control</td></tr>
<tr><td>Participants</td><td colspan="2">Idiopathic PD patients</td></tr>
<tr><td>Number randomised</td><td>14</td><td>10</td></tr>
<tr><td>Mean (SD) age (years)</td><td>71.6(6.6)</td><td>74.9(8.3)</td></tr>
<tr><td>Number of males (n)</td><td>9</td><td>4</td></tr>
<tr><td>Mean (SD) duration of PD (years)</td><td>6.6(4.4)</td><td>5.9(6.2)</td></tr>
</table>
</td>
<td>Intervention: Power based resistance training (PWT) involving the use of evolving optimal loads on 11 pneumatic machines. Each session included 3 circuits of 10-12 repetitions on each machine, twice weekly, for 12 weeks. In addition, two 2-</td>
<td>Upper and lower limb bradykinesia scores, one repetition maximums and peak powers on biceps curl, chest press, leg press, hip abduction and seated calf, and QoL.</td>
<td>
<table>
<tr><td></td><td>Author's judgement</td><td>Description</td></tr>
<tr><td>Adequate sequence generation?</td><td>Yes</td><td>Randomised</td></tr>
<tr><td>Allocation concealment?</td><td>N/A</td><td>N/A</td></tr>
<tr><td>Blinding? All</td><td>Unclear</td><td>Not reported</td></tr>
</table>
</td>
</tr>
</table>

<table>
<tr><th>Full citation</th><th>Methods</th><th>Participants</th><th>Interventions</th><th>Outcomes</th><th>Risk of bias</th></tr>
<tr><td></td><td></td><td></td><td>week combined balance and agility drills were incorporated into the PWT program - 3 months, 2 sessions/week.
Control: 1 hr non-exercise, health education classes, once per month over 12 weeks.</td><td></td><td><table><tr><td>outcomes</td><td></td><td></td></tr></table></td></tr>
<tr><td>Ni,M., Signorile,J.F., Mooney,K., Balachandran,A., Potiaumpai,M., Luca,C., Moore,J.G., Kuenze,C.M., Eltoukhy,M., Perry,A.C., Comparative Effect of Power Training and High-Speed Yoga on Motor Function in Older Patients With Parkinson Disease, Arch Phys Med Rehabil, 97, 345-354, 2016</td><td>Randomised controlled trial (12 weeks)</td><td><table><tr><td></td><td>Intervention 1</td><td>Intervention 2</td><td>Control</td></tr><tr><td>Participants</td><td colspan="3">Idiopathic PD patients</td></tr><tr><td>Number randomised</td><td>14</td><td>13</td><td>10</td></tr><tr><td>Mean (SD) age (years)</td><td>71.6(6.6)</td><td>71.2(6.5)</td><td>74.9(8.3)</td></tr><tr><td>Number of males (n)</td><td>9</td><td>11</td><td>4</td></tr><tr><td>Mean (SD) duration of PD (years)</td><td>6.6(4.4)</td><td>6.9(6.3)</td><td>5.9(6.2)</td></tr></table></td><td>Intervention 1: Power based training (PWT) (high speed, low resistance) using evolving optimal loads on 11 pneumatic machines. Each session included 3 circuits of 10-12 repetitions, twice per week, for 12 weeks (24 sessions). Upper and lower body exercises were alternated during the circuits. In addition, two 2-weeks combined</td><td>UPDRS III
Berg Balance Scale
Mini-Balance Evaluation Systems Test
Timed Up-and-Go
Functional reach
Single leg stance
Postural sway test
10-m usual and maximal walking speed tests
1 repetition maximum</td><td><table><tr><td></td><td>Author's judgement</td><td>Description</td></tr><tr><td>Adequate sequence generation?</td><td>Yes</td><td>Randomised (block randomisation)</td></tr><tr><td>Allocation concealment?</td><td>N/A</td><td>N/A</td></tr><tr><td>Blinding? All outcomes</td><td>Unclear</td><td>Not reported</td></tr></table></td></tr>
</table>

<table>
<tr><th>Full citation</th><th>Methods</th><th>Participants</th><th>Interventions</th><th>Outcomes</th><th>Risk of bias</th></tr>
<tr><td></td><td></td><td></td><td>balance and agility drills were incorporated into the PWT program.
Intervention 2: Power Vinyasa yoga designed to improve movement speed, muscle strength and power and balance specific to PD-related decrements. 1 hour per class, twice per week for 12 weeks (24 classes)
Control: 1 hour non-exercise, health education class, once per month over 12 weeks.</td><td>Peak power for leg press</td><td></td></tr>
<tr><td>Nocera,J.R., Amano,S., Vallabhajosula,S., Hass,C.J., Tai Chi Exercise to Improve Non-Motor Symptoms of Parkinson's Disease, J Yoga.Phys Ther, 3, -, 2013</td><td>Randomised controlled trial (16 weeks)</td><td><table><tr><td></td><td>Intervention</td><td>Control</td></tr><tr><td>Participants</td><td colspan="2">Community-dwelling idiopathic PD patients</td></tr><tr><td>Number randomised</td><td>15</td><td>6</td></tr><tr><td>Mean (SD) age</td><td>66(11)</td><td>65(7)</td></tr></table></td><td>Intervention: Tai Chi, 60 minutes, 3 times per week
Control: No intervention</td><td>Indices of cognitive-executive function including visuomotor tracking and attention, selective attention,</td><td><table><tr><td></td><td>Author's judgement</td><td>Description</td></tr><tr><td>Adequate sequence generation?</td><td>Yes</td><td>Randomised</td></tr></table></td></tr>
</table>

<table>
<tr><th>Full citation</th><th>Methods</th><th>Participants</th><th>Interventions</th><th>Outcomes</th><th>Risk of bias</th></tr>
<tr>
<td></td>
<td></td>
<td>
<table>
<tr><td>(years)</td><td></td><td></td></tr>
<tr><td>Number of males (n)</td><td>7</td><td>4</td></tr>
<tr><td>Mean (SD) duration of PD (years)</td><td>8.1(5.4)</td><td>6.8(1.3)</td></tr>
</table>
</td>
<td></td>
<td>working memory, inhibition, processing speed and task switching.
PDQ-39
Tinetti's Falls Efficacy Scale</td>
<td>
<table>
<tr><td>Allocation concealment?</td><td>N/A</td><td>N/A</td></tr>
<tr><td>Blinding? All outcomes</td><td>Yes</td><td>Assessor-blinded</td></tr>
</table>
</td>
</tr>
<tr>
<td>Park,A., Zid,D., Russell,J., Malone,A., Rendon,A., Wehr,A., Li,X., Effects of a formal exercise program on Parkinson's disease: a pilot study using a delayed start design, Parkinsonism Relat Disord., 20, 106-111, 2014</td>
<td>Randomised pilot delayed-start design study (48 weeks)</td>
<td>
<table>
<tr><td></td><td>Intervention</td><td>Control</td></tr>
<tr><td>Participants</td><td colspan="2">Idiopathic PD patients</td></tr>
<tr><td>Number randomised</td><td>16</td><td>15</td></tr>
<tr><td>Mean (SD) age (years)</td><td>59.8(6.3)</td><td>60.1(6.6)</td></tr>
<tr><td>Number of males (n (%))</td><td>10(63)</td><td>10(67)</td></tr>
</table>
</td>
<td>Intervention: Early start group involving rigorous formal group exercise for 1 hour, 3 times/week for 48 weeks.
Control: Delayed-start group participated in the identical exercise program as the early start group, from weeks 24-48.</td>
<td>UPDRS
Walking Test (Get Up-and-Go)
Tinetti Mobility Test
PDQ-39
Beck Depression Inventory</td>
<td>
<table>
<tr><td></td><td>Author's judgement</td><td>Description</td></tr>
<tr><td>Adequate sequence generation?</td><td>Yes</td><td>Randomised</td></tr>
<tr><td>Allocation concealment?</td><td>N/A</td><td>N/A</td></tr>
<tr><td>Blinding? All outcomes</td><td>Unclear</td><td>Not reported</td></tr>
</table>
</td>
</tr>
<tr>
<td>Qutubuddin,A., Reis,T., Alramadhani,R., Cifu,D.X., Towne,A., Carne,W., Parkinson's disease</td>
<td>Randomised controlled trial (3 months)</td>
<td>
<table>
<tr><td></td><td>Intervention</td><td>Control</td></tr>
</table>
</td>
<td>Intervention: Forced exercise (30 mins) using a motorised stationary bicycle,</td>
<td>Measured during ON state of medication:
UPDRS III</td>
<td>
<table>
<tr><td></td><td>Author's judgement</td><td>Description</td></tr>
</table>
</td>
</tr>
</table>

Full citation	Methods	Participants	Interventions	Outcomes	Risk of bias
and forced exercise: A preliminary study, Journal of Parkinson's Disease, 3, 156-, 2013		Participants: 3-year confirmed PD diagnosis Number randomised: 13 / 10	twice weekly for 8 weeks. Control: Conventional clinic care with no specialised physical therapy or exercise conditioning	Berg Balance Scale Finger tapping test PDQ-39	Adequate sequence generation?: Yes – Randomised Allocation concealment?: N/A – N/A Blinding? All outcomes: Yes – Assessor-blinded
Stozek,J., Rudzinska,M., Pustulka-Piwnik,U., Szczudlik,A., The effect of the rehabilitation program on balance, gait, physical performance and trunk rotation in Parkinson's disease, Aging Clin Exp Res, - , 2015	Randomised controlled trial (4 weeks)	Intervention / Control Participants: PD patients Number randomised: 30 / 31 Mean (SD) age (years): 34.0(9.9) / 67.0(11.3) Number of males (n (%)): 13(43.3) / 16(51.6) Mean (SD) duration of PD (years): 4.6(2.7) / 4.3(2.6)	Intervention: Rehabilitation program consisting of 28 therapeutic sessions. Each lasted 2 hrs with breaks, two times per day during the first 2 weeks and during 2 consecutive weeks: 3 times per week, one session per day. Treatment focused on various exercises improving balance, postural stability, walking and performance of ADL, including	Balance (Pastor test and tandem stance). Gait assessment (10 m walk at preferred speed and 360o turn. Motor performance (Physical Performance Test and timed motor activities). The range of spinal rotation measured in the lumbar and thoraco-	Author's judgement / Description Adequate sequence generation?: Yes – Randomised)computer-generated) Allocation concealment?: N/A – N/A Blinding? All outcomes: Unclear – Not reported

Full citation	Methods	Participants	Interventions	Outcomes	Risk of bias
			changing position of the body. Control: Only medication therapy.	lumbar spin with a tape measure. A digital stopwatch to time the motor tasks.	

D.5.2 Occupational therapy

Study details	Participants	Methods	Results	Comments
Full citation Sturkenboom,I.H., Graff,M.J., Hendriks,J.C., Veenhuizen,Y., Munneke,M., Bloem,B.R., Nijhuis-van der Sanden MW, OTiP study group, 20140708, Efficacy of occupational therapy for patients with Parkinson's disease: a randomised controlled trial.[Erratum appears in Lancet Neurol. 2014 Jun;13(6):536], Lancet Neurology, 13, 557-566, 2014 Ref Id 310044 Country/ies where the study was carried out Netherlands Study type RCT Aim of the study To evaluate the effectiveness of home-based occupational therapy compared to usual care in the improvement of daily activities, social participation and quality of life for Patients with PD	Sample size N=191; intervention n=124, control n=67 caregiver: 117/124 in intervention and 63/67 in control had caregiver who participated Inclusion criteria patients: had diagnosis of PD according to UKBB criteria were living at home reported difficulties in meaningful daily activities Exclusion criteria excluded patients who had: received OT	Details multi-centre assessor-masked randomised controlled clinical trial with 3 and 6 month follow up all patients with diagnosis of PD according to UK BB from 10 centres were invited to participate after baseline assessment, patients randomized to group (2:1) randomization by computer-generated minimisation algorithm assessors masked to tmt allocation. patients and therapists could not be masked Interventions within 2 weeks of randomization the experimental group received 10 weeks of home-based OT according to Dutch guidelines of OT in PD interventions included advice or strategy training activities, or adaptation of tasks, daily routines, or environment in OT intervention, caregivers needs in supporting patient were also assessed and addressed if needed. mix of intervention strategies	Results completion: 3 months intervention: :n = 122 3 month control: n = 63 6 month intervention : n=120 6 month control: N=61 reasons for loss in both groups = acute illness; unexplained withdrawal and general loss to follow up demographics median age intervention = 71 (63.3 - 76), control = 70 (63.0 - 75.0) men 63% int, 61% control disease duration in = 6.0 (4 - 10), control = 6 (3 - 11) UPDRS III: int = 27 (18 - 36), control = 28 (19 - 36) daily LED in = 687.5 (415.5 - 957.7) control = 550 (332.5 - 1033.4) RESULTS key: COPM = Canadian occupational performance measure; p = performance; s = satisfaction; PDQ39 = PD questionnaire 39; BDI = becks depression inventory; PCC = proactive coping competence scale; ERPS = evaluation of rehabilitation-participation satisfaction scale assessment | 3nt MD 95% | 6mnt MD 95% COPM-p | 1.2 (0.8 to 1.6) | 0.9 (0.5 to 1.3) COPM-s | 1.1 (0.7 to 1.5) | 0.9 (0.5 to 1.3) PDQ39 | -1.7 (-3.9 to 0.5) | -2.1 (-4.3 to 0.1) EQ5D | 0.03 (-0.03 to 0.08) | 0.02 (-0.03 to 0.07)	Overall Risk of Bias An appropriate method of randomization was used to allocate pts to treatment groups? Yes There was adequate concealment of allocation : not applicable The groups were comparable at baseline, including all major confounding and prognostic factors? Yes Comparison groups received same care apart from interventions. Yes - best medical treatment Pts receiving care were kept blind to tmt allocation. No - not possible

Study details	Participants	Methods	Results	Comments
and their carers. Study dates Patients recruited and assigned between April 2011 and Nov 2012. Published 2014 Source of funding Study funded by Prinses Beatrix Spierfonds and the Parkinson Vereniging	in preceding 3 months had predominant disabling comorbidity insufficient understanding of the dutch language had an MMSE of <24	used was individually tailored to alleviate the problems in activities prioritised by the patient and to suit the patients coping style, the patients capacity to change, and the environmental and social context in which the targeted activity is usually done depending on complexity of issue addressed, number of sessions could vary, with max of 16hrs over 10 weeks session lengths were mostly 1 hour control group did not receive OT but were allowed to receive other medical, psychosocial, or allied health-care interventions all therapists had extensive experience in OT, median exp of 12 years, and attended a 3 day training course for this study and 1 day booster training halfway through study	BDI: -1.4 (-3.0 to 0.3); -0.8 (-2.5 to 0.8) carer burden: -1.1 (-3.8 to 1.7); -2.5 (-5.3 to 0.4) EQ5D carer: 0.0 (0.02 to 0.11); 0.04 (0.01 to 0.09) HADS carer: 0.3 (-05 to 1.0); 0.0 (0.04 to 0.19) 3 month MD 95% / 6 month MD 95% Fatigue severity: 0.1 (-0.2 to 0.4); 0.0 (-0.3 to 0.3) Utrecht PCC: 0.09 (-0.02 to 1.21); 0.06 (-0.05 to 0.17) Utecht ERPS: 3.2 (-0.6 to 6.8); 2.1 (-3.6 to 5.8) authors conclusions: In this study, OT significantly improved patient's self perceived performance in meaningful daily activities, had positive effects on satisfiaction about performance of daily activities and on participation in instrumental activities, but did not improve carer outcomes apart from EQ5D at 3 months.	Individuals administering care were kept blind to tmt allocation . No - not possible All groups followed up for an equal length of time . yes Groups comparable for treatmen completion? Yes Groups were comparable with respect to avalilability of outcome data? Yes Study had appropriate length of followup. Yes Study used a precise definition of outcome. Yes Valid and reliable method was used to determine the outcome . Yes Investigators were kept blind to participants exposure to the

Study details	Participants	Methods	Results	Comments
				intervention. Yes - blind assessors Investigators were kept blind to other important confounding and prognostic factors. Unclear Low risk of bias

D.5.3 Speech and language therapy

Study details	Participants	Methods	Results	Comments
Full citation Herd,Clare P., Tomlinson,Claire L., Deane-Katherine,H.O., Brady,Marian C., Smith,Christina H., Sackley,Catherine M., Clarke,Carl E., Speech and language therapy versus placebo or no intervention for speech problems in Parkinson's disease, Cochrane Database of Systematic Reviews, -, 2012 Ref Id 257693 Country/ies where the study was carried out UK Study type systematic review found online here: http://onlinelibrary.wiley.com/doi/10.1002/14651858.CD002812.pub2/abstract Aim of the study To compare efficacy of speech and language therapy versus placebo or no intervention for speech and voice problems in patients with PD	Sample size N = 3 studies inc in qualitative synthesis, 2 studies inc in quantitative MA Inclusion criteria see Cochrane review for individual study inclusion criteria http://onlinelibrary.wiley.com/doi/10.1002/14651858.CD002812.pub2/abstract Exclusion criteria see Cochrane review for individual study exclusion criteria http://onlinelibrary.wiley.com/doi/10.1002/14651858.CD002812.pub2/abstract	Details see cochrane review for review and individual study methodology Interventions http://onlinelibrary.wiley.com/doi/10.1002/14651858.CD002812.pub2/abstract 3 studies with 3 interventions: Individual pitch, volume, and prosody training loudness and pitch variation, respiration, voice production and intelligibility group training Lee Silverman coice training Each compared to usual care placebo (i.e. no active intervention).	Results see Cochrane paper: http://onlinelibrary.wiley.com/doi/10.1002/14651858.CD002812.pub2/abstract	Overall Risk of Bias: Serious : see cochrane paper for bias assessment: http://onlinelibrary.wiley.com/doi/10.1002/14651858.CD002812.pub2/abstract Other information N/A

Study details	Participants	Methods	Results	Comments
Study dates Literature search was up to 11th April 2011 Source of funding Cochrane collaboration - individual study funding sources listed in each study data extraction page in Cochrane review				
Full citation Troche,M.S., Okun,M.S., Rosenbek,J.C., Musson,N., Fernandez,H.H., Rodriguez,R., Romrell,J., Pitts,T., Wheeler-Hegland,K.M., Sapienza,C.M., Aspiration and swallowing in Parkinson disease and rehabilitation with EMST: a randomized trial, Neurology, 75, 1912-1919, 2010 Ref Id 306260 Country/ies where the study was carried out USA Study type RCT Aim of the study To test treatment outcome	Sample size N = 68; intervention n= 33, sham n=35 mean age EMST 66.7 (SD 8.9)' sham 68.5 (SD 10.3) UPDRS motor total: EMST pre 39.4 (9.2), post 38.9 (8.1); sham pre 40 (8.5), post 41.5 (10.3) Inclusion criteria Ideopathic PD screened and recruited from movement disorders clinicl at university of Florida. all participants had to: 1) meet diagnostic UK Brain bank criteria for PD 2) report some degree of swallowing difficulty i.e. coughing during meals, increased eating duration 3) remain on same PD medications throughout the study	Details design prospective, blinded RCT design all pts took part in baseline swallowing assessment followed by 4 weeks of intervention or sham following completion of treatment, pts returned for post-treatment assessment baseline/post training pts were assessed during 2 baseline measurement sessions videoflouroscopy assessment was only completed at second baseline in order to limit radiation exposure same assessment	Results 2 pts lost to follow-up in both groups as did not want to travel for post test visit. 1 patent in intervention group became too ill to continue. Total N each group for analyses = 30. swallow safety: Penetration aspiration (PA) no difference in baseline characteristics interaction between time and group reported mean PA scores improved in EMST (MC = 0.61 95% CI: 0.10 to 1.11) no improvement in sham(MC=0.43, 95%CI: -0.82 to -0.04) age sex disease severity all had no significant effect on	Overall Risk of Bias low 1. An appropriate method of randomization was used to allocate pts to treatment groups? Randomization method unclear 2.There was adequate concealment of allocation; yes, aparatus for both groups looked identical, double blind design 3.The groups were comparable at baseline, including all major confounding and prognostic factors? all factors comparable at baseline, no significant differences 4.Comparison groups received same care apart from interventions: yes, same care for both groups 5. Pts receiving care were kept

Study details	Participants	Methods	Results	Comments
of 4 week device-driven expiratory muscle strength training (EMST) progrm om swallow safety and define the physiologic mechanisms through measures of swallow timing and hyoid displacement Study dates 2010 Source of funding National Parkinson Foundation centre of excellence	other inclusion criteria were: aged between 55 and 85; moderate clinical disability (H&Y stages II - IV), score of >24 on MMSE, Exclusion criteria 1) other neuoogical disorders 2) gastrointesinal disease 3) gastroesophageal surgery 4) head and neck cancer 5) history of breathing disorders or disease 6) untreated hypertension 7) heart disease 8) history of smoking in the last 5 years 9) difficulty complying due to neuropsychological dysfunction 10) failing to pass screening test for pulmonary function completed at baseline	protocol was completed following finish of treatment pts were tested for 1 hour of intake of their dopaminergic medications to ensure they were practically deifned as "on" state maximum expiratory pressure (MEP) pts instructed to stand and occlude nose with nose clip MEP measurements completed using pressure manometer With the device mouthpiece placed between the lips and behind teeth, pts instructed to inhale as deeply as possible and blow into manometer tube quickly and forcefully 3 values within 5% of eachother were required to calculate a average videoflouroscopy pts sat upright and their swallowing function was recorded in the lateral viewing plane using a properly collimated flouroscope unit	outcome 11/30 had improved scores (33%) compared to 5 (14%) in sham NNT=5.3 physiologic measures of swallow mechanism no significant changes in hyoid movement over time in EMST group but decreased significantly post intervention in sham group time by treatment group interaction for hyoid movement duration significant time by tmt interactions for hyoid displacement at several swallowing specific events: onset of bolus transit, upper oesophageal sphincter opening, UES at its widest opening UES closure, laryngeal closure, maximum laryngeal closure, laryngeal opening swallowing QoL improvement in swallowing QoL secondary to treatment, independant of tmt group membership (F=3.007, p<0.007)	blind to tmt allocation: both groups blinded 6. Individuals administering care were kept blind to tmt allocation:yes therapists blinded 7. All groups followed up for an equal length of time: yes, both followed up for 4 week period 8. Groups comparable for treatmen completion? yes, same dropout (n=2) for both groups 9.Groups were comparable with respect to avalilability of outcome data? yes - data available both groups 10 Study had appropriate length of followup: unclear what appropriate length of FU would be, however benefits were shown for initial 4 weeks. Need to understand whether these benefits are durable over time. 11. Study used a precise definition of outcome: yes, outcomes clear 12. Valid and reliable method was used to determine the outcome: yes 13. Investigators were kept blind to participants exposure to the intervention: yes, investigators were blinded

Study details	Participants	Methods	Results	Comments
		images digitally recorded pts completed 10 x 5 mL trials of thin liquid by cup and also a trial of one 3oz sequential swallow of thin liquid by cup trials presented in random order pts given liquid and asked by experimentor to put liquid in mouth and swallow when ready Speech pathologists with clinical expertise in evaluating patients with PD analyzed swallow studies and were blinded to pts identity and treatment randomization. 25% of total dataset was re-analyzed to ensure inter-rater reliability Interventions EMST/sham training device set weekly to 75% of the participants average maximum expiratory pressure pts visited weekly during the 4wk tmt phase by a clinician, blinded to tmt randomization sham dvice identical to EMST, except pressure		14. Investigators were kept blind to other important confounding and prognostic factors: Yes, investigators blind to clinical information overall risk of Bias = Low Other information n/a

Study details	Participants	Methods	Results	Comments
		release valve nonfunctional therefore both clinician and patients were blinded sham device also set to 75% MEP using adjustable cap for blinding purpose, however would provde little to no physiologic load to targeted muscles during weekly visit by clinician, pts were reminded how to properly use their device to facilitate independent daily treatment trials pts instructed to wear nose clips, take deep breath, hold cheeks lightly, blow as hard as they could into device, and identify that the air was flowing freely through the device once threshold pressure had been released feedback provided to ensure accuracy of initial training once pts able to identify accurate task completion, clinician-based feedback was eliminated each pt trained at home, independent of clinician,		

Study details	Participants	Methods	Results	Comments
		completing 5 sets of 5 repetitions 5 days out of the week compliance tracked using form provided by clinician		

D.5.4 Nutrition

Study details	Participants	Methods	Results	Comments
Full citation Barichella,M., Marczewska,A., De,Notaris R., Vairo,A., Baldo,C., Mauri,A., Savardi,C., Pezzoli,G., 20070202, Special low-protein foods ameliorate postprandial off in patients with advanced Parkinson's disease, Movement Disorders, 21, 1682-1687, 2006 Ref Id 283693 Country/ies where the study was carried out Italy Study type Randomised Controlled Trial (crossover) Aim of the study	Sample size 21 patients enrolled in total, 18 were included in statistical analysis Inclusion criteria Parkin's disease diagnosed according to Brain Bank criteria On stable antiparkinsonian treatment on L-dopa for at least 2 months Experiencing postprandial motor blocks of at least 30 minutes during the 5 hours after the midday meal Referred to the Clinical Nutrition Unit by a neurologist of the Parkinson Institute Exclusion criteria Patients with any sign of malnutrition (BMI< 18.5 kg/m2, albumin, prealbumin, transferrin, or lymphocytes below the lower reference limit were excluded) Characteristics 12 women and 9 men age: 60.6 ± 7.6 years body weight: 62.0 ± 11.5 kg Body Mass Index: 23.8 ± 3.8 kg/m2 Hoehn & Yahr: stage 2- 19% stage 2.5- 43% stage 3- 38%	Details This was a randomised, cross-over, single blind pilot clinical trial over 4 months At baseline visit all patients were examined by a physician specialised in nutrition and interviewed by a dietician, so that an individualised dietary regimen could be drawn up. At each visit, patients were given 28 diary cards to be filled in daily, specifying hours of sleep, waking hours subdivided into hours on the on and off phases, antiparkinson pharmacological timing, mealtimes and any deviations from the prescribed dietary regimens. On/off status was recorded once every hour by the patients themselves. Interventions At baseline visit all	Results Of the 21 patients recruited, 20 completed the study. 2 did not fill in the diary and therefore 18 were included in the statistical analysis. The diary cards analysed amounted to 759 days on a balanced diet and 848 days the controlled protein diet Post prandial off phases Controlled protein diet: 49 ± 73 minutes Balanced diet: 79 ± 72 minutes Total off phases Controlled protein diet: 164 ± 148 minutes Balanced diet: 271 ± 174 minutes Postprandial on time Controlled protein diet: 250 ± 73 minutes Balanced diet: 220 ± 71 minutes Total on time Controlled protein diet: 852 ± 144 minutes Balanced diet: 738 ± 144 minutes Clinical Global impression scale Subjective benefit (marked and moderate improvement) Controlled protein diet: 9 of 18 participants Balanced diet: 0 of 18 participants	Overall Risk of Bias Has an appropriate method of randomisation been used? YES Was there adequate concealment of allocation? UNCLEAR Were the groups comparable at baseline for all major confounding/prognostic factors? YES Did the comparison groups receive the same care apart from interventions studied? YES Were participants receiving care kept blind to treatment allocation?NO Were the

<table>
<tr><th>Study details</th><th>Participants</th><th>Methods</th><th>Results</th><th>Comments</th></tr>
<tr>
<td>To find the efficacy of special low-protein foods in improving postprandial off in patients with advanced Parkinson's disease. Comparing a balanced diet with a controlled protein diet involving consumption of low protein products in the place of usual food at breakfast and lunch. Each diet was to be followed for 2 months.

Study dates
Published 2006
From March 2004 to April 2005

Source of funding
Fondazione Grigioni per il</td>
<td>Mean duration of disease: 11.5 ± 4.3 years
mean L-dopa dosage: 567.5 ± 226.4 mg
Patients were usually taking L-dopa every 4 hours, and, in particular, half an hour before the beginning of the midday meal.
All patients were receiving a dopamine agonist
Antiparkinsonian drug therapy otherwise varied (table can be found within study)</td>
<td>patients were examined by a physician specialised in nutrition and interviewed by a dietician, so that an individualised dietary regimen could be drawn up.
Energy requirements were calculated on the basis of basal metabolism estimated using the formula of Harris Benedict and adding 20-30% according to reported physical activity.
Mean energy content of all the prescribed diets was 31.1 kcal/kg ideal body weight (range, 30.8-31.8 kcal/kg ideal body weight), and calories were subdived as follows: carbohydrates, mean 61.2%; fate 28.6%; and protein, 10.2%, according to the guidelines for the Italian population. Daily protein intake was established on the basis of ideal body weight (0.8 g/kg ideal body weight). Thus,</td>
<td>Minimal improvement, unchanged or worse
Controlled protein diet: 0 of 18 participants
Balanced diet: 9 of 18 participants

Total compared to optimal postprandial on time can be found in the paper.

Postprandial "On" time
<table>
<tr><th></th><th>Mean</th><th>SD</th><th>Total</th></tr>
<tr><td>Experimental</td><td>250.00</td><td>73.00</td><td>18</td></tr>
<tr><td>Control</td><td>220.00</td><td>71.00</td><td>18</td></tr>
</table>
Postprandial "off" time
<table>
<tr><th></th><th>Mean</th><th>SD</th><th>Total</th></tr>
<tr><td>Experimental</td><td>49.00</td><td>73.00</td><td>18</td></tr>
<tr><td>Control</td><td>79.00</td><td>72.00</td><td>18</td></tr>
</table>
Total "on" time
<table>
<tr><th></th><th>Mean</th><th>SD</th><th>Total</th></tr>
<tr><td>Experimental</td><td>852.00</td><td>144.00</td><td>18</td></tr>
<tr><td>Control</td><td>738.00</td><td>144.00</td><td>18</td></tr>
</table>
Total "off" time
<table>
<tr><th></th><th>Mean</th><th>SD</th><th>Total</th></tr>
</table>
</td>
<td>individuals administering care kept blind to treatment allocation? UNCLEAR
Were groups comparable with respect to availability of outcome data and for how many participants were no outcome data available? YES
Did the study have an appropriate length of follow up? YES
Did the study use a precise definition of outcome? YES
Was a valid and reliable method used to determine that outcome? NO (self reported)
Were investigators kept blind to participant's</td>
</tr>
</table>

<table>
<tr><th>Study details</th><th>Participants</th><th>Methods</th><th>Results</th><th>Comments</th></tr>
<tr>
<td>morbo di Parkinson for financial support</td>
<td></td>
<td>the protein content of the diets was within the normal range
The LPP diet differed from the balanced diet only in the distribution of protein intake during the day. The Low protein products were to be consumed at breakfast and lunch instead of common cereal products.
The food portions were quite equal in the two regimens.</td>
<td>
<table>
<tr><td>Experimental</td><td>164.00</td><td>148.00</td><td>18</td></tr>
<tr><td>Control</td><td>271.00</td><td>174.00</td><td>18</td></tr>
</table>
Clinical Global impression scale (minimum improvement/unchanged/worsened)
<table>
<tr><td></td><td>Events</td><td>Total</td></tr>
<tr><td>Experimental</td><td>0</td><td>18</td></tr>
<tr><td>Control</td><td>9</td><td>18</td></tr>
</table>
Clinical Global Impression scale (marked/moderate improvement)
<table>
<tr><td></td><td>Events</td><td>Total</td></tr>
<tr><td>Experimental</td><td>9</td><td>18</td></tr>
<tr><td>Control</td><td>0</td><td>18</td></tr>
</table>
</td>
<td>exposure to the intervention?
YES
Were investigators kept blind to other important confounding and prognostic factors?
UNCLEAR

Other information</td>
</tr>
<tr>
<td>Full citation
Barichella,M., Savardi,C., Mauri,A., Marczewska,A., Vairo,A., Baldo,C., Massarotto,A., Cordara,S.E., Pezzoli,G., 20080118, Diet with LPP for renal patients increases daily energy</td>
<td>Sample size
6 patients with Parkinson's disease with levodopa

Inclusion criteria
Parkinson's disease diagnosed according to Brain Bank criteria
on L-dopa for at least 2 months
Experiencing postprandial motor blocks of at least 30 minutes during the 5 hours after the midday meal
Referred to the Clinical Nutrition Unit by a neurologist of the Parkinson Institute</td>
<td>Details
This was a randomised, cross-over, single blind pilot clinical trial over 14 days
At baseline visit all patients were examined by a physician specialised in nutrition and interviewed by a dietician, so that an individualised dietary regimen could be</td>
<td>Results
All 6 patients completed the study as per protocol and provided 84 valid diaries, 42 with low protein products and 42 with a low protein dietary regime

24 hour Off time
Low protein products= 3.5 hours
Low protein dietary= 5 hours

24 hour dyskinetic ON time
Low protein products= 6 hours
Low protein dietary= 4.5 hours</td>
<td>Overall Risk of Bias
1. Has an appropriate method of randomisation been used?
YES
2. Was there adequate concealment of allocation?
UNCLEAR
3. Were the</td>
</tr>
</table>

<table>
<tr><th>Study details</th><th>Participants</th><th>Methods</th><th>Results</th><th>Comments</th></tr>
<tr>
<td>expenditure and improves motor function in parkinsonian patients with motor fluctuations, Nutritional Neuroscience, 10, 129-135, 2007
Ref Id
283694
Country/ies where the study was carried out
Italy
Study type
Randomised Controlled Trial (Cross over)

Aim of the study
Do special low-protein foods ameliorate postprandial off effect in patients with advanced Parkinson's disease

Study dates
2006</td>
<td>Exclusion criteria
Dementia

Characteristics
3 women and 3 men
median age 66 (50-76) years
mean body weight 64.3 ± 11.1 kg
body mass index (BMI) 24.1 ± 2.6 kg/m2
median duration of disease 21 (11- 27) years
mean levodopa dosage 579 ± 293 mg/day
all patients were also receiving a dopamine agonist
no patient had dementia</td>
<td>drawn up.
At each visit, patients were given study diaries to be filled in daily, specifying hours of sleep, waking hours subdivided into hours on the on and off phases, antiparkinson pharmacological timing, mealtimes and any deviations from the prescribed dietary regimens. On/off status was recorded by the patients themselves.

Interventions
A low protein dietary regimen (0.8-1 g/kg ideal body weight) achieved using low protein food marketed for renal patients, these products were given to the patient by a physician specialised in nutrition.
A low-protein dietary regimen (0.8-1 g/kg ideal body weight) achieved by diminishing the consumption of protein rich food and not</td>
<td>Mean total energy expenditure
Bodymedia Sensewear Pro2 armband worn over the tricep for the whole 14 day period
Low protein products= 1903 ± 265 kcal/day
Low protein dietary= 1731 ± 265 kcal/day

Time spend in physical activity
Low protein products= 1.75 ± 1.33 hours
Low protein dietary= 1.38 ± 1.32 hours

Patient Global Improvement questionnaire
A benefit
Low protein products= 6 of 6 participants
Low protein dietary= 0 of 6 participants
No benefit or worsening were expressed with the dietary regimen
Low protein products= 0 of 6 participants
Low protein dietary= 6 of 6 participants

Energy expenditure
<table>
<tr><th></th><th>Mean</th><th>SD</th><th>Total</th></tr>
<tr><td>Experimental</td><td>1903.00</td><td>265.00</td><td>6</td></tr>
<tr><td>Control</td><td>1731.00</td><td>265.00</td><td>6</td></tr>
</table>
Time spent in physical activity
<table>
<tr><th></th><th>Mean</th><th>SD</th><th>Total</th></tr>
</table>
</td>
<td>groups comparable at baseline for all major confounding/prognostic factors? YES
4. Did the comparison groups receive the same care apart from interventions studied? YES
5. Were participants receiving care kept blind to treatment allocation? NO
6. Were the individuals administering care kept blind to treatment allocation? UNCLEAR
7. Were groups comparable with respect to availability of outcome data and for how many participants were no</td>
</tr>
</table>

<table>
<tr><th>Study details</th><th>Participants</th><th>Methods</th><th>Results</th><th>Comments</th></tr>
<tr>
<td>Source of funding
Fondazione Grigioni per il morbo di Parkinson</td>
<td></td>
<td>resorting to the usage of any special kind of food.</td>
<td>
<table>
<tr><td>Experimental</td><td>1.75</td><td>1.33</td><td>6</td></tr>
<tr><td>Control</td><td>1.38</td><td>1.32</td><td>6</td></tr>
</table>

Patient Global Improvement (very much better/much better)
<table>
<tr><td></td><td>Events</td><td>Total</td></tr>
<tr><td>Experimental</td><td>6</td><td>6</td></tr>
<tr><td>Control</td><td>0</td><td>6</td></tr>
</table>

Patient global improvement (no benefit/worsening)
<table>
<tr><td></td><td>Events</td><td>Total</td></tr>
<tr><td>Experimental</td><td>0</td><td>6</td></tr>
<tr><td>Control</td><td>6</td><td>6</td></tr>
</table>
</td>
<td>outcome data available? YES
8. Did the study have an appropriate length of follow up? NO
9. Did the study use a precise definition of outcome? YES
10. Was a valid and reliable method used to determine that outcome? NO (self reported)
11. Were investigators kept blind to participant's exposure to the intervention? YES
12. Were investigators kept blind to other important confounding and prognostic factors? UNCLEAR

Other information</td>
</tr>
</table>

Study details	Participants	Methods	Results	Comments
Full citation Bender,A., Koch,W., Elstner,M., Schombacher,Y., Bender,J., Moeschl,M., Gekeler,F., Muller-Myhsok,B., Gasser,T., Tatsch,K., Klopstock,T., 20061108, Creatine supplementation in Parkinson disease: a placebo-controlled randomized pilot trial, Neurology, 67, 1262-1264, 2006 Ref Id 283727 Country/ies where the study was carried out Germany Study type Randomised controlled trial Aim of the study	Sample size 60 participants were enrolled Creatine group= 40 participants Placebo group= 20 participants Inclusion criteria Clinical findings compatible with PD (Hoehn and Yahr <= 2.5) SPECT findings compatible with PD Exclusion criteria Younger than 45 years Known renal disease Prestudy use of Cr PD severity more than 2.5 on the Unified Parkinson Disease Rating Scale (UPDRS). Characteristics Creatine Group Baseline characteristics means (SD): Age (y) 60.0 (9.4) Female patients 12 Male patients 28 Disease duration (y) 2.5 (1.4) Placebo group baseline Characteristics, mean (SD): Age (y) 58.7 (11.3) Female patients 5 Male patients 15 Disease duration (y) 2.1 (2.0)	Details This was a randomised, blinded, placebo controlled trial over 2 years Study visits were performed in the mornings at baseline and after 1, 3, 6, 12, 18, and 24 months. At each visit, patients completed questionnaires on possible adverse effects of Cr. A physical examination was performed, patients were weighed, and blood and urine samples were collected and analyzed in the hospital central laboratory on the same day. Blood tests in serum comprised sodium, potassium , creatinine (Crn) , urea , bilirubin , alkaline phosphatase, γ-glutamyltransferase, alanine aminotransferase, aspartate aminotransferase, cholinesterase, CK,	Results Creatine treatment had no significant effect on SPECT variables. There was no overall treatment effect on UPDRS scores or on SF-36 scores. However an analysis of the UPDRS subscales revealed better results in the "meditation, behaviour, mood" section in the creatine group (P=0.046) UPDRS Mentation, behaviour, mood (mean (SD)) Creatine group (n=40) Baseline= 2.2 (1.9) Creatine group (n=31) 2 years= 1.9 (1.6) Control group (n=20) Baseline= 1.6 (1.5) Control group (n=17) 2 years= 2.4 (1.8) Activities of daily living (mean (SD)) Creatine group (n=40) Baseline= 8.1 (4.6) Creatine group (n=31) 2 years= 9.5 (4.4) Control group (n=20) Baseline= 7.8 (4.8) Control group (n=17) 2 years= 7.9 (4.2) Motor (mean (SD)) Creatine group (n=40) Baseline= 16.3 (7.0) Creatine group (n=31) 2 years= 18.9 (8.7) Control group (n=20) Baseline= 17.4 (11) Control group (n=17) 2 years= 17.8 (10.6) Complications (mean (SD)) Creatine group (n=40) Baseline= 0.8 (1.5)	Overall Risk of Bias Has an appropriate method of randomisation been used? UNCLEAR Was there adequate concealment of allocation? UNCLEAR Were the groups comparable at baseline for all major confounding/prognostic factors? UNCLEAR (only 4 reported) Did the comparison groups receive the same care apart from interventions studied? YES Were participants receiving care kept blind to treatment allocation?YES Were the

Study details	Participants	Methods	Results	Comments
To find the efficacy of creatine supplementation of Parkinson's disease patients in regard to weight gain and safety Study dates Published 2006 Took place between October 2000 and May 2003 Source of funding Grant from the Wilhelm-Sander-Siftung, Munich, Germany		albumin, white blood count, red blood cell count, hemoglobin, hematocrit, platelets, cystatin C (CysC), and β(2)-microglobulin (β(2)M). Urinary tests consisted of a test strip analysis, an analysis of urinary sediment, as well as the quantification of creatinine, total protein content, albumin, and α(1)-microglobulin. Interventions Patients received either oral Cr (n = 40) or a placebo (n = 20) in a blinded fashion at a loading dose of 20 g daily for 6 days, followed by 2 g daily for 6 months, and 4 g daily for the remainder of the study. Patients were allowed all standard symptomatic therapy except for monoamine oxidase B inhibitors. If needed symptomatic dopaminergic therapy could be readjusted during the trial.	Creatine group (n=31) 2 years= 1 (1.9) Control group (n=20) Baseline= 0.7 (1.4) Control group (n=17) 2 years= 0.7 (1.0) Total UPDRS score (mean (SD)) Creatine group (n=40) Baseline= 27.4 (11.7) Creatine group (n=31) 2 years= 31.3 (12.9) Control group (n=20) Baseline= 27.4 (17) Control group (n=17) 2 years= 28.8 (14.3) SF-36 Physical functioning (mean (SD)) Creatine group (n=40) Baseline= 80 (21) Creatine group (n=31) 2 years= 72 (22) Control group (n=20) Baseline= 82 (14) Control group (n=17) 2 years= 78 (20) Role limitations (physical health) (mean (SD)) Creatine group (n=40) Baseline= 68 (38) Creatine group (n=31) 2 years= 48 (39) Control group (n=20) Baseline= 60 (36) Control group (n=17) 2 years= 50 (39) Bodily pain (mean (SD)) Creatine group (n=40) Baseline= 82 (21) Creatine group (n=31) 2 years= 73 (32) Control group (n=20) Baseline= 81 (25) Control group (n=17) 2 years= 78 (32)	individuals administering care kept blind to treatment allocation? UNCLEAR Were groups comparable with respect to availability of outcome data and for how many participants were no outcome data available? YES CREATINE GROUP LOST 9/40 PARTICIPANTS, PLACEBO GROUP LOST 3/20 (This is proportionally similar) Did the study have an appropriate length of follow up? YES Did the study use a precise definition of outcome? YES Was a valid and

Study details	Participants	Methods	Results	Comments
			Social functioning (mean (SD)) Creatine group (n=40) Baseline= 90 (16) Creatine group (n=31) 2 years= 81 (25) Control group (n=20) Baseline= 96 (9) Control group (n=17) 2 years= 83 (21) General mental health (mean (SD)) Creatine group (n=40) Baseline= 71 (17) Creatine group (n=31) 2 years= 72 (16) Control group (n=20) Baseline= 79 (8) Control group (n=17) 2 years= 72 (18) Role limitations (emotional) (mean (SD)) Creatine group (n=40) Baseline= 81 (33) Creatine group (n=31) 2 years= 86 (32) Control group (n=20) Baseline= 96 (12) Control group (n=17) 2 years= 80 (37) Vitality (mean (SD)) Creatine group (n=40) Baseline= 57 (16) Creatine group (n=31) 2 years= 57 (14) Control group (n=20) Baseline= 64 (15) Control group (n=17) 2 years= 57 (17) General health perception (mean (SD)) Creatine group (n=40) Baseline= 58 (16) Creatine group (n=31) 2 years= 52 (18) Control group (n=20) Baseline= 65 (16) Control group (n=17) 2 years= 54 (20) After 2 years patients in the creatine group had a significantly smaller dose	reliable method used to determine that outcome? YES Were investigators kept blind to participant's exposure to the intervention? UNCLEAR Were investigators kept blind to other important confounding and prognostic factors? UNCLEAR Other information

<table>
<tr><th>Study details</th><th>Participants</th><th>Methods</th><th>Results</th><th>Comments</th></tr>
<tr><td></td><td></td><td></td><td>increase of dopaminergic therapy vs patients in the control group.
Agonist dose, mg (mean (SD))
Creatine group (n=40) Baseline= 102 (123)
Creatine group (n=31) 2 years= 255 (168)
Control group (n=20) Baseline= 36 (82)
Control group (n=17) 2 years= 270 (118)

Levodopa dose, mg (mean (SD))
Creatine group (n=40) Baseline= 80 (136)
Creatine group (n=31) 2 years= 152 (182)
Control group (n=20) Baseline= 65 (133)
Control group (n=17) 2 years= 194 (194)

Creatine was well tolerated and had no major adverse effects. In particular renal function was undisturbed.

Levodopa dose change (mean difference from baseline)
<table><tr><td></td><td>Mean</td><td>SD</td><td>Total</td></tr><tr><td>Experimental</td><td>72.00</td><td>160.65</td><td>40</td></tr><tr><td>Control</td><td>129.00</td><td>166.32</td><td>20</td></tr></table>
Dopamine agonist dose change (mean difference from baseline)
<table><tr><td></td><td>Mean</td><td>SD</td><td>Total</td></tr><tr><td>Experimental</td><td>102.00</td><td>147.23</td><td>40</td></tr></table></td><td></td></tr>
</table>

Study details	Participants	Methods	Results	Comments

Control	234.00	101.60	20

SF-36 General Health perception (mean difference from baseline)

	Mean	SD	Total
Experimental	-6.00	17.03	40
Control	-11.00	18.11	20

SF-36 Vitality (mean difference from baseline)

	Mean	SD	Total
Experimental	0.00	15.03	40
Control	-7.00	16.03	20

SF-36 Role limitations (emotional) (mean difference from baseline)

	Mean	SD	Total
Experimental	5.00	32.50	40
Control	-16.00	34.59	20

SF-36 General Mental Health (mean difference from baseline)

	Mean	SD	Total
Experimental	1.00	16.51	40
Control	-7.00	13.93	20

Study details	Participants	Methods	Results	Comments
			SF-36 Social functioning (mean difference from baseline) | | Mean | SD | Total | | Experimental | -9.00 | 20.99 | 40 | | Control | -13.00 | 16.16 | 20 | SF-36 Bodily Pain (mean difference from baseline) | | Mean | SD | Total | | Experimental | -9.00 | 27.06 | 40 | | Control | -3.00 | 28.71 | 20 | SF-36 role limitations (physical health) (mean difference from baseline) | | Mean | SD | Total | | Experimental | -20.00 | 38.50 | 40 | | Control | -10.00 | 37.53 | 20 | SF-36 physical functioning score (change from baseline) | | Mean | SD | Total | | Experimental | -8.00 | 21.51 | 40 | | Control | -4.00 | 17.26 | 20 | Total UPDRS score UPDRS, mean	

Study details	Participants	Methods	Results	Comments

difference from baseline)

	Mean	SD	Total
Experimental	3.90	12.31	40
Control	1.40	15.71	20

UPDRS (complications) mean difference from baseline)

	Mean	SD	Total
Experimental	0.20	1.71	40
Control	0.00	1.22	20

UPDRS (motor) mean difference from baseline)

	Mean	SD	Total
Experimental	2.60	7.90	40
Control	0.40	10.80	20

UPDRS (activities of daily living) mean difference from baseline)

	Mean	SD	Total
Experimental	1.40	4.50	40
Control	0.10	4.51	20

UPDRS (mentation, behaviour and mood) mean difference from baseline)

	Mean	SD	Total

Study details	Participants	Methods	Results	Comments
			Experimental -0.30 1.76 40 Control 0.80 1.66 20	
Full citation Brefel,C., Thalamas,C., Rayet,S., Lopez-Gil,A., Fitzpatrick,K., Bullman,S., Citerone,D.R., Taylor,A.C., Montastruc,J.L., Rascol,O., 19980608, Effect of food on the pharmacokinetics of ropinirole in parkinsonian patients, British Journal of Clinical Pharmacology, 45, 412-415, 1998 Ref Id 283805 Country/ies where the study was carried out France Study type Randomised controlled trial	Sample size 12 participants enrolled Inclusion criteria Suffered from idiopathic PD according to U.K. Brain Bank criteria Mild-to-moderate parkinsonian symptoms Exclusion criteria Suffered from severe parkinsonian symptoms Symptomatic orthostatic hypotension or resting diastolic blood pressure greater than 110 mm Hg Neurological or psychiatric disorders other than PD Clinical dementia Aalcoholism or drug-dependency Any "clinically relevant disease" at the start of the study or within 3 months of its start Characteristics 6 males and 6 females mean age 62±10 years mean weight 71±17 kg Antiparkinsonian medication profiles on study entry included: levodopa monotherapy (mean dose ± s.d., 388 ± 232 mg daily, n = 4); selegiline monotherapy (10 mg daily, n = 4); levodopa and selegiline (600 mg and 750 mg daily and 10 mg and 5 mg daily, respectively, n = 2); levodopa and trihexyphenidyle (400 mg daily and 2 mg daily,	Details This was an open, randomised, cross over controlled trial over two weeks For 1 month, patients were monitored on an out-patient basis; during this time, ropinirole was titrated up to a dose of 2 mg three times daily (after breakfast, lunch and evening meal). One week after completion of dose titration, patients were hospitalised for 2 days in the Clinical Investigation Centre while pharmacokinetic data were collected. Three days later, a further 2 days were spent in the Centre for the second phase of the pharmacokinetic data collection. The primary end-points for this study were ropinirole area under the curve to 8 h AUC(0,8 h) calculated	Results Area under the curve (extent of absorption) (0, 8 hours) Fasted state: 29.1 ± 9.6 ng ml-1h Fed State: 25.9 ± 10.7 ng ml-1h Ratio of fed to fasted (95% CI)= 0.87 (0.77-0.98) Peak plasma concentration Fasted state: 6.53 ± 2.1 ng ml-1 Fed State: 5.01 ± 2.1 ng ml-1 Ratio of fed to fasted (95% CI)= 0.75 (0.64-0.87) Time to reach peak concentration Fasted state: 1.25 hours (range 1-2) Fed State: 4 hours (range 1-5) Ratio of fed to fasted (95% CI)= 2.63 (1.38-3.88) *Estimate means and standard deviation imputed using the methods described by Hozo et al http://www.biomedcentral.com/1471-2288/5/13 outcome to be marked down for imprecision as a result. Safety The most frequently reported adverse event was mild nausea (5 patients)	Overall Risk of Bias Has an appropriate method of randomisation been used? UNCLEAR Was there adequate concealment of allocation? UNCLEAR Were the groups comparable at baseline for all major confounding/prognostic factors? YES Did the comparison groups receive the same care apart from interventions studied? YES Were participants receiving care kept blind to

<table>
<tr><th>Study details</th><th>Participants</th><th>Methods</th><th>Results</th><th>Comments</th></tr>
<tr>
<td>(cross over)

Aim of the study
To examine the effect of a fasted diet upon a dopamine agonist (ropinirole) absorption

Study dates
Published 1998

Source of funding
Not stated</td>
<td>respectively,n = 1).
Concomitant drugs were: hypolipidaemic agents (fenofibrate, ciprofibrate) (n = 4), antihypertensive agents (nicardipine, sotalol, lisinopril and hydrochlorothiazide) (n = 3), psychotropic drugs (zopiclone, amitriptyline, lorazepam) (n = 3) and post-menopausal hormonal replacement (oestradiol and progesterone) (n = 1).
Medical history, physical examination, clinical laboratory tests (including standard haematology, liver and renal functions, and the usual clinical chemistry tests) and electrocardiogram were normal in every patient at the beginning and end of the study.</td>
<td>with log-linear trapezoidal rule and peak plasma concentration (Cmax). The secondary end-point was the time taken to reach Cmax (tmax).

Interventions
Patients were randomized to one of two groups. In the first group (n = 6), the patients first attended the Centre for the 'fasted' pharmacokinetic sampling session and then returned 3 days later for the 'fed' session. In the second group (n = 6), the order of the 'fasted' and 'fed' sessions was reversed.
At 18.00 h on the first day of each hospitalization session (i.e. 12 h before the start of the pharmacokinetic sampling session), all antiparkinsonian treatments except ropinirole were</td>
<td>Mild abdominal pain (4 patients)
Orthostatic hypotension (2 patients)
No serious adverse events and no withdrawal due to adverse events or for any other reason.

Absorption: area under the curve
<table>
<tr><th></th><th>Mean</th><th>SD</th><th>Total</th></tr>
<tr><td>Experimental</td><td>29.10</td><td>9.60</td><td>12</td></tr>
<tr><td>Control</td><td>25.90</td><td>10.70</td><td>12</td></tr>
</table>
Absorption: peak plasma concentration
<table>
<tr><th></th><th>Mean</th><th>SD</th><th>Total</th></tr>
<tr><td>Experimental</td><td>6.53</td><td>2.10</td><td>12</td></tr>
<tr><td>Control</td><td>5.01</td><td>2.10</td><td>12</td></tr>
</table>
Absorption: time to peak blood level
<table>
<tr><th></th><th>Mean</th><th>SD</th><th>Total</th></tr>
<tr><td>Experimental</td><td>1.38</td><td>0.30</td><td>12</td></tr>
<tr><td>Control</td><td>3.50</td><td>1.19</td><td>12</td></tr>
</table>
</td>
<td>treatment allocation?NO
Were the individuals administering care kept blind to treatment allocation? NO
Were groups comparable with respect to availability of outcome data and for how many participants were no outcome data available? YES
Did the study have an appropriate length of follow up? NO (less than 1 month per arm)
Did the study use a precise definition of outcome? YES
Was a valid and reliable method used to determine that outcome? YES
Were</td>
</tr>
</table>

Study details	Participants	Methods	Results	Comments
		stopped. Other concomitant medications were continued. On the second day of hospitalization, patients received ropinirole, 2 mg orally, at 09.00 h, after an overnight fast. Plasma samples (5 ml) were obtained pre-dose, and at 30, 60, 75, 90 min and 2, 3, 4, 5, 6, 8 h post-dose. Antiparkinsonian treatment was resumed after completion of sampling. In the 'fasted' session, PD patients remained fasted until a light lunch was provided 4 h after dosing. The light lunch consisted of 74 g protein (31%), 15 g fat (14%) and 127 g carbohydrate (54%), which provided 905 calories. In the 'fed' session, the PD patients received the drug just after a high-fat breakfast, which was followed by a high-fat meal 4 h post		investigators kept blind to participant's exposure to the intervention? NO Were investigators kept blind to other important confounding and prognostic factors? NO Other information

Study details	Participants	Methods	Results	Comments
		dosing. The high-fat breakfast consisted of approximatiely 33 g protein (14%), 64 g fat (61%) and 58 g carbohydrate (24%) which provided 927 calories. The high-fat lunch, consisted of 43 g protein (13%), 84 g fat (58%) and 89 g carbohydrate (27%), which provided 1260 calories. Beverages containing caffeine (coffee, tea, cola) were not allowed on the two pharmacokinetic study days. Alcohol and grapefruit juice were not allowed for the duration of the study.		
Full citation Croxson,S., Johnson,B., Millac,P., Pye,I., 19911031, Dietary modification of Parkinson's disease, European Journal of Clinical	Sample size 8 participants enrolled Inclusion criteria Idiopathic Parkinson's disease Daily on/off phenomenon Exclusion criteria None stated	Details The supplements were given randomly and in a double blind fashion over 9 weeks. The subjects were assessed initially and after each dietary period at the same time of day . At each visit, the patients impressions of their	Results The time awake was similar over the whole study period for each individual. 5 patients improved on the low protein diet compared to normal, two remained the same and one worsened.; there was no correlation between decrease in protein intake and change in motor function. Total Off time	Overall Risk of Bias Has an appropriate method of randomisation been used? UNCLEAR Was there adequate concealment of allocation?

<table>
<tr><th>Study details</th><th>Participants</th><th>Methods</th><th>Results</th><th>Comments</th></tr>
<tr>
<td>Nutrition, 45, 263-266, 1991
Ref Id
283953
Country/ies where the study was carried out
UK
Study type
Randomised controlled trial (cross over)

Aim of the study
To investigate the efficacy of a low protein diet in Parkinson's patients treated with L-dopa

Study dates
Published 1991

Source of funding
Not stated</td>
<td>Characteristics
Average age: 63 years (range 56-70)
Average duration of disease: 12 years</td>
<td>well being and their weight were documented. A Webster rating was performed each visit as a measure of disability based on parkinsonian features such as rigidity, tremor, gait, speech, writing etc. The patients kept a record of their waking hours and recorded their off periodsby shading the corresponding squares on a chart of the hours of a day. During the study patients recorded all food and drink consumed and maintained the same drug therapy.

Interventions
The protocol followed by the patients sequentially was
Normal diet for two weeks
A low-protein diet of 0.75g protein per kg ideal body weight per day for three weeks
A low-protein diet plus a dietary supplement</td>
<td>Normal diet: 6.0 hours
Low protein diet: 3.5 hours
LNAA supplement: 4.0 hours
Placebo: 4.5 hours
*Estimate means and standard deviation imputed using the methods described by Hozo et al http://www.biomedcentral.com/1471-2288/5/13 outcome to be marked down for imprecision as a result.

There was a significant reduction in time "off" on the low protein diet: Mann-Whitney U test a<0.001. 3 patients stopped their LNAA amino acid supplement early because of worsened off periods. 4 patients noticed similarly that the LNAA supplement was more detrimental than placebo, but the Webster ratings showed no significant differences between these two diets.
Records of food eaten showed good compliance with the diets.

Total "off" time
<table>
<tr><th></th><th>Mean</th><th>SD</th><th>Total</th></tr>
<tr><td>Experimental</td><td>4.08</td><td>4.25</td><td>8</td></tr>
<tr><td>Control</td><td>4.94</td><td>2.91</td><td>8</td></tr>
</table>
</td>
<td>UNCLEAR
Were the groups comparable at baseline for all major confounding/prognostic factors? YES
Did the comparison groups receive the same care apart from interventions studied? YES
Were participants receiving care kept blind to treatment allocation?YES
Were the individuals administering care kept blind to treatment allocation? UNCLEAR
Were groups comparable with respect to availability of outcome data and for how many</td>
</tr>
</table>

Study details	Participants	Methods	Results	Comments
		of LNAA (large neutral amino acids) or placebo amino acid for two weeks A low-protein diet plus the alternative supplement for two weeks The low protein diet of 0.75g average quality protein per kg ideal body weight is the minimum recommended for long term use. Carbohydrate and flavouring were added to give the supplements a similar appearance and taste.		participants were no outcome data available? YES Did the study have an appropriate length of follow up? NO (less than 1 month) Did the study use a precise definition of outcome? YES Was a valid and reliable method used to determine that outcome? NO (self reported) Were investigators kept blind to participant's exposure to the intervention? YES Were investigators kept blind to other important confounding and prognostic factors? UNCLEAR

Study details	Participants	Methods	Results	Comments
				Other information Mean results and standard deviations were estimated from the medians and ranges provided within the study
Full citation Fernandez-Martinez,M.N., Hernandez-Echevarria,L., Sierra-Vega,M., Diez-Liebana,M.J., Calle-Pardo,A., Carriedo-Ule,D., Sahagun-Prieto,A.M., Anguera-Vila,A., Garcia-Vieitez,J.J., 20141023, A randomised clinical trial to evaluate the effects of Plantago ovata husk in Parkinson patients: changes in	Sample size 18 randomised Cross over trial Inclusion criteria Patients with idiopathic Parkinson's disease whose symptoms were controlled by levodopa/carbidopa oral medication at least 3 months of levodopa medication between 60 and 80 years of age Exclusion criteria partients participating in other trials or that have participated in the last month allergy or contraindication to Planta ovata husk Chronic renal failure or hepatic disorders psychiatric disorders patients with diabetes mellitus or in treatment with oral hypoglycaemic agents. Characteristics Sex M/F	Details A randomised double-blind, placebo controlled cross over trial over 35 days. Volunteers were randomly divided into two groups of 9 patients each. To generate the random allocation, a numbered list of the participants was created and an Excel aleatory number generator was used. Absorptions of levodopa was measured using outcomes of: Maximum plasma levodopa	Results Tmax (min), mean ± SD Baseline= 35.83 ± 16.91 Plantago Husk= 39.72 ± 17.19 Placebo= 36.17 ± 26.30 Cmax(ng/ml), mean ± SD Baseline= 603.2 ± 242.4 Plantago Husk= 547.8 ± 192.6 Placebo= 612.0 ± 176.6 AUC (ug. min/ml) Baseline= 62.87 ± 15.77 Plantago Husk= 64.47 ± 15.27 Placebo= 65.10 ± 14.33 elimination rate constant (min-1) Baseline= 0.0096 ± 0.0018 Plantago Husk= 0.0088 ± 0.0020 Placebo= 0.0097 ± 0.0018	Overall Risk of Bias Has an appropriate method of randomisation been used? YES Was there adequate concealment of allocation? UNCLEAR Were the groups comparable at baseline for all major confounding/prognostic factors? YES Did the comparison

Study details	Participants	Methods	Results	Comments
levodopa pharmacokinetics and biochemical parameters, BMC Complementary & Alternative Medicine, 14, 296-, 2014 Ref Id 284162 Country/ies where the study was carried out Spain Study type Randomised Controlled Trial Aim of the study To evaluate the effects of this fibre on several biochemical parameters including levodopa absorption. Study dates Published 2014 Between April 2006 and November 2006	Group 1 (n=9)= 5/4 Group 2 (n=9)= 5/4 Age (mean ± SD), y Group 1 (n=9)= 68.7 ± 3.1 Group 2 (n=9)= 70.3 ± 4.3 Disease Duration (mean ± SD), y Group 1 (n=9)= 1.4 ± 0.6 Group 2 (n=9)= 1.3 ± 0.4 Duration of levodopa treatment (mean ± SD) y Group 1 (n=9)= 0.7 ± 0.3 Group 2 (n=9)= 0.8 ± 0.5	concentration (Cmax), time to reach maximum concentration (Tmax), the area under the curve (AUC). Interventions Both groups received alternatively two treatments: treatment A, administration of Plantago ovata husk; and treatment B, administration of placebo. During treatment A (Plantago ovata husk administration), volunteers received their usual levodopa/carbidopa oral dose (100/25 mg), three times a day and, immediately before, 3.5 g Plantago ovata husk dispersed into 200 ml water. The other 9 patients (treatment B) received placebo instead of fiber. Patients followed these treatments for 14 days, and after a wash-out period of 7	Volume of distribution at a steady rate (l) Baseline= 0.1845 ± 0.0628 Plantago Husk= 0.1929 ± 0.0521 Placebo= 0.1699 ± 0.0468 Clearance (Cl/F) Baseline= 0.0017 ± 0.0004 Plantago Husk= 0.0016 ± 0.0004 Placebo= 0.0016 ± 0.0004 The area under the first moment curve (ug.min2/ml) Baseline= 7881.7 ± 2630.3 Plantago Husk= 8313.7 ± 2284.4 Placebo= 8327.1 ± 2651.9 Mean residence time (min) Baseline= 125.1 ± 29.9 Plantago Husk= 129.2 ± 21.7 Placebo= 126.6 ± 24.2 Minimum plasma levodopa concentration (ng/ml) Baseline= 6.02 ± 3.41 Plantago Husk= 6.31 ± 7.10 Placebo= 7.34 ± 7.98 Half life associated with elimination rate (min) Baseline= 75.2 ± 16.0 Plantago Husk= 81.9 ± 15.3 Placebo= 74.0 ± 16.9	groups receive the same care apart from interventions studied? YES Were participants receiving care kept blind to treatment allocation?YES Were the individuals administering care kept blind to treatment allocation? UNCLEAR Were groups comparable with respect to availability of outcome data and for how many participants were no outcome data available? YES Did the study have an appropriate length of follow up? NO (less than a month per arm)

<table>
<tr><th>Study details</th><th>Participants</th><th>Methods</th><th>Results</th><th>Comments</th></tr>
<tr>
<td>Source of funding
Unclear.
Authors declare no competing interests.
Collaboration with Rottapharm.</td>
<td></td>
<td>days, the other treatment (A or B) as given.</td>
<td>Absorption: area under the curve
<table>
<tr><td></td><td>Mean</td><td>SD</td><td>Total</td></tr>
<tr><td>Experimental</td><td>64.47</td><td>15.27</td><td>18</td></tr>
<tr><td>Control</td><td>65.10</td><td>14.33</td><td>18</td></tr>
</table>
Absorption: peak plasma concentration
<table>
<tr><td></td><td>Mean</td><td>SD</td><td>Total</td></tr>
<tr><td>Experimental</td><td>192.60</td><td>192.60</td><td>18</td></tr>
<tr><td>Control</td><td>612.00</td><td>176.60</td><td>18</td></tr>
</table>
Absorption: time to peak blood level
<table>
<tr><td></td><td>Mean</td><td>SD</td><td>Total</td></tr>
<tr><td>Experimental</td><td>39.72</td><td>17.19</td><td>18</td></tr>
<tr><td>Control</td><td>36.17</td><td>26.30</td><td>18</td></tr>
</table>
</td>
<td>Did the study use a precise definition of outcome? YES
Was a valid and reliable method used to determine that outcome? YES
Were investigators kept blind to participant's exposure to the intervention? YES
Were investigators kept blind to other important confounding and prognostic factors? UNCLEAR

Other information</td>
</tr>
<tr>
<td>Full citation
Hass,C.J., Collins,M.A., Juncos,J.L., 20070418, Resistance training with</td>
<td>Sample size
Randomised =20 patients
Creatine group= 10 patients
Placebo group= 10 patients

Inclusion criteria</td>
<td>Details
Randomised double blind placebo controlled trial for 12 weeks
Data collection began with a 2-week</td>
<td>Results

Hoehn & Yahr
Baseline
Placebo group (n=10)= 2.2 ± 0.2
Creatine resistance (n=10)= 2.1 ± 0.2</td>
<td>Overall Risk of Bias
Has an appropriate method of randomisation been used?</td>
</tr>
</table>

Study details	Participants	Methods	Results	Comments
creatine monohydrate improves upper-body strength in patients with Parkinson disease: a randomized trial, Neurorehabilitation & Neural Repair, 21, 107-115, 2007 Ref Id 229147 Country/ies where the study was carried out USA Study type Randomised Controlled Trial Aim of the study To test the efficacy of resistance training with creatine monohydrate in Parkinson's disease patients Study dates Published 2007	Parkinsons disease Hoehn and Yahr stage 3 or lower ambulatory clinically stable and nonfluctuating Exclusion criteria Participated in any consistent exercise program or experimental study for at least 6 months prior to enrollment. presence of active medical or psychiatric conditions or orthopedic or rheumatic conditions that would preclude ability to participate in the exercises. previous history of renal disorders experiencing more than mild cognitive impairment (Mini mental <26/30) Characteristics Age, y Placebo group (n=10)= 62.8 ± 2.6 Creatine resistance (n=10)= 62.2 ± 2.6 Gender M/F Placebo group (n=10)= 9/1 Creatine resistance (n=10)= 8/2 Disease duration, mo Placebo group (n=10)= 59.0 ± 14.8 Creatine resistance (n=10)= 47.8 ± 8.3	acclimation phase in which patients were orientated to the exercise machines. Neurological evaluation: Participants were evaluated in the morning during their period of maximal therapeutic benefit on motor function using the H&Y staging and the Unified Parkinson Disease Rating Scale by board certified neurologist. Dynamic Muscular Strength Testing. the 1-repetition maximum was used as a measure of dynamic concentration muscle strength of the legs, chest, and biceps using the leg extension, chest press and biceps curl machines Muscular endurance testing was measured for the chest press and leg extension. The subjects were asked to lift a weight	Post training Placebo group (n=10)= 2.6 ± 0.2 Creatine resistance (n=10)= 2.1 ± 0.2 UPDRS total Baseline Placebo group (n=10)= 41.8 ± 7.1 Creatine resistance (n=10)= 34.2 ± 5.0 Post training Placebo group (n=10)= 42.8 ± 7.1 Creatine resistance (n=10)= 33.5 ± 5.0 UPDRS mental Baseline Placebo group (n=10)= 2.7 ± 0.5 Creatine resistance (n=10)= 1.3 ± 0.6 Post training Placebo group (n=10)= 2.1 ± 0.5 Creatine resistance (n=10)= 1.1 ± 0.6 UPDRS ADL Baseline Placebo group (n=10)= 13.4 ± 2.1 Creatine resistance (n=10)= 10.9 ± 2.3 Post training Placebo group (n=10)= 12.4 ± 2.2 Creatine resistance (n=10)= 9.7 ± 2.5 UPDRS motor Baseline Placebo group (n=10)= 25.7 ± 4.4 Creatine resistance (n=10)= 22.1 ± 4.9	UNCLEAR Was there adequate concealment of allocation? UNCLEAR Were the groups comparable at baseline for all major confounding/prognostic factors? YES Did the comparison groups receive the same care apart from interventions studied? YES Were participants receiving care kept blind to treatment allocation?YES Were the individuals administering care kept blind to treatment allocation? YES Were groups comparable with respect to

<table>
<tr><th>Study details</th><th>Participants</th><th>Methods</th><th>Results</th><th>Comments</th></tr>
<tr>
<td>Source of funding
Supported by the National Institues of Health grant and the American Parkinson Disease Association Center for Research Excellence at Emory University.</td>
<td></td>
<td>representing 60% of a 1 rep maximum until failure.
Body Compositional analysis was performed
Functional Test: Individuals performed 3 consecutive chair stands as a functional measure of their lower extremity performance.

Interventions
Creatine supplementation protocol: 20 g/d for 5 to 7 days followed by a maintenance dose of 3 to 5g/d.
The placebo group consumed lactose monohydrate using an identical dosing scheme.</td>
<td>Post training
Placebo group (n=10)= 28.3 ± 4.5
Creatine resistance (n=10)= 20.8 ± 5.0

Mass, kg
Baseline
Placebo group (n=10)= 95.7 ± 5.9
Creatine resistance (n=10)= 81.9 ± 5.9
Post training
Placebo group (n=10)= 97.3 ± 5.2
Creatine resistance (n=10)= 83.9 ± 6.4

Mass, Kg (mean difference from baseline)
<table>
<tr><td></td><td>Mean</td><td>SD</td><td>Total</td></tr>
<tr><td>Experimental</td><td>2.00</td><td>6.16</td><td>10</td></tr>
<tr><td>Control</td><td>1.60</td><td>5.56</td><td>10</td></tr>
</table>
Hoehn & Yahr scores (mean difference from baseline)
<table>
<tr><td></td><td>Mean</td><td>SD</td><td>Total</td></tr>
<tr><td>Experimental</td><td>0.00</td><td>0.20</td><td>10</td></tr>
<tr><td>Control</td><td>0.40</td><td>0.20</td><td>10</td></tr>
</table>
Total UPDRS score UPDRS, mean difference from baseline)
<table>
<tr><td></td><td>Mean</td><td>SD</td><td>Total</td></tr>
</table>
</td>
<td>availability of outcome data and for how many participants were no outcome data available? YES
Did the study have an appropriate length of follow up? YES
Did the study use a precise definition of outcome? YES
Was a valid and reliable method used to determine that outcome? YES
Were investigators kept blind to participant's exposure to the intervention? YES
Were investigators kept blind to other important confounding and prognostic factors?</td>
</tr>
</table>

<table>
<tr><th>Study details</th><th>Participants</th><th>Methods</th><th>Results</th><th>Comments</th></tr>
<tr><td></td><td></td><td></td><td>
<table>
<tr><td>Experimental</td><td>-0.70</td><td>5.00</td><td>10</td></tr>
<tr><td>Control</td><td>1.00</td><td>7.10</td><td>10</td></tr>
</table>
UPDRS (motor) mean difference from baseline)
<table>
<tr><td></td><td>Mean</td><td>SD</td><td>Total</td></tr>
<tr><td>Experimental</td><td>-1.30</td><td>4.95</td><td>10</td></tr>
<tr><td>Control</td><td>2.60</td><td>4.45</td><td>10</td></tr>
</table>
UPDRS (activities of daily living) mean difference from baseline)
<table>
<tr><td></td><td>Mean</td><td>SD</td><td>Total</td></tr>
<tr><td>Experimental</td><td>-1.20</td><td>2.40</td><td>10</td></tr>
<tr><td>Control</td><td>-1.00</td><td>2.15</td><td>10</td></tr>
</table>
UPDRS (mentation, behaviour and mood) mean difference from baseline)
<table>
<tr><td></td><td>Mean</td><td>SD</td><td>Total</td></tr>
<tr><td>Experimental</td><td>-0.20</td><td>0.60</td><td>10</td></tr>
<tr><td>Control</td><td>-0.60</td><td>0.50</td><td>10</td></tr>
</table>
</td><td>UNCLEAR

Other information</td></tr>
<tr><td>Full citation
Nathan,J., Panjwani,S., Mohan,V., Joshi,V., Thakurdesai,P.A., Efficacy and</td><td>Sample size
Randomised= 50
IBHB group= 23
Placebo group= 19

Inclusion criteria</td><td>Details
A randomised, double blind, placebo controlled trial over 6 months.
Randomised in a 1:1 ratio according to a</td><td>Results
Total UPDRS and H&Y staging after 6 months of treatment with IBHB and Placebo as an adjuvant to L-dopa to patients with Parkinson's Disease.

UPDRS total, mean (SD), 6 months</td><td>Overall Risk of Bias
Has an appropriate method of randomisation been used?</td></tr>
</table>

Study details	Participants	Methods	Results	Comments
safety of standardized extract of Trigonella foenum-graecum l seeds as an adjuvant to L-dopa in the management of patients with Parkinson's disease, Phytotherapy Research.28 (2) (pp 172-178), 2014.Date of Publication: February 2014., 172-178, 2014 Ref Id 285161 Country/ies where the study was carried out India Study type Randomised controlled trial Aim of the study To find the efficacy and safety of Standardized Extract of	Age 18-70 years Stable dose of L-dopa with carbodopa Willing to adhere to the protocol requirement during the trial period Exclusion criteria One who refused or was not able to give informed consent pregnant or lactating women having history of hypersensitivity to the study drug or related products significant history or presence of gastrointestinal, liver or kidney, cardiac disease or who are on maintenance therapy with any other drug, having any serious neurological or psychological disease apart from Parkinson's Disease. History of drug or alcohol dependency Characteristics Gender, M/F IBHB group (n=23)= 19/4 Placebo group (n=19)= 13/6 Age, y, mean (SD) IBHB group (n=23)= 61.68 (5.9) Placebo group (n=19)= 60.6 (6.2) UPDRS total, mean (SD) IBHB group (n=23)= 43.09 (16.72) Placebo group (n=19)= 37.53 (15.1) UPDRS mentation, behaviour and mood, mean (SD)	computer generated randomisation list. Outcome measures: UPDRS, Hoehn and Yahr staging, safety assessment, Patients and Investigators Global Assessment. Interventions Active treatment product is a capsule containing 300 mg of IBHB, a standardised hydroalcoholic extract of Trigonella foenum graecum L. seeds. IBHB group recieved 300 mg capsules with water twice a day (1 hour before breakfast and 1 hour before evening tea) Placebo group recieved matching capsules of di-calcium phosphate.	IBHB group (n=23)= 43.52 (15.52) Placebo group (n=19)= 43.32 (22.57) UPDRS total, Clinically important difference IBHB group (n=23)= +0.5 Placebo group (n=19)= +5.79 UPDRS mentation, behaviour and mood, mean (SD), 6 months IBHB group (n=23)= 2.04 (2.12) Placebo group (n=19)= 2.42 (2.83) UPDRS mentation, behaviour and mood, mean (SD), Clinically important difference IBHB group (n=23)= -0.39 Placebo group (n=19)= +0.26 UPDRS ADL, mean (SD), 6 months IBHB group (n=23)= 10.91 (6.96) Placebo group (n=19)= 10.26 (6.51) UPDRS ADL, mean (SD), Clinically important difference IBHB group (n=23)= -0.09 Placebo group (n=19)= -0.16 UPDRS Motor, mean (SD), 6 months IBHB group (n=23)= 30.57 (9.24) Placebo group (n=19)= 30.63 (15.32) UPDRS Motor, mean (SD), Clinically	YES Was there adequate concealment of allocation? YES Were the groups comparable at baseline for all major confounding/prognostic factors? YES Did the comparison groups receive the same care apart from interventions studied? YES Were participants receiving care kept blind to treatment allocation?YES Were the individuals administering care kept blind to treatment allocation? UNCLEAR (but double blind) Were groups comparable

Study details	Participants	Methods	Results	Comments
Trigonella foenum-graecum L seeds as an adjuvant to L-dopa in the management of patients with Parkinson's Disease Study dates Published 2013 Source of funding Indus Biotech Private Limited	IBHB group (n=23)= 2.15 (1.86) Placebo group (n=19)= 2.43 (2.12) UPDRS ADL, mean (SD) IBHB group (n=23)= 10.42 (5.67) Placebo group (n=19)= 11.0 (5.26) UPDRS Motor, mean (SD) IBHB group (n=23)= 1.68 (1.11) Placebo group (n=19)= 2.35 (1.37) Hoehn and Yahr staging, mean (SD) IBHB group (n=23)= 1.52 (0.561) Placebo group (n=19)= 1.74 (0.69)		Important Difference IBHB group (n=23)= +0.92 Placebo group (n=19)= +5.68 Hoehn and Yahr staging, stage reversal, n, (%) IBHB group (n=23)= 5 (21.73) Placebo group (n=19)= 1 (5.26) Hoehn and Yahr staging, no change in staging, n, (%) IBHB group (n=23)= 15 (65.21) Placebo group (n=19)= 15 (78.94) Hoehn and Yahr staging, stage advancement, n, (%) IBHB group (n=23)= 3 (13.04) Placebo group (n=19)= 3 (15.78) IBHB treatment was well tolerated by patients. Number of dropouts in IBHB-treated group was 2 of 25. IBHB treatment was well tolerated by patients. Number of dropouts in IBHB-treated group was 6 of 25. There were no deaths or serious adverse events during the study. Safety parameter data for haematology, biochemistry, liver function test and kidney function test found no significant difference between values at baseline and at 6 months.	with respect to availability of outcome data and for how many participants were no outcome data available? YES (6 dropout for placebo, 2 for treatment group) Did the study have an appropriate length of follow up? YES Did the study use a precise definition of outcome? YES Was a valid and reliable method used to determine that outcome? YES Were investigators kept blind to participant's exposure to the intervention? YES Were investigators

Study details	Participants	Methods	Results	Comments
			Hoehn and Yahr stage reversal <table><tr><td></td><td>Events</td><td>Total</td></tr><tr><td>Experimental</td><td>5</td><td>23</td></tr><tr><td>Control</td><td>1</td><td>19</td></tr></table> Hoehn and Yahr stage unchanged <table><tr><td></td><td>Events</td><td>Total</td></tr><tr><td>Experimental</td><td>15</td><td>23</td></tr><tr><td>Control</td><td>15</td><td>19</td></tr></table> Hoehn and Yahr stage advancement <table><tr><td></td><td>Events</td><td>Total</td></tr><tr><td>Experimental</td><td>3</td><td>23</td></tr><tr><td>Control</td><td>3</td><td>19</td></tr></table> Total UPDRS score UPDRS, mean difference from baseline) <table><tr><td></td><td>Mean</td><td>SD</td><td>Total</td></tr><tr><td>Experimental</td><td>0.43</td><td>0.50</td><td>23</td></tr><tr><td>Control</td><td>5.79</td><td>18.55</td><td>19</td></tr></table> UPDRS (motor) mean difference from baseline) <table><tr><td></td><td>Mean</td><td>SD</td><td>Total</td></tr></table>	kept blind to other important confounding and prognostic factors? UNCLEAR Other information

Study details	Participants	Methods	Results	Comments
			<table><tr><td>Experimental</td><td>0.92</td><td>10.55</td><td>23</td></tr><tr><td>Control</td><td>5.68</td><td>12.43</td><td>19</td></tr></table> UPDRS (activities of daily living) mean difference from baseline) <table><tr><td></td><td>Mean</td><td>SD</td><td>Total</td></tr><tr><td>Experimental</td><td>-0.09</td><td>6.17</td><td>23</td></tr><tr><td>Control</td><td>-0.16</td><td>6.10</td><td>19</td></tr></table> UPDRS (mentation, behaviour and mood) mean difference from baseline) <table><tr><td></td><td>Mean</td><td>SD</td><td>Total</td></tr><tr><td>Experimental</td><td>-0.39</td><td>2.13</td><td>23</td></tr><tr><td>Control</td><td>0.26</td><td>2.39</td><td>19</td></tr></table>	
Full citation Storch,A., Jost,W.H., Vieregge,P., Spiegel,J., Greulich,W., Durner,J., Muller,T., Kupsch,A., Henningsen,H., Oertel,W.H., Fuchs,G., Kuhn,W., Niklowitz,P., Koch,R., Herting,B.,	Sample size 131 subjects underwent randomization Placebo group- 67 Coenzyme Q10- 64 Inclusion criteria between 40 to 75 years old diagnosis of Parkinson's Disease according to the UK Brain Bank criteria A rating on the modified Hoehn-Yahr scale between II and III 16 points or more on the UPDRS motor score on stable antiparkinsonian medication with or without levodopa for at least 4 weeks prior to	Details Randomised, double-blind, placebo-controlled trial over 5 months. Treatment finished at 3 months. Randomisation from a list which was stratified for comedication of levodopa. After 3 months the subjects underwent a withdrawal from study drug for 2 months and	Results The mean of the primary outcome measure (combined UPDRS ADL/motor scale scores) at 5 months mean (SD) baseline: Placebo group (n=67)= 35.5 ± 13.6 CoQ10 group (n=64)= 32.6 ± 11.8 mean (SD) 5 months: Placebo group (n=67)= 32.5 ± 4.00 CoQ10 group (n=64)= 31.25 ± 4.25 *Data was extracted from a combination of data provided in baseline characteristics table and read from a graph	Overall Risk of Bias Has an appropriate method of randomisation been used? YES Was there adequate concealment of allocation? YES Were the groups comparable at

Study details	Participants	Methods	Results	Comments
Reichmann,H., German,Coenzyme Q., 20070831, Randomized, double-blind, placebo-controlled trial on symptomatic effects of coenzyme Q(10) in Parkinson disease, Archives of Neurology, 64, 938-944, 2007 Ref Id 216479 Country/ies where the study was carried out Germany Study type Randomised Controlled Trial Aim of the study Efficacy of Coenzyme Q10 in treating the symptoms of Parkinson Disease Study dates	study enrollment Exclusion criteria Exposed to CoQ10 during the last 3 months prior to study inclusion Taking more than 149 IU of vitamin E or calcium, magnesium, and/or other vitamins for more than 3 months prior to study inclusion. recieving cholesterol-lowering drugs thyroid hormones antiarrythmic compounds warfarin metformin clozapine Had an identifiable cause of parkinsonism or signs for atypical parkinsonian disorders Hypothyroidism Current evidence of epilepsy or pdychosis levodopa-induced motor fluctuations or dyskinesias Characteristics Male sex (%): Placebo group (n=67)= 70.1 CoQ10 group (n=64)= 68.7 Age, mean (SD): Placebo group (n=67)= 62.3 (7.9) CoQ10 group (n=64)= 60.7 (9.1) BMI, mean (SD): Placebo group (n=67)= 25.23 (3.59)	a final assessment of the severity of symptoms was made. Doses of levodopa and all other antiparkinsonian medication were kept constant throughout the study. Interventions Coenzyme Q10 suspension 100 mg 3 times a day for 3 months Matching placebo for 3 months	The mean of the primary outcome measure (combined UPDRS ADL/motor scale scores) at 3 months mean (SD) baseline: Placebo group (n=67)= 35.5 ± 13.6 CoQ10 group (n=64)= 32.6 ± 11.8 mean (SD) 3 months: Placebo group (n=67)= 31.25 ± 4.00 CoQ10 group (n=64)= 30.5 ± 4.00 mean change from baseline 3 months: Placebo group (n=67)= -3.69 CoQ10 group (n=64)= -3.33 *Data was extracted from a combination of data provided in baseline characteristics table and read from a graph The Hoehn and Yahr scores alone decreased significantly in the CoQ10 group: Placebo group (n=67)= -0.01 CoQ10 group (n=64)= -0.16 Between groups P=0.04 analysis according to the stratification revealed significant changes only in the levodopa stratum of the CoQ10 group (P=0.007) Safety and tolerability The percentage of patients reporting any adverse events was not significantly different between groups (%):	baseline for all major confounding/prognostic factors? YES Did the comparison groups receive the same care apart from interventions studied? YES Were participants receiving care kept blind to treatment allocation?YES Were the individuals administering care kept blind to treatment allocation? YES Were groups comparable with respect to availability of outcome data and for how many participants were no outcome data available? YES (12 in the

Study details	Participants	Methods	Results	Comments
Published 2007 between September 2003 and January 2005 Source of funding This study was supported by a grant from the Deutsche Parkinson-Vereiniguing eV (German Parkinson Association)	CoQ10 group (n=64)= 25.52 (3.02) total UPDRS, mean (SD): Placebo group (n=67)= 38.6 (15.3) CoQ10 group (n=64)= 35.5 (12.8) Mental component part 1, mean (SD): Placebo group (n=67)= 1.9 (1.6) CoQ10 group (n=64)= 1.6 (1.4) ADL component, mean (SD): Placebo group (n=67)= 10.5 (5.3) CoQ10 group (n=64)= 9.1 (4.9) Motor component, mean (SD): Placebo group (n=67)= 25.0 (9.1) CoQ10 group (n=64)= 23.5 (7.9) ADL/Motor component sum score, mean (SD): Placebo group (n=67)= 35.5 (13.6) CoQ10 group (n=64)= 32.6 (11.8) Schwab and England scale score, mean (SD): Placebo group (n=67)= 83.6 (9.6) CoQ10 group (n=64)= 84.1 (9.8) Hoehn and Yahr scale score, mean (SD): Placebo group (n=67)= 2.3 (0.4) CoQ10 group (n=64)= 2.3 (0.4)		Placebo group (n=67)= 28.4 CoQ10 group (n=64)= 31.3 Most frequently reported adverse events (occurring in at least 2 patients) Viral infection (%) Placebo group (n=67)= 9.0 CoQ10 group (n=64)= 3.1 Diarrhea (%) Placebo group (n=67)= 1.5 CoQ10 group (n=64)= 7.8 acute hearing loss (%) Placebo group (n=67)= 1.5 CoQ10 group (n=64)= 1.6 night sweats (%) Placebo group (n=67)= 1.5 CoQ10 group (n=64)= 1.6 Nausea (%) Placebo group (n=67)= 1.5 CoQ10 group (n=64)= 1.6 Bronchitis (%) Placebo group (n=67)= 0 CoQ10 group (n=64)= 4.7 The occurence of serious adverse events was similar in both groups: Placebo group (n=67)= 2 patients CoQ10 group (n=64)= 4 patients Adverse events leading to withdrawal from study or discontinuation of drug: Placebo group (n=67)= 3 CoQ10 group (n=64)= 2	placebo group and 13 in the treatment group prematurely discontinued treatment) Did the study have an appropriate length of follow up? YES Did the study use a precise definition of outcome? YES Was a valid and reliable method used to determine that outcome? YES Were investigators kept blind to participant's exposure to the intervention? YES Were investigators kept blind to other important confounding and prognostic factors? UNCLEAR

<table>
<tr><th>Study details</th><th>Participants</th><th>Methods</th><th>Results</th><th>Comments</th></tr>
<tr>
<td></td>
<td>Antiparkinsonian medication
Levodopa (%):
Placebo group (n=67)= 68.7
CoQ10 group (n=64)= 67.2
Dopamine agonists (%):
Placebo group (n=67)= 82.1
CoQ10 group (n=64)= 84.4
Other antiparkinsonian agents (%):
Placebo group (n=67)= 23.9
CoQ10 group (n=64)= 25.0

Coenzyme Q10 plasma levels, mean (SD)
Placebo group (n=67)= 0.94 (0.34)
CoQ10 group (n=64)= 0.99 (0.44)

There were no significant differences between the groups for any of the above characteristics.</td>
<td></td>
<td>UPDRS Combined ADL/motor scores (mean difference from baseline)<table><tr><td></td><td>Mean</td><td>SD</td><td>Total</td></tr><tr><td>Experimental</td><td>-2.10</td><td>8.81</td><td>64</td></tr><tr><td>Control</td><td>-4.25</td><td>10.02</td><td>64</td></tr></table></td>
<td>Other information
Some data was extracted from a combination of data provided in baseline characteristics table and read from a graph</td>
</tr>
<tr>
<td>Full citation
Suzuki,M., Yoshioka,M., Hashimoto,M., Murakami,M., Noya,M., Takahashi,D., Urashima,M., 20130617, Randomized, double-blind, placebo-controlled trial of vitamin D supplementation in Parkinson</td>
<td>Sample size
Randomised= 137
Vitamin D group= 55
Placebo group= 57

Inclusion criteria
diagnosed with Parkinson's Disease by >= 2 neurologists
Aged 45-85 years
Did not have first- or second- degree relatives with Parkinson's Disease

Exclusion criteria
History of stones in the urinary tract</td>
<td>Details
Randomised, double blind, placebo controlled trial over 12 months.
A central computerized procedure was used to randomly assign patients in permutated blocks of 4 to recieve either vitamin D or placebo.
Outcomes were HY stage, UPDRS, and MMSE which were</td>
<td>Results
HY stage (stages 1-5)
Change (after- before) Mean (SD)
Vitamin D3 (n=55)= 0.02 (0.62)
Placebo (n=57)= 0.33 (0.70)
Not worsened or improved, n (%)
Vitamin D3 (n=55)= 16 (29.1)
Placebo (n=57)= 7 (12.3)
Relative risk= 2.37 (1.06-5.31)
Risk Difference= 0.17 (0.02-0.32)

UPDRS total (0-195)
Change (after- before) Mean (SD)
Vitamin D3 (n=55)= -0.87 (12.8)</td>
<td>Overall Risk of Bias
Has an appropriate method of randomisation been used? YES
Was there adequate concealment of allocation? YES
Were the groups comparable at</td>
</tr>
</table>

Study details	Participants	Methods	Results	Comments
disease, American Journal of Clinical Nutrition, 97, 1004-1013, 2013 Ref Id 285686 Country/ies where the study was carried out Japan Study type Randomised controlled trial Aim of the study To find the efficacy of vitamin D in inhibiting the progression of Parkinson's disease. Study dates Published 2013 Source of funding Supported by the Ministry of	already taking vitamin D3 supplementation or activated vitamin D diagnosed with osteoporosis or bone fractures severe dementia or depression severe psychosis and hallucinations considered incapable of taking part in the study Characteristics Male sex (%): Vitamin D3 group (n=56)= 52 Placebo group (n=58)= 53 Age, y, mean (SD): Vitamin D3 group (n=56)= 72.5 (6.6) Placebo group (n=58)= 71.2 (6.9) BMI, kg/m2, mean (SD): Vitamin D3 group (n=56)= 22.7 (2.8) Placebo group (n=58)= 22.8 (3.7) Disease duration, months, median (interquartile range): Vitamin D3 group (n=56)= 24 (2-60) Placebo group (n=58)= 13 (3-42) Levodopa dose equivalency, mg, median (interquartile range): Vitamin D3 group (n=56)= 300 (150-550) Placebo group (n=58)= 300 (150-600) Disease duration, months, median (interquartile range):	scored by the same neurologists, PDQ39 and EQ-5D were answered by patients. Interventions Vitamin D group: 1200 IU daily for 12 months Placebo group: matched placebo	Placebo (n=57)= 4.20 (14.5) Not worsened or improved, n (%) Vitamin D3 (n=55)= 21 (38.2) Placebo (n=57)= 22 (38.6) Relative risk= 0.99 (0.62-1.58) Risk Difference= -0.00 (0.14-0.16) UPDRS part 1 (0-16) Change (after- before) Mean (SD) Vitamin D3 (n=55)= 0.11 (1.30) Placebo (n=57)= 0.49 (1.63) Not worsened or improved, n (%) Vitamin D3 (n=55)= 12 (21.8) Placebo (n=57)= 12 (21.1) Relative risk= 1.04 (0.51-2.11) Risk Difference= 0.01 (-0.14-0.16) UPDRS Part II (0-48) Change (after- before) Mean (SD) Vitamin D3 (n=55)= -0.87 (12.8) Placebo (n=57)= 4.37 (14.6) Not worsened or improved, n (%) Vitamin D3 (n=55)= 26 (47.3) Placebo (n=57)= 16 (28.1) Relative risk= 1.68 (1.02-2.78) Risk Difference= 0.19 (0.02-0.37) UPDRS part III (0-108) Change (after- before) Mean (SD) Vitamin D3 (n=55)= -1.05 (10.0) Placebo (n=57)= 1.05 (9.09) Not worsened or improved, n (%)	baseline for all major confounding/prognostic factors? YES Did the comparison groups receive the same care apart from interventions studied? YES Were participants receiving care kept blind to treatment allocation?YES Were the individuals administering care kept blind to treatment allocation? YES Were groups comparable with respect to availability of outcome data and for how many participants were no outcome data available? YES (1 in the

Study details	Participants	Methods	Results	Comments
Education, Culture, Sports, Science and Technology. The Japan-Supported Program for the Strategic Research Foundation at Private Universities and the Jikei University School of Medicine.	Vitamin D3 group (n=56)= 24 (2-60) Placebo group (n=58)= 13 (3-42) Modified Hoehn and Yahr, stage Vitamin D3 group, n: 1/1.5= 5/1 2/2.5= 26/13 3= 9 4= 1 5= 1 Placebo group, n: 1/1.5= 10/2 2/2.5= 23/9 3= 12 4= 2 5= 0 UPDRS total, median (interquartile range) Vitamin D3 group (n=56)= 34 (22.5-48.5) Placebo group (n=58)= 32 (20-44) UPDRS Part I: mentation, mood and behaviour, median (interquartile range) Vitamin D3 group (n=56)= 1 (0-2) Placebo group (n=58)= 0.5 (0-1) UPDRS Part II: activities of daily living, median (interquartile range) Vitamin D3 group (n=56)= 9 (6.5-13.5) Placebo group (n=58)= 8 (5-12) UPDRS Part III: motor examination, median		Vitamin D3 (n=55)= 27 (49.1) Placebo (n=57)= 27 (47.4) Relative risk= 1.04 (0.71, 1.52) Risk Difference= 0.02 (-0.11, 0.16) UPDRS part IV (0-23) Change (after- before) Mean (SD) Vitamin D3 (n=55)= 0.35 (1.54) Placebo (n=57)= 0.44 (1.32) Not worsened or improved, n (%) Vitamin D3 (n=55)= 9 (16.4) Placebo (n=57)= 8 (14.0) Relative risk= 1.17 (0.48, 2.80) Risk Difference= 0.02 (-0.11, 0.16) MMSE (stages 1-5) Change (after- before) Mean (SD) Vitamin D3 (n=55)= -0.33 (2.16) Placebo (n=57)= 0.27 (1.74) Not worsened or improved, n (%) Vitamin D3 (n=55)= 31 (63.3) Placebo (n=57)= 43 (78.2) Relative risk= 0.81 (0.63, 1.04) Risk Difference= -0.15 (-0.32, 0.02) PDQ39 total Change (after- before) Mean (SD) Vitamin D3 (n=55)= -5.41 (17.4) Placebo (n=57)= -3.15 (17.5) Not worsened or improved, n (%) Vitamin D3 (n=55)= 33 (67.3) Placebo (n=57)= 31 (56.4)	placebo group and 1 in the treatment group had no outcome data analysed) Did the study have an appropriate length of follow up? YES Did the study use a precise definition of outcome? YES Was a valid and reliable method used to determine that outcome? YES Were investigators kept blind to participant's exposure to the intervention? YES Were investigators kept blind to other important confounding and prognostic factors? UNCLEAR Other

Study details	Participants	Methods	Results	Comments
	(interquartile range) Vitamin D3 group (n=56)= 22 (13-32) Placebo group (n=58)= 20 (14-29) UPDRS Part IV: complications of therapy, median (interquartile range) Vitamin D3 group (n=56)= 0 (0-1) Placebo group (n=58)= 0 (0-1) MMSE, median (interquartile range) Vitamin D3 group (n=56)= 28 (26-30) Placebo group (n=58)= 28 (26-30) 25(OH)D, ng/mL, mean (SD) Vitamin D3 group (n=56)= 22.5 (9.7) Placebo group (n=58)= 21.1 (8.8) 1,25(OH)D, pg/mL, mean (SD) Vitamin D3 group (n=56)= 61.3 (17.1) Placebo group (n=58)= 60.4 (16.8)		Relative risk= 1.19 (0.88-1.62) Risk Difference= 0.11 (-0.08, 0.30) PDQ39 mobility Change (after- before) Mean (SD) Vitamin D3 (n=55)= -3.80 (25.3) Placebo (n=57)= -0.77 (26.5) Not worsened or improved, n (%) Vitamin D3 (n=55)= 24 (50) Placebo (n=57)= 24 (43.6) Relative risk= 1.15 (0.76-1.73) Risk Difference= 0.06 (-0.13, 0.26) PDQ39 activities of daily living Change (after- before) Mean (SD) Vitamin D3 (n=55)= -2.47 (23.9) Placebo (n=57)= -0.83 (24.7) Not worsened or improved, n (%) Vitamin D3 (n=55)= 29 (59.2) Placebo (n=57)= 21 (38.2) Relative risk= 1.55 (1.03, 2.33) Risk Difference= 0.21 (0.02, 0.40) PDQ39 emotional well being Change (after- before) Mean (SD) Vitamin D3 (n=55)= -5.27 (22.6) Placebo (n=57)= -3.56 (21.8) Not worsened or improved, n (%) Vitamin D3 (n=55)= 31 (63.3) Placebo (n=57)= 24 (43.6) Relative risk= 1.45 (1.00, 2.10) Risk Difference= 0.20 (0.01, 0.38)	information

Study details	Participants	Methods	Results	Comments
			PDQ39 stigma Change (after- before) Mean (SD) Vitamin D3 (n=55)= 0.30 (23.9) Placebo (n=57)= -5.45 (16.5) Not worsened or improved, n (%) Vitamin D3 (n=55)= 18 (36.7) Placebo (n=57)= 23 (41.8) Relative risk= 0.88 (0.54-1.42) Risk Difference= -0.05 (-0.24, 0.14) PDQ39 communication Change (after- before) Mean (SD) Vitamin D3 (n=55)= -5.73 (18.81) Placebo (n=57)= -3.56 (21.8) Not worsened or improved, n (%) Vitamin D3 (n=55)= 21 (43.8) Placebo (n=57)= 21 (38.2) Relative risk= 1.15 (0.72-1.82) Risk Difference= 0.06 (-0.13, 0.25) PDQ39 bodily support Change (after- before) Mean (SD) Vitamin D3 (n=55)= -7.64 (20.8) Placebo (n=57)= -1.97 (22.2) Not worsened or improved, n (%) Vitamin D3 (n=55)= 29 (60.4) Placebo (n=57)= 23 (41.8) Relative risk= 1.44 (0.98-2.13) Risk Difference= 0.19 (-0.00, 0.38) PDQ39 social support	

Study details	Participants	Methods	Results	Comments
			Change (after- before) Mean (SD) Vitamin D3 (n=55)= -3.65 (19.7) Placebo (n=57)= 0.00 (17.3) Not worsened or improved, n (%) Vitamin D3 (n=55)= 03 (27.1) Placebo (n=57)= 12 (21.8) Relative risk= 1.24 (0.63-2.46) Risk Difference= 0.05 (-0.11, 0.22) PDQ39 cognitive impairment Change (after- before) Mean (SD) Vitamin D3 (n=55)= -2.86 (17.0) Placebo (n=57)= -1.36 (18.5) Not worsened or improved, n (%) Vitamin D3 (n=55)= 18 (37.5) Placebo (n=57)= 25 (45.5) Relative risk= 0.83 (0.52-1.31) Risk Difference= -0.08 (-0.27, 0.11) EQ-5Q Change (after- before) Mean (SD) Vitamin D3 (n=55)= 0.01 (0.20) Placebo (n=57)= -0.04 (0.31) Not worsened or improved, n (%) Vitamin D3 (n=55)= 12 (25.0) Placebo (n=57)= 18 (32.7) Relative risk= 0.76 (0.41-1.42) Risk Difference= -0.08 (-0.25, 0.10) Visual analog scale Change (after- before) Mean (SD) Vitamin D3 (n=55)= -4.58 (16.0)	

Study details	Participants	Methods	Results	Comments
			Placebo (n=57)= -1.51 (20.0) Not worsened or improved, n (%) Vitamin D3 (n=55)= 25 (52.1) Placebo (n=57)= 34 (61.8) Relative risk= 0.84 (0.60-1.19) Risk Difference= -0.10 (-0.29, 0.09) EQ-5Q | | Mean | SD | Total | | Experimental | 0.01 | 0.20 | 55 | | Control | -0.04 | 0.31 | 57 | PDQ39 total (mean difference from baseline) | | Mean | SD | Total | | Experimental | -5.41 | 17.40 | 55 | | Control | 3.15 | 17.50 | 57 | PDQ39 cognitive impairment (mean difference from baseline) | | Mean | SD | Total | | Experimental | -2.86 | 17.00 | 55 | | Control | -1.36 | 18.50 | 57 | PDQ39 social support(mean difference from baseline) | | Mean | SD | Total |	

Study details	Participants	Methods	Results	Comments

Experimental	-3.65	19.70	55
Control	0.00	17.30	57

PDQ39 bodily support (mean difference from baseline)

	Mean	SD	Total
Experimental	-7.64	20.80	55
Control	-1.97	22.20	57

PDQ39 communication (mean difference from baseline)

	Mean	SD	Total
Experimental	-5.73	18.81	55
Control	-3.56	21.80	57

PDQ39 stigma (mean difference from baseline)

	Mean	SD	Total
Experimental	0.30	23.90	55
Control	-5.45	16.50	57

PDQ39 emotional well being (mean difference from baseline)

	Mean	SD	Total
Experimental	-5.27	22.60	55

Study details	Participants	Methods	Results	Comments

Control	-3.56	21.80	57

PDQ39 activities of daily living (mean difference from baseline)

	Mean	SD	Total
Experimental	-2.47	23.90	55
Control	-0.83	24.70	57

PDQ39 Mobility (mean difference from baseline)

	Mean	SD	Total
Experimental	-3.80	25.30	55
Control	-0.77	26.50	57

MMSE (stage 1-5) (mean difference from baseline)

	Mean	SD	Total
Experimental	-0.33	2.16	55
Control	0.27	1.74	57

Hoehn & Yahr scores (mean difference from baseline)

	Mean	SD	Total
Experimental	0.02	0.62	55
Control	0.33	0.70	57

Study details	Participants	Methods	Results	Comments
			Total UPDRS score UPDRS, mean difference from baseline) | | Mean | SD | Total | | Experimental | -0.87 | 12.80 | 55 | | Control | 4.20 | 14.50 | 57 | UPDRS (complications) mean difference from baseline) | | Mean | SD | Total | | Experimental | 0.35 | 1.54 | 55 | | Control | 0.44 | 1.32 | 57 | UPDRS (motor) mean difference from baseline) | | Mean | SD | Total | | Experimental | -1.05 | 10.00 | 55 | | Control | 1.05 | 9.09 | 57 | UPDRS (activities of daily living) mean difference from baseline) | | Mean | SD | Total | | Experimental | -0.87 | 12.80 | 55 | | Control | 4.37 | 14.60 | 57 | UPDRS (mentation, behaviour and mood)	

<table>
<tr><th>Study details</th><th>Participants</th><th>Methods</th><th>Results</th><th>Comments</th></tr>
<tr><td></td><td></td><td></td><td>mean difference from baseline)
<table><tr><td></td><td>Mean</td><td>SD</td><td>Total</td></tr><tr><td>Experimental</td><td>0.11</td><td>1.30</td><td>55</td></tr><tr><td>Control</td><td>0.49</td><td>1.63</td><td>57</td></tr></table></td><td></td></tr>
<tr><td>Full citation
Tsui,J.K., Ross,S., Poulin,K., Douglas,J., Postnikoff,D., Calne,S., Woodward,W., Calne,D.B., 19890510, The effect of dietary protein on the efficacy of L-dopa: a double-blind study, Neurology, 39, 549-552, 1989
Ref Id
285767
Country/ies where the study was carried out
Canada
Study type
Randomised controlled trial (cross-over)

Aim of the study</td><td>Sample size
10 participants

Inclusion criteria
Idiopathic Parkinson's disease

Exclusion criteria
None stated

Characteristics
4 men and 6 women
all had unpredictable fluctuations
five had freezing episodes
All had normal minimental states
Mean age 64 (range 48-81)
Mean duration of illness 12.4 years (range 6-19)
All taking L-dopa administered with carbidopa (mean daily dose of 535 mg (range 300-875))
7 taking bromocriptine (mean daily dose 49.6 mg (range 22.5-80))
5 taking deprenyl (mean daily dose 5 mg (range 2.5-7.5))</td><td>Details
Double blind, crossover, randomised controlled study over 2 weeks
Blood levels of L-dopa were estimated in sequence after intake of L-dopa to study the effect of the amount of protein on drug absorption. Clinical efficacy was compared while the patients were on the two diets.
The patients were admitted to hospital and spent the first 3 days familiarising themselves with the self-evaluation fluctuation charts. In randomised order they were started on the first special diet for 5 days and then put on the second diet for another 5 days with a 2 day rest period in between. All treatment</td><td>Results
Modified Columbia Scores
Low protein diet (n=10) = 17.85 ± 12.21
High protein diet (n=10) = 21.83 ± 12.52
*This data was estimated and drawn off a graph provided within the study, means and standard deviations for each individual were subsequently combined using an online tool found at https://www.statstodo.com/ComMeans_Pgm.php. This outcome is subsequently marked down for imprecision.

Percentage of "on" hours while awake (%)
Low protein diet (n=10) = 70.6 ± 13.85
High protein diet = 59.95 ± 19.70
*This data was estimated and drawn off a graph provided within the study, means and standard deviations for each individual were subsequently combined using an online tool found at https://www.statstodo.com/ComMeans_Pgm.php. This outcome is subsequently marked down for imprecision.

Modified Columbia scores</td><td>Overall Risk of Bias
Has an appropriate method of randomisation been used?
UNCLEAR
Was there adequate concealment of allocation?
UNCLEAR
Were the groups comparable at baseline for all major confounding/prognostic factors?
YES
Did the comparison groups receive the same care apart from interventions studied? YES
Were participants</td></tr>
</table>

Study details	Participants	Methods	Results	Comments
To compare the effect of high and low protein diets on the efficacy of l-dopa Study dates Published 1989 Source of funding None stated		and daily routines remained unchanged. Strict diet control was exercised during all phases of the study. Between meal snacks were allowed from a list drawn up by the dieticians; medications were taken with fruit juice. Each day the patients filled in a fluctuation chart, which consisted of a record of "on" or "off" and the occurrence of dyskinesia or tremor every hour. At the end of the study the patients identified which week they felt better. Interventions Patients received two special diets identical in taste and appearance, differing only in protein content while bulk (volume and fiber contents) remained unchanged.	<table><tr><td></td><td>Mean</td><td>SD</td><td>Total</td></tr><tr><td>Experimental</td><td>17.85</td><td>12.21</td><td>10</td></tr><tr><td>Control</td><td>21.83</td><td>12.52</td><td>10</td></tr></table> Percentage "on" hours <table><tr><td></td><td>Mean</td><td>SD</td><td>Total</td></tr><tr><td>Experimental</td><td>70.60</td><td>13.85</td><td>10</td></tr><tr><td>Control</td><td>59.95</td><td>19.70</td><td>10</td></tr></table>	receiving care kept blind to treatment allocation?YES Were the individuals administering care kept blind to treatment allocation? YES Were groups comparable with respect to availability of outcome data and for how many participants were no outcome data available? YES Did the study have an appropriate length of follow up? NO Did the study use a precise definition of outcome? NO ("averages" reported and data presented in graphs with poor labeling and no tables)

<table>
<tr><th>Study details</th><th>Participants</th><th>Methods</th><th>Results</th><th>Comments</th></tr>
<tr><td></td><td></td><td></td><td></td><td>Was a valid and reliable method used to determine that outcome? YES (only on/off self reported)
Were investigators kept blind to participant's exposure to the intervention? YES
Were investigators kept blind to other important confounding and prognostic factors? YES

Other information</td></tr>
<tr><td>Full citation
Cucca,A., Mazzucco,S., Bursomanno,A., Antonutti,L., Di Girolamo,F.G., Pizzolato,G., Koscica,N., Gigli,G.L., Catalan,M., Biolo,G., Amino</td><td>Sample size
22

Inclusion criteria
A diagnosis of PD by a neurologist specialised in movement disorders according to the UK PD Brain Bank criteria
Patients (aged from 50 to 90 years, with a BMI lower than 30kg/m2) on l-dopa therapy for at least 2 years with a suggested protein redistribution diet</td><td>Details
This is a monocentric, prospective, randomised, double-blind study on two groups PD-affected, protein-restricted, patients

Interventions</td><td>Results

Mass, Kg (mean difference from baseline)<table><tr><td></td><td>Mean</td><td>SD</td><td>Total</td></tr><tr><td>Experimental</td><td>64.60</td><td>6.87</td><td>7</td></tr><tr><td>Control</td><td>71.10</td><td>6.87</td><td>7</td></tr></table>
UPDRS (motor) mean difference from</td><td>Overall Risk of Bias
Has an appropriate method of randomisation been used? UNCLEAR
Was there adequate</td></tr>
</table>

<table>
<tr><th>Study details</th><th>Participants</th><th>Methods</th><th>Results</th><th>Comments</th></tr>
<tr>
<td>acid supplementation in l-dopa treated Parkinson's disease patients, Clin Nutr, 34, 1189-1194, 2015
Ref Id
675544
Country/ies where the study was carried out
Italy
Study type
Randomised, double-blind pilot study

Aim of the study
To investigate the effect of 6 months of AA supplementation in PD-affected patients chronically treated with l-dopa showing fluctuations in their therapeutic response.

Study dates
2010-2013</td>
<td>Exclusion criteria
- Diabetes, kidney failure, heart failure, liver cirrhosis or any other relevant systemic comorbidity.

Characteristics
<table><tr><td></td></tr><tr><td>Number</td></tr><tr><td>Sex (F/M)</td></tr><tr><td>Age (y)</td></tr><tr><td>BMI (kg/m2)</td></tr><tr><td>Waist circumference (cm)</td></tr><tr><td>Disease duration (y)</td></tr></table></td>
<td>Intervention: Amino acid supplementation. Patients took 8 g of essential AA mixture 60 min after lunch and 60 min after dinner, for a total daily dose of 16g, each time at least 60 min before the following l-dopa administration. Every administration of AA mixture corresponds to 28g of proteins.
Control group: Placebo tablets</td>
<td>baseline)<table><tr><td></td><td>Mean</td><td>SD</td><td>Total</td></tr><tr><td>Experimental</td><td>16.30</td><td>7.67</td><td>7</td></tr><tr><td>Control</td><td>13.10</td><td>5.02</td><td>7</td></tr></table></td>
<td>concealment of allocation? UNCLEAR
Were the groups comparable at baseline for all major confounding/prognostic factors? YES
Did the comparison groups receive the same care apart from interventions studied? YES
Were participants receiving care kept blind to treatment allocation? UNCLEAR
Were the individuals administering care kept blind to treatment allocation? UNCLEAR
Were groups comparable with respect to availability of</td>
</tr>
</table>

Study details	Participants	Methods	Results	Comments
Source of funding No funding reported				outcome data and for how many participants were no outcome data available? YES Did the study have an appropriate length of follow up? YES Did the study use a precise definition of outcome? YES Was a valid and reliable method used to determine that outcome? YES Were investigators kept blind to participant's exposure to the intervention? UNCLEAR Were investigators kept blind to other important confounding and prognostic factors? UNCLEAR

Study details	Participants	Methods	Results	Comments
				Serious risk of bias
Full citation Negida,A., Menshawy,A., El,Ashal G., Elfouly,Y., Hani,Y., Hegazy,Y., El,Ghonimy S., Fouda,S., Rashad,Y., Coenzyme Q10 for Patients with Parkinson's Disease: A Systematic Review and Meta-Analysis, CNS Neurol Disord Drug Targets, 15, 45-53, 2016 Ref Id 675545 Country/ies where the study was carried out Egypt Study type A systematic	Sample size 5 RCTs (981 patients) Inclusion criteria RCTs comparing CoQ10 supplementation with palcebo Intervention: Drug: CoQ10 Dose: all doses from 300mg/d to 2400mg/d are eligible Physical form: hydrophobic form "Ubiquinone" Preparation: Both the standard formulation and nanoparticle are eligible Supplementary Vit E may be administrated with CoQ10 Comparator: Placebo (control group) Population: Patients with early or midstage idiopathic PD Outcome: at least one of the following outcomes - UPDRS (mental, ADL, motor, total) and ADL on Schwab and England score Exclusion criteria Studies that used a form of CoQ10 other than the Ubiguinone. Characteristics	Details Authors followed the PRISMA statement guidelines during the preparation of this review and meta-analysis. Medical electronic databases searched: PubMed, Ovid Medline, EBSCO and Web of science through December 2014 using the following query: "Coenzyme Q10 AND Parkinson's disease". Three authors applied the selection criteria, 6 authors extracted data independently and 2 authors independently assessed the quality of each included study in strict accordance with the Cochrane handbook of systematic reviews of interventions 5.1.0. Measures of treatment effect: Schwab and	Results UPDRS total: MD -0.05 [-0.25, 0.15] UPDRS mental: MD -0.03 [-0.23, 0.17] UPDRS ADL: MD -0.10 [-0.35, 0.15] UPDRS motor: MD 0.05 [-0.07, 0.17] ADL Schwab and England score: MD 0.08 [-0.13, 0.29]	Overall Risk of Bias Authors' judgement: "The quality of this evidence is credible as it is based on high quality studies as indicated by risk of bias assessment. Search methods and eligibility criteria were well defined."

<table>
<tr><th>Study details</th><th>Participants</th><th>Methods</th><th>Results</th><th>Comments</th></tr>
<tr>
<td>review and meta-analysis

Aim of the study
To synthesize evidence from published RCTs about the benefit of CoQ10 supplementation for patients with PD

Study dates
December 2014

Source of funding
Financial support for the LS-1 study was provided by National Institute of Neurological Disorders and Stroke (NINDS)</td>
<td>
<table>
<tr><th>Study</th><th>Intervention</th><th>Population</th></tr>
<tr><td>QE3 investigators 2014</td><td>1200 mg/d or 2400mg/d of CoQ10 vs placebo</td><td>Patients with idiopathic PD diagnosed within the past 5 years</td></tr>
<tr><td>NINDS NET-PD 2007</td><td>2400mg/d of CoQ10 or 4000mg GPI-1485 vs placebo</td><td>patients who had a diagnosis with PD and not requring any medication for their symptoms</td></tr>
<tr><td>Storch et al 2007</td><td>300mg/d nanoparticular CoQ10 vs placebo</td><td>PD patients without fluctuations and on a stable anti-PD treatment</td></tr>
<tr><td>Muller et al 2003</td><td>360mg/d of CoQ10 vs placebo</td><td>PD patients on stable anti-PD treatment</td></tr>
<tr><td>Shults et al 2002</td><td>300mg/d, 600mg/d or 2400mg/d of CoQ10 vs placebo</td><td>Patients with idiopathic PD diagnosed within the past 5 years</td></tr>
</table>
</td>
<td>England score, UPDRS score and its subscales.
The search strategy retrieved 1251 unique citations, 20 full texts were retrieved and reviewed and 5 met the inclusion criteria and were included in this review.

Interventions
Coenzyme Q10 (all doses from 300mg to 2400mg/d) vs. placebo</td>
<td></td>
<td></td>
</tr>
</table>

D.6 Advanced therapies: deep brain stimulation and levodopa–carbidopa intestinal gel

D.6.1 Brain stimulation, levodopa–carbidopa intestinal gel and best medical treatment for advanced Parkinson's disease

DBS -v- BMT

Bibliographic reference	**Deuschl,G., Schade-Brittinger,C., Krack,P., Volkmann,J., Schafer,H., Botzel,K., Daniels,C., Deutschlander,A., Dillmann,U., Eisner,W., Gruber,D., Hamel,W., Herzog,J., Hilker,R., Klebe,S., Kloss,M., Koy,J., Krause,M., Kupsch,A., Lorenz,D., Lorenzl,S., Mehdorn,H.M., Moringlane,J.R., Oertel,W., Pinsker,M.O., Reichmann,H., Reuss,A., Schneider,G.H., Schnitzler,A., Steude,U., Sturm,V., Timmermann,L., Tronnier,V., Trottenberg,T., Wojtecki,L., Wolf,E., Poewe,W., Voges,J., German Parkinson Study Group,Neurostimulation Section, 20060905, A randomized trial of deep-brain stimulation for Parkinson's disease.[Erratum appears in N Engl J Med. 2006 Sep 21;355(12):1289], New England Journal of Medicine, 355, 896-908, 2006**
Country/ies where the study was carried out	Germany and Austria (10 centres)
Study type	RCT of DBS for PD compared to best medical management
Aim of the study	Changes in the quality of life and motor function, the latter assessed while the patient was not receiving medication, were the primary outcomes
Study dates	No dates given, published 2006
Source of funding	Supported by a grant from the German Federal Ministry of Education and Research.
Sample size	N = 156 (78 per arm)
Inclusion criteria	Patients were eligible for enrolment if they: • had received a clinical diagnosis of idiopathic Parkinson's disease according to the British Parkinson's Disease Society Brain Bank criteria at least five years previously; • were under 75 years of age; • had parkinsonian motor symptoms or dyskinesias that limited their ability to perform the activities of daily living, despite receipt of optimal medical therapy; • had no dementia or major psychiatric illness and • had no contraindications to surgery Neurologists specializing in movement disorders at the participating centres gave their assurance that each patient had received state-of-the-art antiparkinsonian medication.
Exclusion criteria	See inclusion criteria

Bibliographic reference	**Deuschl,G., Schade-Brittinger,C., Krack,P., Volkmann,J., Schafer,H., Botzel,K., Daniels,C., Deutschlander,A., Dillmann,U., Eisner,W., Gruber,D., Hamel,W., Herzog,J., Hilker,R., Klebe,S., Kloss,M., Koy,J., Krause,M., Kupsch,A., Lorenz,D., Lorenzl,S., Mehdorn,H.M., Moringlane,J.R., Oertel,W., Pinsker,M.O., Reichmann,H., Reuss,A., Schneider,G.H., Schnitzler,A., Steude,U., Sturm,V., Timmermann,L., Tronnier,V., Trottenberg,T., Wojtecki,L., Wolf,E., Poewe,W., Voges,J., German Parkinson Study Group,Neurostimulation Section, 20060905, A randomized trial of deep-brain stimulation for Parkinson's disease.[Erratum appears in N Engl J Med. 2006 Sep 21;355(12):1289], New England Journal of Medicine, 355, 896-908, 2006**
Details	Centres enrolled patients in pairs, with one randomly assigned to neurostimulation within six weeks and the other to best medical treatment Randomisation, monitoring and data management were performed by the Coordinating Centre for Clinical Trials at Philipps University, Marburg, Germany
Interventions	Intervention: Bilateral stereotactic surgery under local anaesthesia. The STN was targeted by MRI, ventriculography, microelectrode recording or a combination of these (varied by centre). Kinetra Medtronic implants used. Standard pulse setting was 60µsec in duration at 130Hz, with voltage adjusted to the individual patient Best medical treatment - individualised optimal drug therapy according to the guidelines of the German Society of Neurology. Drugs adjusted to patient need throughout the study
Results	Demographics: • Mean age = 60.7 (7.6) • Disease duration = 13.4 years (5.7) • Female = 56 /156 (36%) Results:

index_measure	DBS_baseline	BMC_baseline	DBS_6mnt	BMC_6mnt	DBS_change	BMC_ change
PDQ-39 index	41.8 (13.9)	39.6 (SD 16.0)	31.8 (SD 16.3)	40.2 (SD 14.4)	9.5 (5.9, 13.1)	-0.2 (-2.9, 2.4)
UPDRS III off	48.0 (SD 12.3)	46.8 (SD 12.1)	28.3 (SD 14.7)	46.0 (SD 12.6)	19.6 (16.1, 23.2)	0.4 (-1.8, 2.6)
UPDRS III on	18.9 (SD 9.3)	17.3 (SD 9.6)	14.6 (SD 8.5)	17.85 (SD 10.6)	4.0 (1.7, 6.4)	-0.4 (-2.2, 1.4)
UPDRS II off	22.5 (SD 7.2)	21.9 (SD 6.4)	13.7 (SD 7.9)	22.9 (SD 5.7)	8.8 (6.8, 10.8)	-0.8 (-2.3, 0.7)
UPDRS II on	9.0 (SD 5.5)	7.9 (SD 5.8)	7.6 (SD 5.4)	9.0 (SD 5.3)	1.5 (0.2, 2.7)	-1.1 (-2.3, 0.1)
Dyskinesia off	0.5 (SD 2.0)	0.5 (SD 1.7)	0.2 (SD 1.7)	0.1 (SD 0.6)	0.2 (-0.4, 0.7)	0.2 (-0.2, 0.6)
Dyskinesia on	6.7 (SD 5.3)	8.4 (SD 5.9)	3.1 (SD 3.5)	8.6 (SD 5.5)	3.4 (2.3, 4.5)	-0.4 (-1.5, 0.7)*
SES off	47 (SD 19)	48 (SD 19)	70 (SD 20)	45 (SD 18)	-23 (-28, 18)	1 (-2, 5)

Bibliographic reference	**Deuschl,G., Schade-Brittinger,C., Krack,P., Volkmann,J., Schafer,H., Botzel,K., Daniels,C., Deutschlander,A., Dillmann,U., Eisner,W., Gruber,D., Hamel,W., Herzog,J., Hilker,R., Klebe,S., Kloss,M., Koy,J., Krause,M., Kupsch,A., Lorenz,D., Lorenzl,S., Mehdorn,H.M., Moringlane,J.R., Oertel,W., Pinsker,M.O., Reichmann,H., Reuss,A., Schneider,G.H., Schnitzler,A., Steude,U., Sturm,V., Timmermann,L., Tronnier,V., Trottenberg,T., Wojtecki,L., Wolf,E., Poewe,W., Voges,J., German Parkinson Study Group,Neurostimulation Section, 20060905, A randomized trial of deep-brain stimulation for Parkinson's disease.[Erratum appears in N Engl J Med. 2006 Sep 21;355(12):1289], New England Journal of Medicine, 355, 896-908, 2006**

SES on	80 (SD 19)	82 (SD 17)	83 (SD 16)	79 (SD 15)	-4 (-7, 0)	3 (0, 7)
Ldopa (mg/day)	1176 (SD 517)	1175 (SD 461)	597 (SD 381)	1060 (SD 467)	-593 (-722, -463)*	-95 (-187, -3)*
MDRS	139.6 (SD 3.8)	140.3 (SD 3.4)	137.5 (SD 5.7)	139.6 (SD 4.7)	2.0 (0.8, 3.2)	0.5 (-0.5, 1.5)
MADRS	8.5 (SD 5.5)	7.7 (SD 5.8)	8.1 (SD 6.6)	8.5 (SD 5.4)	0.3 (-1.5, 2.1)	-0.6 (-2.1, 0.9)
BPRS	27.7 (SD 5.2)	27.1 (SD 6.2)	24.8 (SD 5.3)	26.4 (SD 5.3)	2.7 (1.0, 4.4)	0.8 (-0.7, 2.3)

*sign corrected from paper

Other information	None
Overall Risk of Bias	1. An appropriate method of randomization was used to allocate pts to treatment groups: Yes - patient randomized externally in pairs 2. There was adequate concealment of allocation: Unclear 3. The groups were comparable at baseline, including all major confounding and prognostic factors: Yes - matched pairs randomized 4. Comparison groups received same care apart from interventions: Yes 5. Pts receiving care were kept blind to tmt allocation: No - not possible 6. Individuals administering care were kept blind to tmt allocation: No 7. All groups followed up for an equal length of time: Yes 8. Groups comparable for treatment completion: Yes 9. Groups were comparable with respect to availability of outcome data: Yes 10. Study had appropriate length of follow-up: Yes - further follow up reported in Witt et al., 2013 paper 11. Study used a precise definition of outcome: Yes - clearly defined outcomes 12. Valid and reliable method was used to determine the outcome: Yes - well-validated measures used 13. Investigators were kept blind to participants exposure to the intervention: No 14. Investigators were kept blind to other important confounding and prognostic factors: Investigators initially kept blind to patient details but intervention group known (surgical scars obvious)

Bibliographic reference	**Okun,M.S., Gallo,B.V., Mandybur,G., Jagid,J., Foote,K.D., Revilla,F.J., Alterman,R., Jankovic,J., Simpson,R., Junn,F., Verhagen,L., Arle,J.E., Ford,B., Goodman,R.R., Stewart,R.M., Horn,S., Baltuch,G.H., Kopell,B.H., Marshall,F., Peichel,P., Pahwo,R., Lyons,K.E.,Trster,A.I., Vitek,J.L., Tagliati,M., for the SJM DBS Study Group., Subthalmic deep brain stimulation with a constant-current device in Parkinson's disease: an open-label randomised controlled trial, The Lancet Neurology. 11 (pp140-149), 2012. Date of Publication: 11 January 2012**
Country/ies where the study was carried out	USA
Study type	Randomised controlled open-label study
Aim of the study	To assess the safety and efficacy of bilateral constant-current DBS of the subthalmic nucleus.
Study dates	September 2005 – August 2010
Source of funding	St Jude Medical Neuromodulation division (Note: all authors have multiple conflicts of interests with a range of research and pharmaceutical companies)
Sample size	N = 136; n immediate DBS = 101, n delayed DBS = 35
Inclusion criteria	• Adults aged 18-80 years of age • Diagnosed with Parkinson's disease (UK Parkinson's Disease Society Brain Bank criteria) for at least 5 years • At least 6 hours daily "off-time" or moderate to severe dyskinesias during waking hours • A history of improvement of Parkinson's symptoms of levodopa therapy • Willing to maintain a constant dose of anti-Parkinson's disease medication for at least one month prior to study enrolment • Available for appropriate follow-up times for the length of the study
Exclusion criteria	• Any major illness or medical condition that would interfere with participation in the study • Currently suffers from untreated, major depression • An electrical or electromagnetic implant (e.g. cochlear prosthesis or pacemaker) • A prior surgery for the treatment of PD symptoms, including previous DBS surgery • Dementia • Drug or alcohol abuse • Woman of child-bearing potential • History of seizures
Details	Patients randomly assigned to either immediate DBS or 3-month delayed stimulation The randomisation ratio was 3:1, to maximise the number of patients exposed to stimulation Randomisation was computer-generated (SAS version 9.2) in blocks of four at each site before the start of the trial Patients and raters were aware of group assignment after device implantation

<table>
<tr><th>Bibliographic reference</th><td>Okun,M.S., Gallo,B.V., Mandybur,G., Jagid,J., Foote,K.D., Revilla,F.J., Alterman,R., Jankovic,J., Simpson,R., Junn,F., Verhagen,L., Arle,J.E., Ford,B., Goodman,R.R., Stewart,R.M., Horn,S., Baltuch,G.H., Kopell,B.H., Marshall,F., Peichel,P., Pahwo,R., Lyons,K.E.,Trster,A.I., Vitek,J.L., Tagliati,M., for the SJM DBS Study Group., Subthalmic deep brain stimulation with a constant-current device in Parkinson's disease: an open-label randomised controlled trial, The Lancet Neurology. 11 (pp140-149), 2012. Date of Publication: 11 January 2012</td></tr>
<tr><td>Interventions</td><td>Bilateral lead implantations were done either in one surgery (simultaneous bilateral implantation) or in a staged procedure with the two lead implantations separated by 2–4 weeks
DBS devices (Libra DBS device) were implanted by use of MRI or CT-MRI fusion for targeting and microelectrode recording for target refinement, followed by intra- operative test stimulation of the DBS lead. The pulse generators were placed in a subclavicular position either on the same day or within a maximum of 6 weeks of lead implantation.
All participating centres used microelectrode recording to refine targeting and DBS placement
All participating centres used existing DBS surgery equipment and were asked to physiologically refine the DBS targets based on their best medical practices. Devices implanted into patients in the stimulation group were programmed within 7 days after surgical implantation (day 0); those in the control group were not programmed until 3 months after implantation (day 90).

Statistical analyses
The analysis of the primary outcome was based on the difference between groups (stimulation vs control) in the duration of on time measured by patients' diaries at 3 months. This change was done by a two-way analysis of covariance that included the effects of treatment, study centre, and good quality on time at baseline. Study centres with fewer than four patients (n=2) were pooled to create a composite centre. Treatment effect was tested by a two-sided test at a significance level of 5%.</td></tr>
<tr><td>Results</td><td>Demographics:

<table>
<tr><td>Characteristic</td><td>Stimulation group (n=101)</td><td>Control group (n=35)</td></tr>
<tr><td>Age (years)</td><td>60.6 (SD 8.3)</td><td>59.5 (SD 8.2)</td></tr>
<tr><td>% Male</td><td>62%</td><td>60%</td></tr>
<tr><td>Disease duration (years)</td><td>12.1 (SD 4.9)</td><td>11.7 (SD 4.1)</td></tr>
<tr><td>% White</td><td>90</td><td>89</td></tr>
<tr><td>% African-American</td><td>1</td><td>0</td></tr>
<tr><td>% Hispanic</td><td>8</td><td>9</td></tr>
<tr><td>% Other ethnic origin</td><td>1</td><td>3</td></tr>
</table>
</td></tr>
</table>

Bibliographic reference	**Okun,M.S., Gallo,B.V., Mandybur,G., Jagid,J., Foote,K.D., Revilla,F.J., Alterman,R., Jankovic,J., Simpson,R., Junn,F., Verhagen,L., Arle,J.E., Ford,B., Goodman,R.R., Stewart,R.M., Horn,S., Baltuch,G.H., Kopell,B.H., Marshall,F., Peichel,P., Pahwo,R., Lyons,K.E.,Trster,A.I., Vitek,J.L., Tagliati,M., for the SJM DBS Study Group., Subthalmic deep brain stimulation with a constant-current device in Parkinson's disease: an open-label randomised controlled trial, The Lancet Neurology. 11 (pp140-149), 2012. Date of Publication: 11 January 2012**

Weight (kg)	80.6 (SD 18.3)	74.8 (SD 15.6)
Height (cm)	173.5 (SD 11.2)	171.2 (SD 10.4)

Efficacy analysis

Measure	Intervention (baseline)	Control (baseline)	Intervention (3m)	Control (3m)	Intervention (change)*	Control (change)*	Difference in change (95% CI)
Good quality on time	6.7 (SD 3.1)	7.4 (SD 2.5)	11.2 (SD 4.5)	8.9 (SD 2.9)	4.27	1.77	2.25 (0.87, 4.16)
UPDRS on	39.6 (SD 13.0)	38.6 (SD 14.4)	32.7 (SD 14.8)	44.6 (SD 13.6)	-6.83	5.33	-12.2 (-17.3, -7.0)
UPDRS 1 on	1.97 (SD 1.88)	1.77 (SD 1.69)	2.02 SD 91.87)	1.97 (SD 1.51)	0.17	0.18	0.00 (-0.68, 0.68)
UPDRS 2 on	9.2 (SD 5.6)	9.9 (SD 6.3)	10.3 (SD 6.5)	11.7 (SD 7.2)	1.02	1.93	-0.91 (-3.43, 1.61)
UPDRS 3 off1	40.8 (SD 10.8)	44.1 (SD 14.0)	38.5 (SD 13.4)	40.4 (SD 11.6)	-1.97	-2.56	0.59 (-3.06, 4.24)
UPDRS 3 off2	40.8 (SD 10.8)	44.1 (SD 14.0)	24.8 (SD 10.1)	40.4 (SD 11.6)	-16.1	-2.1	-14.0 (-17.5, -10.5)
UPDRS 3 on	18.3 (SD 9.5)	17.8 (SD 10.1)	15.1 (SD 8.2)	22.3 (SD 10.5)	-3.01	4.37	-7.38 (-10.18, -4.57)
UPDRS 4 on	8.8 (SD 3.5)	9.6 (SD 3.6)	4.5 (SD 2.9)	8.0 (SD 4.1)	-4.40	-1.00	-3.41 (-4.62, -2.19)
Ldopa dose (mg)	1311 (SD 615)	1459 (SD 991)	864 (SD 551)	1272 (SD 608)	-492	-131	-361 (-529, -193)

Bibliographic reference	**Okun,M.S., Gallo,B.V., Mandybur,G., Jagid,J., Foote,K.D., Revilla,F.J., Alterman,R., Jankovic,J., Simpson,R., Junn,F., Verhagen,L., Arle,J.E., Ford,B., Goodman,R.R., Stewart,R.M., Horn,S., Baltuch,G.H., Kopell,B.H., Marshall,F., Peichel,P., Pahwo,R., Lyons,K.E.,Trster,A.I., Vitek,J.L., Tagliati,M., for the SJM DBS Study Group., Subthalmic deep brain stimulation with a constant-current device in Parkinson's disease: an open-label randomised controlled trial, The Lancet Neurology. 11 (pp140-149), 2012. Date of Publication: 11 January 2012**

SES on	77.6 (SD 16.8)	76.5 (SD 16.3)	86.1 (SD 11.4)	76.8 (SD 17.7)	8.8	-0.5	9.3 (4.4, 15.3)
HDI	66.1 (SD 13.2)	69.3 (SD13.7)	57.4 (SD 13.7)	66.2 (SD 11.9)	-9.14	-1.80	-7.34 (-12.37, -2.31)
D-KEFS	10.6 (SD 3.8)	9.9 (SD 3.6)	8.7 (SD 3.6)	8.6 (SD 3.6)	-1.90	-1.52	-0.38 (-1.39, 0.63)
Hoehn and Yahr off	2.94 (SD 0.80)	3.30 (SD 0.89)	2.38 (SD 0.07)	3.14 (SD 0.95)	-0.64	-0.07	-0.57 (-0.81, -0.32)

*Adjusted for study site and baseline. [1]Comparison of baseline off medication with 3 months stimulation off and medication off. [2]Comparison of baseline off medication with 3 months stimulation on and medication off

Other information

Adverse events	Stimulation (0-3m)		Control (0-3m)		All patients (3-12m)	
	No events (%)	No patients (%)	No events (%)	No patients (%)	No events (%)	No patients (%)
All SAEs (n=50)	20 (40)	14 (14)	7 (14)	4 (11)	23 (46)	23 (17)
Confusion	1 (2)	1 (1)	0	0	0	0
CSF leakage	1 (2)	1 (1)	0	0	0	0
Depression	0	0	0	0	1 (2)	1 (<1)
Erosion through skin	0	0	0	0	1 (2)	1 (<1)
Gait disorder	1 (2)	1 (1)	0	0	3 (6)	3 (2)
Hardware problem (lead)	1 (2)	1 (1)	0	0	0	0
Infection	3 (6)	2 (2)	1 (2)	1 (3)	2 (4)	2 (1)
ICH	3 (6)	3 (3)	1 (2)	1 (3)	0	0

Bibliographic reference	Okun,M.S., Gallo,B.V., Mandybur,G., Jagid,J., Foote,K.D., Revilla,F.J., Alterman,R., Jankovic,J., Simpson,R., Junn,F., Verhagen,L., Arle,J.E., Ford,B., Goodman,R.R., Stewart,R.M., Horn,S., Baltuch,G.H., Kopell,B.H., Marshall,F., Peichel,P., Pahwo,R., Lyons,K.E.,Trster,A.I., Vitek,J.L., Tagliati,M., for the SJM DBS Study Group., Subthalmic deep brain stimulation with a constant-current device in Parkinson's disease: an open-label randomised controlled trial, The Lancet Neurology. 11 (pp140-149), 2012. Date of Publication: 11 January 2012						
	Lead migration	2 (4)	2 (2)	0	0	0	0
	Loss of stimulation	0	0	0	0	1 (2)	1 (<1)
	Motor fluctuations	1 (2)	1 (1)	0	0	0	0
	Worsening of PD	1 (2)	1 (1)	1 (2)	1 (3)	1 (2)	1 (<1)
	Pneumonia	0	0	1 (2)	1 (3)	0	0
	Psychiatric disturbances	0	0	0	0	1 (2)	1(<1)
	Seizures or convulsions	1 (2)	1 (1)	0	0	0	0
	Tremor	1 (2)	1 (1)	0	0	0	0
	Unrelated events	4 (8)	3 (3)	3 (6)	2 (6)	13 (26)	13 (10)
Overall Risk of Bias	1. An appropriate method of randomization was used to allocate pts to treatment groups: Yes 2. There was adequate concealment of allocation: Yes 3. The groups were comparable at baseline, including all major confounding and prognostic factors: Yes 4. Comparison groups received same care apart from interventions: Yes 5. Pts receiving care were kept blind to tmt allocation: No 6. Individuals administering care were kept blind to tmt allocation: No 7. All groups followed up for an equal length of time: Yes 8. Groups comparable for treatment completion: Yes 9. Groups were comparable with respect to availability of outcome data: Yes 10. Study had appropriate length of follow-up: Yes 11. Study used a precise definition of outcome: Yes - clearly defined outcomes 12. Valid and reliable method was used to determine the outcome: Yes - well-validated measures used 13. Investigators were kept blind to participants exposure to the intervention: No 14. Investigators were kept blind to other important confounding and prognostic factors: Yes						

Bibliographic reference	Perestelo-Perez,L., Rivero-Santana,A., Perez-Ramos,J., Serrano-Perez,P., Panetta,J., Hilarion,P., Deep brain stimulation in Parkinson's disease: meta-analysis of randomized controlled trials, Journal of NeurologyJ Neurol, 261, 2051-2060, 2014
Country/ies where the study was carried out	Spain
Study type	Meta-analysis: 6 x RCTs of DBS vs BSC
Aim of the study	To perform a a systematic analysis and to evaluate the efficacy of DBS to improve motor signs, functionality, and quality of life in PD patients
Study dates	Published 2014
Source of funding	Spanish health ministry
Sample size	6 RCT's, N = 1,184
Inclusion criteria	RCT's that compared DBS plus medication vs medication (alone or + sham device) in PD patients
Exclusion criteria	None listed.
Details	The following databases consulted up to April 2013: Medline, PreMedline, EMBASE, PsychInfo, CINAHL, Cochrane library, and center for reviews & dissemination Search strategy developed for each database using a combination of medical subject heading and free text terms: deep brain stimulation, electic stimulation therapy, DBS, bilateral DBS, cortical stimulation, brain pacemaker, neurostimulat [brain, cerebral, cingulate, cinguli, capsule, striatum, accumbens, thalam, cortex, hebenula, subthalamic nucleaus, STN, excitation, stimul, deep, depth, electric] Outcome measures of interest were: motor function (UPDRS III), waking time on good function without troubling dyskinesia, LEDD reduction, medication-induced complications, ADL, HRQoL, neurocognitive, psychiatric effects. 2 review authors screened all reporws of RCT;s and 5 extacted data independently. Resolved inconsistencies by discussion consensus Risk of bias done according to Cochrane criteria for judging risk of bias. Risk of bias assessed by 2 review authors indepdendently
Interventions	Deep brain stimulation: in all cases, an electrode was bilaterally implanted in the STN, except for 1/2 of intervention group in Weaver et al, and 4 participants in Williams et al., who received surgery in globus pallidus interna (GPi)
Results	Demographics Mean age 60, except in Shupbach (recruited early disease) where mean ages for both studies were 48 and 52 years Follow up time ranged from 3 months to 24 months. None of the studies were sham-controlled. Okun et al., controlled for implantation effect since all patients underwent the surgical procedure.

Bibliographic reference	**Perestelo-Perez,L., Rivero-Santana,A., Perez-Ramos,J., Serrano-Perez,P., Panetta,J., Hilarion,P., Deep brain stimulation in Parkinson's disease: meta-analysis of randomized controlled trials, Journal of NeurologyJ Neurol, 261, 2051-2060, 2014**

Randomized-pairs design was applied by 2 studies, whereas in another study, (PDSURG) this was left to participating centers.

Randomization method explicitly reported in 4 studies and allocation concealment described in 2 studies

Motor function assessments conducted by blind raters only in 2 studies

Participants lost to follow-up were approximately 14% in one study and <10% in the remaining studies

Main outcomes:

Outcome	K	n	MD	95%_L	95%_U	Het I2
UPDS III off	5	1001	15.2	12.23	18.18	77
UPDRS III on	5	1018	4.36	2.8	5.92	54
Time on w/o troublesome dyskinesia	4	719	3.25	1.78	4.71	75
ldopa recuction mg/d	4	759	452.31	288.48	616.14	87
Med induced complication (UPDRS IV)	4	820	3.67	3.03	4.31	48
ADL off (UPDRS II)	4	641	7.39	5.65	9.12	55
ADL on (UPDRS II)	6	1041	1.77	0.11	3.44	82
PDQ-39	5	980	7.43	5.61	9.26	25
UPDRS I	5	1029	0.29	0.05	0.35	0

Significant effect of DBS on:

- UPDRS III off and on states (15.2 and 4.36 points, respectively)
- waking time without troublesome dyskinesia (3.25 hrs)
- LEDD dose (452.3 mg/d)
- med-induced complications (3.67 points
- ADL off (7.39 points)
- ADL on (1.77 points)
- PDQ-39 (7.43 points)
- Neurocognitive effects - 5 studies applied UPDRS 1 (mood mental status, behavioural problems). Significant result favored

Bibliographic reference	**Perestelo-Perez,L., Rivero-Santana,A., Perez-Ramos,J., Serrano-Perez,P., Panetta,J., Hilarion,P., Deep brain stimulation in Parkinson's disease: meta-analysis of randomized controlled trials, Journal of NeurologyJ Neurol, 261, 2051-2060, 2014**
	DBS (0.29, 95%CI: 0.06, 0.53) Outcomes in favor of medication group (i.e. worse in DBS) 4 studies assessed dementia (Mattis dementia scale) significant result in favor medication group (MD = -1.01, 95%CI = -1.74, -0.28) 4 studies assessed semantic fluency, 3 verbal fluency. Both worse in DBS group: (SMD = -0.34, 95%CI: -0.52, -0.16) verbal(SMD = -0.56, 95%CI: -0.73, -0.38) 2 studies assessed verbal and visuospatial memory. No statistically significant differences observed same studies assessed stroop, worse in DBS (SMD = -0.26, 95%CI: -0.47, -0.06) Psychiatric effects: 2 studies used brief psychiatric rating scale to assess mental health: statistically in favor of DBS (MD = 2.07, 0.61 to 3.53) 3 studies examined depressionwith Montgomery Asberg depression rating scale (MADRS) - signifiacntly in favor of DBS (MD = 2.00, 95%CI: 0.69, 3.30) Conclusions: Results show DBS is an effecive treatment to control patients symptoms and improve functionality and quality of life
Other information	None
Overall Risk of Bias	NICE meta-analysis quality checklist: • The review address an appropriate and clearly focused question is relevant to the guideline review question: Yes - clearly focused review question that matches review question defined in present review protocol. • The review collects the type of studies you consider to the question review question: Yes - all relevant studies are assessed by the review. • The literature search sufficient rigorous to identify all the relevant studies: Yes - Literature search was sufficiently and almost replicates that carried out by NICE. The following databases were searched: MEDLINE, Pre-Medline, EMBASE, PsycInfo, CINAHL, Cochrane Library and centre for reviews and dissemination. • Study quality is assessed and reported: Yes - study quality assessed for each of the RCTs according to the Cochrane criteria for risk of bias. • An adequate description of the methodology used is included, and the methods used are appropriate to the question: Yes - review performed in accordance with PRISMA statement which provides structured advice on reporting style. Methods for the review are detailed and all relevant methodologies for each of the RCT's are detailed within the paper.

Bibliographic reference	**Weaver,Frances M., Follett,Kenneth, Stern,Matthew, Hur,Kwan, Harris,Crystal, Marks,William J.J., Rothlind,Johannes, Sagher,Oren, Reda,Domenic, Moy,Claudia S., Pahwa,Rajesh, Burchiel,Kim, Hogarth,Penelope, Lai,Eugene C., Duda,John E., Holloway,Kathryn, Samii,Ali, Horn,Stacy, Bronstein,Jeff, Stoner,Gatana, Heemskerk,Jill, Huang,Grant D., Study Group, Bilateral deep brain stimulation vs best medical therapy for patients with advanced Parkinson disease: a randomized controlled trial, JAMAJ.Am.Med.Assoc., 301, 63-73, 2009**
Country/ies where the study was carried out	USA
Study type	RCT
Aim of the study	To compare 6 month outcomes of patients who received DBS or best medical care (BMC)
Study dates	Patients recruited between May 2002 and Oct 2005. Study published Feb 2010.
Source of funding	The Cooperative Studies Program of the Department of Veterans Affairs Office of Research and Development, the National Institute of Neurological Disorders and Stroke, and Medtronic Neuromodulation provided financial support for this study.
Sample size	N= 255 : DBS StN n=60, DBS GP = 61, BMC = 134
Inclusion criteria	Patients with ideopathic PD were eligible if they • Were classified as H&Y stage 2 or greater while not taking medication • Were responsive to levodopa • Had persistent disabling symptoms (e.g. motor fluctuations, dyskinesia) • Experienced 3 + hrs per 24hr period with poor motor function or symptom control • Were receiving stable medical therapy for 1 month or greater, and • Were aged 21 or older. • Patients were not required to have a caregiver. • Further requirement: 3hr off time and/or on time with troubling dyskinesia per day eligibility criteria
Exclusion criteria	• Atypical syndromes • Previous surgery for PD • Surgical contraindications • Active alcohol or drug abuse • Dementia (MMSE <25), or • Pregnancy
Details	Randomization • Randomization to DBS or BMC included stratification by study site and patient age (<70 vs > 70). Motor function assessments were conducted by raters blinded to treatment

Bibliographic reference	**Weaver,Frances M., Follett,Kenneth, Stern,Matthew, Hur,Kwan, Harris,Crystal, Marks,William J.J., Rothlind,Johannes, Sagher,Oren, Reda,Domenic, Moy,Claudia S., Pahwa,Rajesh, Burchiel,Kim, Hogarth,Penelope, Lai,Eugene C., Duda,John E., Holloway,Kathryn, Samii,Ali, Horn,Stacy, Bronstein,Jeff, Stoner,Gatana, Heemskerk,Jill, Huang,Grant D., Study Group, Bilateral deep brain stimulation vs best medical therapy for patients with advanced Parkinson disease: a randomized controlled trial, JAMAJ.Am.Med.Assoc., 301, 63-73, 2009**
	Study procedure • Recruitment included referrals to neurologists and patient self-referrals. study sites were Seven Veterans Affairs and 6 affiliated university medical centres. • Study sites were selected on a competitive basis and required the participation of a movement disorder neurologist, a surgeon with expertise in globus pallidus and subthalamic nucleus deep brain stimulation implants and microelectrode recording, and appropriate supportive services (e.g., neuropsychologists). • Patients arrived at clinic having stopped their medications the night before. UPDRS motor subscale conducted in 'off state' by neurologist. A second, blinded neurologist independently completed motor subscale. All patients wore caps during assessment to ensure blinding from craniotomy scars. • Patients took their medications and were assessed 1 hour later in 'on' state. - H&Y, stand-walk-sit test, UPDRS subscales, PDQ-39. Nurse recorded medications and physical health status and PD status • Neurocognitive test battery undertaken - Mattis dementia rating scale, tests of attention, working memory, visuomotor speed, WASI III, verbal fluency, Stroop, card sorting, Boston naming test, verbal learning test, manual tapping speed, and mood. • Patients completed diaries and recorded which of 4 categories (on, on with troubling dyskinesia, off, or asleep) best reflected their predominant functioning for the prior 30mins in 30min intervals for 2 days to determine study eligibility. Patients unaware of 3hr off time and/or on time with troubling dyskinesia per day eligibility criteria when completing diaries. Follow up: • Patients returned to their study site at 3 and 6 months • Abbreviated motor function and quality-of-life assessments were conducted at 3 months. The entire baseline assessment was repeated at 6 months. • Study neurologists and blinded neurologists independently assessed patients' UPDRS motor scores while patients were not taking medication. • Patients receiving deep brain stimulation kept their stimulators on for the first assessment, then had them deactivated for return 1 hour later for assessment off medication, off stimulation. • Patients receiving best medical therapy remained off medication and returned for a second assessment to equalize assessments in each group. After the second assessment, the deep brain stimulation systems were reactivated. All patients took their medications and returned 1 hour later for a third blinded and unblinded assessment. • Patients completed the remaining assessments, including the UPDRS and neurocognitive tests, while taking medication. Statistical analysis • Analyses were based on the intent-to-treat principle. For patients with at least 1 follow-up visit but incomplete follow-up, the

Bibliographic reference	**Weaver,Frances M., Follett,Kenneth, Stern,Matthew, Hur,Kwan, Harris,Crystal, Marks,William J.J., Rothlind,Johannes, Sagher,Oren, Reda,Domenic, Moy,Claudia S., Pahwa,Rajesh, Burchiel,Kim, Hogarth,Penelope, Lai,Eugene C., Duda,John E., Holloway,Kathryn, Samii,Ali, Horn,Stacy, Bronstein,Jeff, Stoner,Gatana, Heemskerk,Jill, Huang,Grant D., Study Group, Bilateral deep brain stimulation vs best medical therapy for patients with advanced Parkinson disease: a randomized controlled trial, JAMAJ.Am.Med.Assoc., 301, 63-73, 2009**
	last observation was carried forward and treated as the 6-month observation. • For patients without baseline data, follow-up data, or both, the change score was set to zero. A second analysis excluded those without follow-up or baseline data. The primary outcome was the baseline to 6-month change in time spent in the on state without troubling dyskinesia. • The mean group change was compared between treatment groups using a 2-sample t test. Secondary outcomes were measured as baseline to 6-month changes. • Medication usage was converted to levodopa equivalents for analysis
Interventions	Patients who received deep brain stimulation were further randomized to subthalamic nucleus or globus pallidus targets and underwent surgery within 1 month. Patients were blinded to the target. The study was conducted under an investigational device exemption because the deep brain stimulation system (Kinetra system, Medtronic Inc, Minneapolis, Minnesota) was not approved for use by the US Food and Drug Administration when the study began. Patients underwent bilateral deep brain stimulation lead implantation while awake, during 1 procedure whenever possible; however, some patients returned for the second lead implant due to patient fatigue or technical issues. Lead implantation was accomplished using stereotactic frames with magnetic resonance imaging, computed tomographic guidance, or both. Initial targets were based on standard coordinates for subthalamic nucleus and globus pallidus. Intraoperative microelectrode recording and test stimulation were mandatory to optimize uniformity of implant technique and target localization. Microelectrode recording was expected to demonstrate neuronal activity stereotypical for subthalamic nucleus or globus pallidus targets. Intraoperative test stimulation was performed to assess improvement of parkinsonian signs and occurrence of stimulation-induced adverse effects. All surgeons had significant pre-study expertise with deep brain stimulation surgery and microelectrode recording involving the subthalamic nucleus and globus pallidus and used their clinical judgment to identify the best location for lead implantation. Lead position was revised from the original target at the discretion of the surgeon based on the results of microelectrode recording and test stimulation. The neurostimulator was usually implanted (under general anesthesia) on the same day immediately following lead implantation. Once the stimulator was turned on, patients in the deep brain stimulation group received continuous stimulation. Patients returned as needed for stimulation-parameter adjustments using a standardized protocol to maximize symptom control and minimize adverse effects. Stimulation and medication adjustments were conducted by clinicians unblinded to treatment. Patients who received best medical therapy were managed actively by study movement disorder neurologists after randomization. Neurologists applied state-of-the-art care, including adjuvant medication, and made adjustments to the

Bibliographic reference	**Weaver,Frances M., Follett,Kenneth, Stern,Matthew, Hur,Kwan, Harris,Crystal, Marks,William J.J., Rothlind,Johannes, Sagher,Oren, Reda,Domenic, Moy,Claudia S., Pahwa,Rajesh, Burchiel,Kim, Hogarth,Penelope, Lai,Eugene C., Duda,John E., Holloway,Kathryn, Samii,Ali, Horn,Stacy, Bronstein,Jeff, Stoner,Gatana, Heemskerk,Jill, Huang,Grant D., Study Group, Bilateral deep brain stimulation vs best medical therapy for patients with advanced Parkinson disease: a randomized controlled trial, JAMAJ.Am.Med.Assoc., 301, 63-73, 2009**
	dosages, frequency, or timing of medication, and to nonpharmacological therapy (eg, physical, occupational, and speech therapy) as needed to achieve best symptom control and optimal functioning.
Results	A total of 255 patients with PD were randomized to receive best medical therapy (n=134) or bilateral deep brain stimulation (n=121; of these patients, 61 were additionally randomized to globus pallidus and 60 to subthalamic nucleus) 19 patients withdrew consent and did not participate (9 DBS 9 BMC); 1 patient died in DBS; 6 people administratively withdrawn when BMC group closed Of 255, 211 completed 3 month evaluation and 224 completed 6 month Characteristics: 82%male, 69% married, mean age = 62.4 (8.9) mean 12.4 (5.8) years since diagnosis, 25% aged 70 or older. No differences in any baseline measure between groups, except: BMC group treated with PD meds for longer (12.6 vs 10.8 yrs) and had lower working memory (97 vs 101) Motor diary • DBS gained a mean of 4.6 hours per day of on time without troubling dyskinesia, while the mean change for the best medical therapy group was 0 hours (95% CI, 3.7-5.4, P<.001). • Off time decreased by 2.4 hours per day and on time with troubling dyskinesia by 2.6 hours per day in patients in the deep brain stimulation group compared with 0 and 0.3 hours per day in patients iBMC group (P<.001). • Asleep time did not change significantly over time by group. • Among those aged 70 years or older, patients receiving DBS gained an average of 3.8 hours of on time per day, whereas patients receiving BMC lost 0.5 hours per day (P<.001). Motor function • Change in off time significantly greater in DBS compared to BMC over 6 months • Motor functioning improved by 12.4 points in DBS vs 1.7 in BMC. In those >70yrs, motor function improved by 9.9 points in DBS vs 1 point in BMC • UPDRS ADL improved significantly in all domains for DBS • When data re-examined using 5 point change in UPDRS as measure of MID, 71% DBS vs 32% BMC improved in motor function at 6 months, 3% DBS and 21% BMC clinical worsening • Walk to sit test: DBS 9s improvement, BMC worsened by 0.2s • Medication decreased by 296mg in DBS and increased by 15mg over baseline for patients in BMC. Quality of Life

Bibliographic reference	**Weaver,Frances M., Follett,Kenneth, Stern,Matthew, Hur,Kwan, Harris,Crystal, Marks,William J.J., Rothlind,Johannes, Sagher,Oren, Reda,Domenic, Moy,Claudia S., Pahwa,Rajesh, Burchiel,Kim, Hogarth,Penelope, Lai,Eugene C., Duda,John E., Holloway,Kathryn, Samii,Ali, Horn,Stacy, Bronstein,Jeff, Stoner,Gatana, Heemskerk,Jill, Huang,Grant D., Study Group, Bilateral deep brain stimulation vs best medical therapy for patients with advanced Parkinson disease: a randomized controlled trial, JAMAJ.Am.Med.Assoc., 301, 63-73, 2009**
	• Patients who received DBS experienced significant improvements on summary measure and on 7 of 8 PDQ-39 subscales compared with BMC (social support subscale did not change) Neurocognitive function • DBS performed significantly better at baseline on WM tasks • Treatment differences in change between baseline and FU on composite WM, processing speed, phonemic fluency, and delayed recall of brief visuospatial memory test • BMC showed significant improvement 1-2 point increase; DBS group significant decrease 1 - 3.5 points • Neither treatment associated with significant change on Mattis dementia or beck dementia inventory or majority of exec functioning, language, learning and memory The overall incidence risk of experiencing a serious adverse event was 3.8 times higher (95%CI, 2.3-6.3) in deep brain stimulation patients than in best medical therapy patients DBS patients reported 659 moderate/severe adverse events; BMC patients reported 236 moderate/severe adverse events. The most frequent adverse events were falls, gait disturbance, dyskinesia, motor dysfunction, balance disorder, depression, and dystonia (≥9% patients for each). During the 6-month follow-up, there were significantly more events for the deep brain stimulation group than the best medical therapy group for falls (P < .01), gait disturbance (P = .03), depression (P = .03), and dystonia (P<. 01). Surgical site infection (9.9%) and surgical site pain (9.0%) occurred only in the deep brain stimulation group. There was no study site variation in infection rates, ranging from 0 to 2 infections per site. Most differences in adverse events between the 2 groups occurred in the first 3 months; only falls and dystonia were significantly greater for the deep brain stimulation group than for the best medical therapy group in the later 3 months (Table 4). The majority of adverse events (83%) in both groups had resolved by the 6-month follow-up. Forty-nine deep brain stimulation patients (40%) experienced 82 serious adverse events. 68 serious adverse events (83%) were attributed to the surgical procedure, stimulation device, or stimulation therapy. Of the 39 serious adverse events related to the surgical procedure, 26 also were attributed to other concurrent causes. Two deep brain stimulation patients died; 1 death was secondary to cerebral haemorrhage that occurred 24 hours after lead implantation. The second death was due to lung cancer; however, the patient withdrew participation prior to deep brain stimulation implantation. The most common serious adverse event was surgical site infection. Twelve patients had 16 infections related to the surgical procedure or device. These infections resulted in antibiotic therapy and removal of the leads, neurostimulator, or both. By the 6-month follow-up, some patients received implants again. Other serious adverse events included nervous system disorders

Bibliographic reference	**Weaver,Frances M., Follett,Kenneth, Stern,Matthew, Hur,Kwan, Harris,Crystal, Marks,William J.J., Rothlind,Johannes, Sagher,Oren, Reda,Domenic, Moy,Claudia S., Pahwa,Rajesh, Burchiel,Kim, Hogarth,Penelope, Lai,Eugene C., Duda,John E., Holloway,Kathryn, Samii,Ali, Horn,Stacy, Bronstein,Jeff, Stoner,Gatana, Heemskerk,Jill, Huang,Grant D., Study Group, Bilateral deep brain stimulation vs best medical therapy for patients with advanced Parkinson disease: a randomized controlled trial, JAMAJ.Am.Med.Assoc., 301, 63-73, 2009**
	(n=15), psychiatric disorders (n=11), device-related complications (such as lead migration and defective lead wire; n=8), cardiac disorders (n=4), other infections (n = 2), and other events (n=20). Six patients experienced falls resulting in injury. Fifteen best medical therapy patients (11%) experienced 19 serious adverse events. Events included nervous system (n=3), psychiatric (n=2), and cardiac (n=2) disorders; falls (n=2); other infections (n=2); and other events (n=8). Serious adverse events were resolved in 99% of cases by 6 months. Although the serious adverse event rate was higher for deep brain stimulation patients than for best medical therapy patients, there was no difference in the serious adverse event rate between older (26%) and younger (25%) patients. Also, there were no differences in types of serious adverse events experienced by age (results not shown).
Other information	None
Overall Risk of Bias	1. An appropriate method of randomization was used to allocate pts to treatment groups: Yes - patient randomized and stratified according to site 2. There was adequate concealment of allocation: Unclear 3. The groups were comparable at baseline, including all major confounding and prognostic factors: Yes 4. Comparison groups received same care apart from interventions: Yes 5. Pts receiving care were kept blind to tmt allocation: No - not possible 6. Individuals administering care were kept blind to tmt allocation: No 7. All groups followed up for an equal length of time: Yes 8. Groups comparable for treatment completion: Yes 9. Groups were comparable with respect to availability of outcome data: Yes 10. Study had appropriate length of follow-up: Yes 11. Study used a precise definition of outcome: Yes - clearly defined outcomes 12. Valid and reliable method was used to determine the outcome: Yes - well-validated measures used 13. Investigators were kept blind to participants exposure to the intervention: blinded assessment done where possible 14. Investigators were kept blind to other important confounding and prognostic factors: Yes, blinded assessment done where possible

Bibliographic reference	**Williams,A., Gill,S., Varma,T., Jenkinson,C., Quinn,N., Mitchell,R., Scott,R., Ives,N., Rick,C., Daniels,J., Patel,S., Wheatley,K., Deep brain stimulation plus best medical therapy versus best medical therapy alone for advanced Parkinson's disease (PD SURG trial): a randomised, open-label trial, The Lancet Neurology.9 (6) (pp 581-591), 2010.Date of Publication: June 2010., 581-591, 2010**
Country/ies where the study was carried out	UK
Study type	RCT: BMC vs DBS + BMC Randomized open-label trial
Aim of the study	Aimed to assess whether surgery and best medical therapy improved self-reported QoL more than therapy alone in patient's with advanced PD
Study dates	Between November 2000 and December 2006, study published 2010
Source of funding	Funding from UK medical Research council and Parkinson's UK. Birmingham university clinical trials unit received funding from the UK dept of health to cover some of costs of surgery
Sample size	N = 366, immediate DBS = 183; medical therapy alone = 183
Inclusion criteria	Patient's with PD for whom current medical therapy was not providing adequate symptomatic control were eligible. Inclusion criteria = diagnosis of PD according to UKBB criteria, age-adjusted score of >5 on dementia rating scale II (DRS II) and fitness for surgery
Exclusion criteria	None listed. Unfit for anaesthesia.
Details	Randomization • Patients randomly assigned by telephone call made to central office. Allocation (1:1) to surgery and BMC or BMC alone - done by use of computerised minimisation procedure with following categoriesL age at entry (<60, 60-69, >70), years since diagnosis of PD (<5, 5-9, 10-14, >15); H&Y stage in on state (<2.0, 2.5, 3, >4), reason for considering surgery (tremor, dyskinesia, severe off periods, other reasons); type of surgery (stimulation or lesion), and region to be targeted if allocated to surgery (StN or GP pars interna) and drug therapy to be given if allocated to medical therapy (apomorphine or other std drug tmt for PD). • Pair-wise randomization option available so that centres could enter 2 patients together with one allocated to surgery and one to BMC • Patients and clinicians unmasked to treatment allocation. The local clinician selected surgical techniques and postoperative management of stimulator settings for each patient.
Interventions	DBS • Patients allocated to surgery could receive any std procedure in use at time: either stimulation or lesioning of either the StN or globus pallidus pars interna.

<table>
<tr><th>Bibliographic reference</th><th>Williams,A., Gill,S., Varma,T., Jenkinson,C., Quinn,N., Mitchell,R., Scott,R., Ives,N., Rick,C., Daniels,J., Patel,S., Wheatley,K., Deep brain stimulation plus best medical therapy versus best medical therapy alone for advanced Parkinson's disease (PD SURG trial): a randomised, open-label trial, The Lancet Neurology.9 (6) (pp 581-591), 2010.Date of Publication: June 2010., 581-591, 2010</th></tr>
<tr><td></td><td>• Surgery was to be done within 4 weeks of allocation
BMC
• Patients in both groups received medical therapy, which could include apomorphine according to local practice, other dopamine agonists, monoamine oxidase type B inhibitors, catechol-O-methyltransferase inhibitors, amantadine, or other drugs for treatment of Parkinson's disease symptoms.
• Levodopa equivalents were calculated on the basis of 100 mg/day of standard levodopa being equivalent to the following doses of other drugs: 133 mg controlled-release levodopa; 1 mg pergolide, pramipexole, cabergoline, or rasagiline; 1·25 mg sublingual selegiline; 2 mg benzhexol; 3·3 mg rotigotine; 5 mg ropinirole; 10 mg bromocriptine, oral selegiline, or apomorphine; and 100 mg amantadine. The total levodopa dose was multiplied by 1·33 for entacapone and by 1·5 for tolcapone.
• Apart from the random treatment allocation, all other aspects of the management of patients were at the discretion of the local clinicians. Patients in the medical therapy group could cross over to receive surgery after about 1 year.
Assessments:
• PDQ-39 - primaty outcome of interest
Secondary outcomes:
• UPDRS in both on and off
Neurospsych assessments also done in subset of patients and involved clinical interview and battery of 16 psychometric tests and questionnaires. ** Neuropsych could not be done in all patients because trained examiners were not available in some centres. For centres that did not have trained examiners, a similar method to that used in a previous multicentre randomised controlled trial was adopted, where possible, psychologists (based on oxford) visited centres to complete assessments as required</td></tr>
<tr><td>Results</td><td>366 patients from 13 centres randomly assigned to surgery or BMC. Baseline characteristics similar. 348/366 patients were less 70yrs. 341 patients had PD for at least 5 years (mean duration 11.4 years)
5 patients in surgery group did not have surgery: 3 refused; 1 unfit for anasthesia; 1 died before surgery

<table>
<tr><td>Outcome</td><td>MD</td><td>95%CI_L</td><td>95%CI_U</td></tr>
<tr><td>UPDRS II (on)</td><td>-1</td><td>-2.4</td><td>0.4</td></tr>
<tr><td>UPDRS II off</td><td>-6.3</td><td>-8.2</td><td>-4.4</td></tr>
</table>
</td></tr>
</table>

Bibliographic reference	**Williams,A., Gill,S., Varma,T., Jenkinson,C., Quinn,N., Mitchell,R., Scott,R., Ives,N., Rick,C., Daniels,J., Patel,S., Wheatley,K., Deep brain stimulation plus best medical therapy versus best medical therapy alone for advanced Parkinson's disease (PD SURG trial): a randomised, open-label trial, The Lancet Neurology.9 (6) (pp 581-591), 2010.Date of Publication: June 2010., 581-591, 2010**
	<table><tr><td>UPDRS III on</td><td>-4.5</td><td>-6.8</td><td>-2.2</td></tr><tr><td>UPDRS III off</td><td>-16.6</td><td>-20.4</td><td>-12.9</td></tr><tr><td>UPDRS IV</td><td>-4.6</td><td>-5.4</td><td>-3.7</td></tr><tr><td>DRS-II</td><td>0.5</td><td>-0.3</td><td>1.2</td></tr><tr><td>PDQ-39 (summ index)</td><td>-5.6</td><td>-8.9</td><td>-2.4</td></tr></table> Adverse events: Total serious events = 96 (in 65 people) in DBS / 29 (26 people) in BMC NB** 12 patients in BMC group received DBS surgery between baseline and 1 year follow-up (total N in each group = 183)
Other information	Bias notes: Pair-wise randomization option available so that centres could enter 2 patients together with one allocated to surgery and one to BMC Patients and clinicians unmasked to treatment allocation. Neuropsych not carried out on all patients Targets and methods (stimulation or lesion) left to individual clinician - no control! NB: Authors confirm that all patients had stimulation - no lesioning was carried out.
Overall Risk of Bias	1. An appropriate method of randomization was used to allocate pts to treatment groups: Yes - Pair-wise randomization option available so that centres could enter two patients together 2. There was adequate concealment of allocation: No 3. The groups were comparable at baseline, including all major confounding and prognostic factors: Yes 4. Comparison groups received same care apart from interventions: No - those in surgical condition attended significantly more follow-up appointments with PD nurses and clinical team than those in medical care 5. Pts receiving care were kept blind to tmt allocation: No - not possible 6. Individuals administering care were kept blind to tmt allocation: No 7. All groups followed up for an equal length of time: Yes 8. Groups comparable for treatment completion: Yes 9. Groups were comparable with respect to avalilability of outcome data: Yes

Bibliographic reference	Williams,A., Gill,S., Varma,T., Jenkinson,C., Quinn,N., Mitchell,R., Scott,R., Ives,N., Rick,C., Daniels,J., Patel,S., Wheatley,K., Deep brain stimulation plus best medical therapy versus best medical therapy alone for advanced Parkinson's disease (PD SURG trial): a randomised, open-label trial, The Lancet Neurology.9 (6) (pp 581-591), 2010.Date of Publication: June 2010., 581-591, 2010
	10. Study had appropriate length of follow-up: Yes 11. Study used a precise definition of outcome: Yes - clearly defined outcomes 12. Valid and reliable method was used to determine the outcome: Yes - well-validated measures used 13. Investigators were kept blind to participants exposure to the intervention: No 14. Investigators were kept blind to other important confounding and prognostic factors: Unclear Serious risk of bias: No blinding was carried out, patients in surgical condition recieved significantly more medical attention in the form of clinic and follow-up appointments than those in best medical care arm.

Bibliographic reference	Witt,K., Granert,O., Daniels,C., Volkmann,J., Falk,D., van,Eimeren T., Deuschl,G., 20130829, Relation of lead trajectory and electrode position to neuropsychological outcomes of subthalamic neurostimulation in Parkinson's disease: results from a randomized trial, Brain, 136, 7-19, 2013
Country/ies where the study was carried out	Germany
Study type	NB: THIS STUDY IS A FOLLOW-UP ON NEUROPSYCHOLOGY FROM DEUSCHL ET AL., 2006 (randomized controlled trial)
Aim of the study	To assess the impact of DBS on neuropsychological changes compared to best medical therapy
Study dates	published 2013
Source of funding	Study was supported by the German ministry of research and technology, the German research council, and the internatinal Parkinson Fond Europe K Witt has received lecture fees from medtronic an has been serving as consultant for UCB
Sample size	THIS STUDY IS A FOLLOW-UP ON NEUROPSYCHOLOGY FROM DEUSCHL ET AL., 2006 Subsample of all patients from a single centre (out of 10 centres) in Kiel, Germany n=62
Inclusion criteria	See Deuschl et al., 2006 Subsample of all patients from a single centre (out of 10 centres) in Kiel, Germany
Exclusion criteria	See Deuschl et al., 2006

Bibliographic reference	**Witt,K., Granert,O., Daniels,C., Volkmann,J., Falk,D., van,Eimeren T., Deuschl,G., 20130829, Relation of lead trajectory and electrode position to neuropsychological outcomes of subthalamic neurostimulation in Parkinson's disease: results from a randomized trial, Brain, 136, 7-19, 2013**
	Subsample of all patients from a single centre (out of 10 centres) in Kiel, Germany
Details	See Deuschl et al., 2006
Interventions	See Deuschl et al., 2006
Results	Demographics (n=62) Mean age = 59.4 (8.6) Disease duration = 13.2 years (5.4) Female = 28 /62 (45%)

Test	DBS_change score	BMC_change score
UPDRS motor	20.0 (11.8)	2.9(9.9)
MDRS	-2.5 (4.9)	-1.1 (4.2)
Backward digit span task	-0.6 (1.6)	0.03 (1.9)
Verbal fluency semantic	-6.1 (11.6)	0.3 (10.3)
Stroop_intereference (Time, sec)	-12.3(51.1)	0.3 (18.3)
Stroop_interference (error rate)	-0.5 (3.6)	-0.3 (2.3)
Verbal fluency letter	-1.9(8.1)	-0.5 (6.0)

Other information	
Overall Risk of Bias	See Deuschl et al., 2006 for risk of bias asssessment

LCIG -v- BMT

Bibliographic reference	**Olanow,C.W., Kieburtz,K., Odin,P., Espay,A.J., Standaert,D.G., Fernandez,H.H., Vanagunas,A., Othman,A.A., Widnell,K.L., Robieson,W.Z., Pritchett,Y., Chatamra,K., Benesh,J., Lenz,R.A., Antonini,A., Continuous intrajejunal infusion of levodopa-carbidopa intestinal gel for patients with advanced Parkinson's disease: A randomised, controlled, double-blind, double-dummy study, The Lancet Neurology.13 (2) (pp 141-149), 2014.Date of Publication: February 2014., 141-149, 2014**
Country/ies where the study	USA (Germany, New Zealand, USA)

Bibliographic reference	Olanow,C.W., Kieburtz,K., Odin,P., Espay,A.J., Standaert,D.G., Fernandez,H.H., Vanagunas,A., Othman,A.A., Widnell,K.L., Robieson,W.Z., Pritchett,Y., Chatamra,K., Benesh,J., Lenz,R.A., Antonini,A., Continuous intrajejunal infusion of levodopa-carbidopa intestinal gel for patients with advanced Parkinson's disease: A randomised, controlled, double-blind, double-dummy study, The Lancet Neurology.13 (2) (pp 141-149), 2014.Date of Publication: February 2014., 141-149, 2014
was carried out	
Study type	Randomised controlled double-blind double-dummy study
Aim of the study	To assess the efficacy and safety of levodopa-carbidopa intestinal gel delivered continuousy through an intrajejunal percutaneous tube (LCIG)
Study dates	Published Feb 2014, no other dates given
Source of funding	Abbvie (Note: all authors have multiple conflicts of interests with a range of research and pharmaceutical companies)
Sample size	N = 71; n LCIG = 37, n immediate-release oral levodopa-carbidopa = 34
Inclusion criteria	• Adults aged > or = 30 years with advanced PD according to UKBB criteria that was complicated by off-periods that could not be satisfcatorily controlled with optimal medical therapy (excluding apomorphine). • Participants must have received stable doses of levodopa for at least 4 weeks before entollment in the study and had recognizable on-time and off-time with a minimum of 3h of off-time per day based on home assessment • Sustained-release ldopa, stalevo, or other formulations of ldopa wer permitted; doses converted into equivalent doses of immediate-release oral levodopa
Exclusion criteria	Atypical or secondary parkinsonism, previous neurosurgery, psychiatric, or lab abnormalities in the judgement of the investigator, or any condition that may interfere with absorbtion, distribution, metabolism, or excretion of the study drug or contraindicate intrajejunal percutaneous gastrojejunostomy tube
Details	Eligible participants were admitted to hospital for jejunal placement of a percutansous gastrojejunostomy tube under local anaesthesia with endoscopic or fluroscopic guidance, and then randomly allocated (1:1) to tmt with either over-encapsulated immediate-release oral levodopa + placebo LCIG, or LCIG + oral placebo ldopa Randomization done with a central, computer-generated, predetermined, randomization code, and was stratified by site, with a mixed-block size of 2 or 4. An interactive voice response generated the randomization schedule and assigned participantts to tmt group All participants and investigators were masked to group assignment Data analysers were masked until after database was locked Simultaneous titration of active and placebo therapy was done for patients in both groups to maintain the integrity of the masking.
Interventions	Intestinal gel and immediate-release oral forms of Ldopa-cdopa were initially administered at participant's baseline total daily ldopa dose before randomization

Bibliographic reference	**Olanow,C.W., Kieburtz,K., Odin,P., Espay,A.J., Standaert,D.G., Fernandez,H.H., Vanagunas,A., Othman,A.A., Widnell,K.L., Robieson,W.Z., Pritchett,Y., Chatamra,K., Benesh,J., Lenz,R.A., Antonini,A., Continuous intrajejunal infusion of levodopa-carbidopa intestinal gel for patients with advanced Parkinson's disease: A randomised, controlled, double-blind, double-dummy study, The Lancet Neurology.13 (2) (pp 141-149), 2014.Date of Publication: February 2014., 141-149, 2014**
	LCIG delivered as aqueous formulation (20mg/mL ldopa and 5mg/mL carbidopa monohydrate solution) in 100g cassettes or matching placebo gel (sodium carboxymethylase solution alone) administered as morning bolus (5-10 mL) followed by continuous infusion at constant rate for rest of participants waking day (~16hr). Infusion stopped overnight Immediate release ldopa capsules containing 25mg carbidopa and 100mg levodopa or matching placebo initially initiated in divded doses overwaking day beginning at same time as infusion and at same dose frequeny as baseline. 4 titration during which dosing for patients in either group could be adjusted by changing the infusion rate in 100mg daily increments; ldop/cdopa immediate-release could be adjusted by changing infusion rate in 100mg daily increments Changes in dose made soley on basis of investigator judgement; participants could not change dose or schedule any change in dose of active intervention in a participant had to be matched by corresponding change in placebo (to maintain masking) Dose adjustment could be made in either LCIG or oral Ldopa/cdopa treatments so that all patients were titrated to their optimum state Titration period was followed by 8 week maintenence period during which patients were maintained on stable doses of their asisigned treatment Open-label immediate-release oral ldopa/cdopa could be used as rescue therapy for persistent off-episodes for patients in either group Study visits conducted as baseline and weeks 1, 2, 3, 4, 6, 8, 10, and 12 For 3 consecutiv days before each visit begginning at week 2, pts completed a 24hr diary asssessment of motor status at 30min intervals, recording if they were in an off-state in an on-state without dyskinesia, in an on-state with non-troublesome dyskinesia, in a on-state with troublesome dyskinesia, or asleep Before assesment, pts trained in use of diary and had to have >75% concordance with investigator and .75% compliance with completing diary Additional assessments at each visit included assessment of vital signs, UPDRS in on and off states, PDQ-39, EQ5D, zarit carer burden interview, and investigator-rated CGIC Safety assessments done at each visit In 1st 20 participants, plasma concentrations of levodopa measures at multiple time points after initiation of LCIG For remaining pts, sampling done at 6 weeks before start of infusion and 1, 2, 4, 8hr after infusion Statistical analyses

<table>
<tr><td>Bibliographic reference</td><td>Olanow,C.W., Kieburtz,K., Odin,P., Espay,A.J., Standaert,D.G., Fernandez,H.H., Vanagunas,A., Othman,A.A., Widnell,K.L., Robieson,W.Z., Pritchett,Y., Chatamra,K., Benesh,J., Lenz,R.A., Antonini,A., Continuous intrajejunal infusion of levodopa-carbidopa intestinal gel for patients with advanced Parkinson's disease: A randomised, controlled, double-blind, double-dummy study, The Lancet Neurology.13 (2) (pp 141-149), 2014.Date of Publication: February 2014., 141-149, 2014</td></tr>
<tr><td></td><td>• Analysed primary end point with ANCOVA model, including effects for treatment group and country, with baseline off time and average daily rescue levodopa</td></tr>
<tr><td>Results</td><td>Demographics:
• Gender: 65% male in both groups
• Disease duration: 10 (4.6) LCIG, 11.8 (5.6) Ldopa
• UPDRS (overall): 31.5 (18.0) LCIG, 35.8 (18.9) ldopa
• MMSE = 28.8 (1.4) both groups
Completion: 35 in LCIG: 2 drop out: 1 halllucination and psychosis, 1 protocol disorder; 31 in ldopa: 3 drop-out; 1 peritonitis, 1 stoma dysfunction, 1 lack of efficacy
71 patients enrolled at 26 centres - mean 2.6 patients per centre
Titration to stable dose achieved at mean 7 days (2.5) for participants in LCIG and 8 days (2.5) in immediate-release oral levodopa carbidopa group - 88% subjects titrated to stable dose in < or = 9 days

Efficacy analysis
Significant improvements in LCIG for off-time on time without duskinesia, PDQ-39, CGIC, UPDRS II.
For off time per day LCIG > reduction in off-time between baseline and wk 12 than immediate-release ldopa, also ass with > improvement in on-time without troublesome dyskinesia, and on-time without dskinesia.
<table>
<tr><td>Outcome</td><td>LCIG</td><td>Ldopa</td><td>MD 95%CI</td></tr>
<tr><td>Off-time h/d</td><td>-4.04(0.65)</td><td>-2.14 (0.66)</td><td>-1.91(-3.05 to -0.76)</td></tr>
<tr><td>On time w/o trouble dysk</td><td>4.11 (0.75)</td><td>2.24 (0.76)</td><td>1.86 (0.56 to 3.17)</td></tr>
<tr><td>On time w/o dysk</td><td>3.37 (1.04)</td><td>1.09(1.05)</td><td>2.28 (0.47 to 4.09)</td></tr>
<tr><td>On-time with dysk</td><td>0.81 (0.86)</td><td>1.54 (0.86)</td><td>-0.73 (-2.22 to 0.76)</td></tr>
<tr><td>PDQ-39 (summ index)</td><td>-10.9 (3.3)</td><td>-3.9 (3.2)</td><td>-7.0 (-12.6 to - 1.4)</td></tr>
<tr><td>CGIC</td><td>2.3 (0.4)</td><td>3.0 (0.4)</td><td>-0.7 (-1.4 to -0.1)</td></tr>
</table></td></tr>
</table>

Bibliographic reference	**Olanow,C.W., Kieburtz,K., Odin,P., Espay,A.J., Standaert,D.G., Fernandez,H.H., Vanagunas,A., Othman,A.A., Widnell,K.L., Robieson,W.Z., Pritchett,Y., Chatamra,K., Benesh,J., Lenz,R.A., Antonini,A., Continuous intrajejunal infusion of levodopa-carbidopa intestinal gel for patients with advanced Parkinson's disease: A randomised, controlled, double-blind, double-dummy study, The Lancet Neurology.13 (2) (pp 141-149), 2014.Date of Publication: February 2014., 141-149, 2014**

UPDRS II	-1.8 (1.3)	1.3 (1.3)	-3.0 (-5.3 to -0.8)
UPDRS III	-1.5 (2.4)	-2.9 (2.4)	1.4 (-2.8 to 5.6)
EQ5D	0.05 (0.04)	-0.02 (0.04)	0.07 (-0.01 to 0.15)
Carer burden	-2.8 (3.7)	1.7 (3.3)	-4.5 (-10.7 to 1.7)
Levodopa total daily dose	91.7 (96.6)	249.7 (94.9)	-158.0 (-324 to 8.5)
Overall mean ldopa rescue dose	139.8 (20.3)	180.6 (21.9)	-40.8 (-100.4 to 18.8)

Other information

Adverse events	LCIG (n=37)	ldopa (n=34)	overall (n=71)
Any adverse event	35 (97%)	34 (100%)	69
Serious adverse event	5 (14%)	7 (21%)	12
Abdominal pain	19 (51%)	11 (32%)	30
Wound infection	4 (11%)	8 (24%)	12
Device complications	34 (92%)	29 (85%)	63

Most adverse events were related to the surgucal procedure or device, mild to moderate in severity, occurred almost exclusively within the first week, and resolved in all cases.

Overall Risk of Bias

1. An appropriate method of randomization was used to allocate pts to treatment groups: Yes - patient randomized externally
2. There was adequate concealment of allocation: Yes
3. The groups were comparable at baseline, including all major confounding and prognostic factors: Yes
4. Comparison groups received same care apart from interventions: Yes
5. Pts receiving care were kept blind to tmt allocation: Yes - all participants blind to condition
6. Individuals administering care were kept blind to tmt allocation: Yes
7. All groups followed up for an equal length of time: Yes

Bibliographic reference	Olanow,C.W., Kieburtz,K., Odin,P., Espay,A.J., Standaert,D.G., Fernandez,H.H., Vanagunas,A., Othman,A.A., Widnell,K.L., Robieson,W.Z., Pritchett,Y., Chatamra,K., Benesh,J., Lenz,R.A., Antonini,A., Continuous intrajejunal infusion of levodopa-carbidopa intestinal gel for patients with advanced Parkinson's disease: A randomised, controlled, double-blind, double-dummy study, The Lancet Neurology.13 (2) (pp 141-149), 2014.Date of Publication: February 2014., 141-149, 2014
	8. Groups comparable for treatment completion: Yes 9. Groups were comparable with respect to availability of outcome data: Yes 10. Study had appropriate length of follow-up: Yes 11. Study used a precise definition of outcome: Yes - clearly defined outcomes 12. Valid and reliable method was used to determine the outcome: Yes - well-validated measures used 13. Investigators were kept blind to participants exposure to the intervention: Yes 14. Investigators were kept blind to other important confounding and prognostic factors: Yes

D.6.2 Deep brain stimulation compared with best medical treatment for earlier Parkinson's disease

Bibliographic reference	Schüpbach,W.M.M., Maltete,D., Houeto,J.L., du Montcel,S.T., Mallet,L., Welter,M.L., Gargiulo,M., Behar,C., Bonnet,A.M., Czernecki,V., Pidoux,B., Navarro,S., Dormont,D., Cornu,P., Agid,Y., Neurosurgery at an earlier stage of Parkinson disease: A randomized, controlled trial, Neurology.68 (4) (pp 267-271), 2007.Date of Publication: January 2007., 267-271, 2007
Country/ies where the study was carried out	France
Study type	PILOT -RCT- full version pulished Schüpbach, Rau et al., 2013
Aim of the study	To examine whether surgery at an early stage of PD would maintain quality of life as well as improve motor function
Study dates	patient screened between 2002 and 2003 - study published 2006
Source of funding	Medtronic sponsored study
Sample size	N= 20 (n = 10 DBS, n=10 BMC)
Inclusion criteria	Inclusion criteria: • Younger than 55 years • Duration of PD 5 - 10 years • Mild to moderate motor symptoms, H&Y stage <or=3 • Motor fluctuations with off periods for >25% of the day • Normal brain MRI • Absence of severe psychiatric disease

Bibliographic reference	**Schüpbach,W.M.M., Maltete,D., Houeto,J.L., du Montcel,S.T., Mallet,L., Welter,M.L., Gargiulo,M., Behar,C., Bonnet,A.M., Czernecki,V., Pidoux,B., Navarro,S., Dormont,D., Cornu,P., Agid,Y., Neurosurgery at an earlier stage of Parkinson disease: A randomized, controlled trial, Neurology.68 (4) (pp 267-271), 2007.Date of Publication: January 2007., 267-271, 2007**
	• Absence of dementia (MDRS >130/144) • Impaired social and occupational functioning due to PD (SOFAS score 51-80%)
Exclusion criteria	Reasons for exclusion: • Absence of professional activity • Too mild disease • Abnormal brain MRI • Disease duration >10 years • Age > 55 years
Details	Patients included prospectively in pairs and randomized to surgery/medical care matched for disease duration, age, activities of daily living, motor functioning, and PD-related psychosocial situation and handicap Patients were first paired and then within each pair of patents randomization was first performed externally, with no knowledge of the patients except date of birth, into a group that would undergo surgery for bilateral STN stmulation (n = 10, 3 women), or best possible medical treatment only (n=10, 5 women) Patients ID numbers were provided by fax to the randomization centre in blocks of 2- randomized using SAS
Interventions	Sham surgery was considered unethical, therefore assessments were not blinded BMC Best medical care was individually adapted to suit each patient's motor symptoms and included: 1) A treatment with dopaminergic agonist available in Francce (pegolide ropinirole, bromocriptine, piribedil) in a dose that was well tolerated by the patient; 2) Addition of levodopa/carbidopa or levodopa/benzerazide in fluctuating patients who tolerated it well and showed benefit 3) Addition of entacapone in fluctuating patients who tolerated it well and showed benefit 4) Amantadine used as antidyskinetic in patients who tolerated it well STN DBS • Localizing procedures described elsewhere *Bejjani 2000 • Same team performed all operations • At end of study, STN stimulatioon in surgical patients was single monopolar cathodic in 9 and double monopolar cathodic on both sides in 1 • Stimulation performed at 3.1 +/- 0.4V with a pulse width of 69 +/-14 and a frequency of 167 +/- 26 Hz

<table>
<tr><th>Bibliographic reference</th><td>Schüpbach,W.M.M., Maltete,D., Houeto,J.L., du Montcel,S.T., Mallet,L., Welter,M.L., Gargiulo,M., Behar,C., Bonnet,A.M., Czernecki,V., Pidoux,B., Navarro,S., Dormont,D., Cornu,P., Agid,Y., Neurosurgery at an earlier stage of Parkinson disease: A randomized, controlled trial, Neurology.68 (4) (pp 267-271), 2007.Date of Publication: January 2007., 267-271, 2007</td></tr>
<tr><td></td><td>• All patients offered surgery after end of study
• Primary end point was relative change in overall QoL</td></tr>
<tr><td>Results</td><td>Quality of life did not change in patents in BMC but improved by 24% by end of study in those receiving STN DBS - attributed to improvement o stigmatization and bodily discomfor subdomains of assessment scale
<table>
<tr><td>Index_measure</td><td>BMC_baseline</td><td>BMC_18mnt</td><td>DBS_baseline</td><td>DBS_18mnt</td></tr>
<tr><td>PDQ39 summ index</td><td>37.9 (23.4 - 53.1)</td><td>41.9 (13.5 - 57.3)</td><td>35.4 (24.4 - 51.5)</td><td>28.9 (5.7 - 53.1)</td></tr>
<tr><td>UPDRS II (ADL)off</td><td>17.8 (6.8)</td><td>21.7 (6.3)</td><td>19.2 (7.7)</td><td>12.9 (5.7)</td></tr>
<tr><td>UPDRS II (ADL) on</td><td>3.3 (3.3)</td><td>6.3 (2.7)</td><td>2.3 (2.7)</td><td>5.1 (2.1)</td></tr>
<tr><td>MDRS</td><td>142 (137 - 144)</td><td>143 (134 - 144)</td><td>140.5 (132 - 144)</td><td>140.5 (128-144)</td></tr>
<tr><td>Frontal score</td><td>47 (38 - 50)</td><td>48.5 (31 - 50)</td><td>48 (29 - 50)</td><td>47.5 (23 - 50)</td></tr>
<tr><td>CPRS</td><td>15 (9-27)</td><td>11.5 (6 - 30)</td><td>14 (3-22)</td><td>10 (0 - 17)</td></tr>
<tr><td>MADRS</td><td>5 (0-13)</td><td>5 (2-14)</td><td>7 (0 - 12)</td><td>3 (0-9)</td></tr>
<tr><td>BAS</td><td>8 (2-11)</td><td>4 (0-9)</td><td>5 (0 - 8)</td><td>3 (0-4)</td></tr>
</table></td></tr>
<tr><td>Other information</td><td>None</td></tr>
<tr><td>Overall Risk of Bias</td><td>1. An appropriate method of randomization was used to allocate pts to treatment groups? Yes - patient randomized externally at central centre 2. There was adequate concealment of allocation: No 3. The groups were comparable at baseline, including all major confounding and prognostic factors? yes 4. Comparison groups received same care apart from interventions: Yes 5. Pts receiving care were kept blind to tmt allocation: No - not possible 6. Individuals administering care were kept blind to tmt allocation: No 7. All groups followed up for an equal length of time: Yes 8. Groups comparable for treatment completion? Yes 9. Groups were comparable with respect to availability of outcome data? Yes 10. Study had appropriate length of followup: yes 11. Study used a precise definition of outcome: yes - clearly defined outcomes 12. Valid and reliable method was used to determine the outcome: yes - well-validated measures used 13. Investigators were kept blind to participants exposure to the intervention: no - no blinded assessment 14. Investigators were kept blind to other important confounding and prognostic factors:no blinded assessment</td></tr>
</table>

Bibliographic reference	**Schüpbach,W., Rau,J., Knudsen,K., Volkmann,J., Krack,P., Timmermann,L., Halbig,T.D., Hesekamp,H., Navarro,S.M., Meier,N., Falk,D., Mehdorn,M., Paschen,S., Maarouf,M., Barbe,M.T., Fink,G.R., Kupsch,A., Gruber,D., Schneider,G.H., Seigneuret,E., Kistner,A., Chaynes,P., Ory-Magne,F., Brefel Courbon,C., Vesper,J., Schnitzler,A., Wojtecki,L., Houeto,J.L., Bataille,B., Maltete,D., Damier,P., Raoul,S., Sixel-Doering,F., Hellwig,D., Gharabaghi,A., Kruger,R., Pinsker,M.O., Amtage,F., Regis,J.M., Witjas,T., Thobois,S., Mertens,P., Kloss,M., Hartmann,A., Oertel,W.H., Post,B., Speelman,H., Agid,Y., Schade-Brittinger,C., Deuschl,G., EARLYSTIM Study Group, Neurostimulation for Parkinson's disease with early motor complications, The New England journal of medicineN Engl J Med, 368, 610-622, 2013**
Country/ies where the study was carried out	Germany and France
Study type	RCT: multicentre parallel group design comparing DBS + BSC with BSC alone (optimal medical therapy) in patients with early PD (disease duration .4yrs, H&Y <3)
Aim of the study	To assess benefit of DBS in patients with early motor complications compared to optimal medical therapy
Study dates	July 2006 to November 2009. Study published 2015.
Source of funding	German ministry of research
Sample size	N=251
Inclusion criteria	Age 18 - 60 years Disease duration > or = 4 years Disease severity rating <3 on H&Y Improvement of motor signs of 50% or more with dopaminergic medication, as assessed by UPDRS III Fluctuations or dyskinesia present for 3 years or less Score >6 ADL in the worst condition despite medical treatment (UPDRS II) Mild to moderate impairment in social and occupational functioning
Exclusion criteria	Dementia (score <or=130 on Mattis dementia) Major depression with suicidal ideation, score >25 on Beck depression inventory Disease duration < 4 years excluded because atypical forms of Parkinsonism would be expected to be identified before then
Details	Study was investigator-initiated, randomized multicentre, parallel-group design comparing DBS + BSC with medical therapy alone. Randomization performed at central coordination centre with use of randomisation lists with randomly permuted blocks lengths stratified according to centre Full source-data verification was performed by monitors from German or French coordination centers (for each country) Assessments scheduled at baseline and at 5, 12, and 24 months. Levodopa challenge test performed at baseline and 24 months

<table>
<tr><th>Bibliographic reference</th><td>Schüpbach,W., Rau,J., Knudsen,K., Volkmann,J., Krack,P., Timmermann,L., Halbig,T.D., Hesekamp,H., Navarro,S.M., Meier,N., Falk,D., Mehdorn,M., Paschen,S., Maarouf,M., Barbe,M.T., Fink,G.R., Kupsch,A., Gruber,D., Schneider,G.H., Seigneuret,E., Kistner,A., Chaynes,P., Ory-Magne,F., Brefel Courbon,C., Vesper,J., Schnitzler,A., Wojtecki,L., Houeto,J.L., Bataille,B., Maltete,D., Damier,P., Raoul,S., Sixel-Doering,F., Hellwig,D., Gharabaghi,A., Kruger,R., Pinsker,M.O., Amtage,F., Regis,J.M., Witjas,T., Thobois,S., Mertens,P., Kloss,M., Hartmann,A., Oertel,W.H., Post,B., Speelman,H., Agid,Y., Schade-Brittinger,C., Deuschl,G., EARLYSTIM Study Group, Neurostimulation for Parkinson's disease with early motor complications, The New England journal of medicineN Engl J Med, 368, 610-622, 2013</td></tr>
<tr><td></td><td>Blinded assessment based on perioperative an postoperative standardized video recordings obtained at baseline and 24 months.
Videos recorded for each motor condition (according to whether patient was receiving medication or stimulation, or not).
UPDRS III assessed by 2 expert raters who were unaware of study assignment, except for assessment of rigidity, except on assessment of rigidity
During follow-up adjustments to medication and stimulation were performed according to predefined standards (EFNS)
specific procedure for monitoring risk of suicidality, established after 2 suicides had occurred during the study, consisted of baseline assessment of general risk and then semi-structured phone interview every 2 months to assess status, with psychiatric follow-up as needed.
Adverse events
All AEs reported and coded according to medical dictionary for regulatory activities (v14.1).
Serious AEs defined as any events that led to death, disability, or prolonged or new hospitalization with serious health impairment.</td></tr>
<tr><td>Interventions</td><td>Patients assigned to DBS underwent bilateral stereotactic surgery of the subthalamic nucleus with the implantation of the electrodes and pulse generator within 6 weeks after randomization. Patients then started receiving stimulation according to standards established for this study</td></tr>
<tr><td>Results</td><td>Of 392 patients assessed, 251 enrolled, n=124 DBS, n=127 BMC
Total of 25 patients had major protocol deviation: per-protocol analysis included n=116 DBS and n=110 in BMC
Baseline characteristics did not differ between treatment groups: mean:
• Age = 52 (6.3)
• Disease duration = 7.5 years (3.0)
Patients included in study after mean 1.7 years after onset of levodopa-induced motor complications of any severity
<table>
<tr><td>outcome</td><td>MD</td><td>95%CI_L</td><td>95%CI_U</td></tr>
<tr><td>PDQ39 ITT</td><td>8</td><td>4.2</td><td>11.9</td></tr>
<tr><td>PDQ39 PP</td><td>8.1</td><td>2.8</td><td>13.4</td></tr>
</table></td></tr>
</table>

Bibliographic reference	**Schüpbach,W., Rau,J., Knudsen,K., Volkmann,J., Krack,P., Timmermann,L., Halbig,T.D., Hesekamp,H., Navarro,S.M., Meier,N., Falk,D., Mehdorn,M., Paschen,S., Maarouf,M., Barbe,M.T., Fink,G.R., Kupsch,A., Gruber,D., Schneider,G.H., Seigneuret,E., Kistner,A., Chaynes,P., Ory-Magne,F., Brefel Courbon,C., Vesper,J., Schnitzler,A., Wojtecki,L., Houeto,J.L., Bataille,B., Maltete,D., Damier,P., Raoul,S., Sixel-Doering,F., Hellwig,D., Gharabaghi,A., Kruger,R., Pinsker,M.O., Amtage,F., Regis,J.M., Witjas,T., Thobois,S., Mertens,P., Kloss,M., Hartmann,A., Oertel,W.H., Post,B., Speelman,H., Agid,Y., Schade-Brittinger,C., Deuschl,G., EARLYSTIM Study Group, Neurostimulation for Parkinson's disease with early motor complications, The New England journal of medicineN Engl J Med, 368, 610-622, 2013**

UPDRS III off	16.4	13.7	19.1
UPDRS II during worst cond	6.2	4.5	8
UPDRS IV	4.1	3.2	4.9
time good mobility no dys	1.9	0.4	3.4
UPDRS III off	8.6	6.4	10.9
UPDRS III on	4.5	2.7	6.4
UPDRS II best cond	0.5	-0.8	1.7
LEDD	-609.1	-662.1	-556.1
Mattis dementia	0.7	-0.6	1.9
brief pscyh rating scale	2.2	0.2	4.1
Becks depression inventory	1.9	0.3	3.6

Other information	ADVERSE EVENTS Serious AE = 123 (total N=124) in DBS and 128 in BMC (total N=127) Death by suicide = 2 in DBS and 1 in BMC. Suicide attempts, n = 2 in each group. Life-threatening event = 12 in DBS and 9 in BMC Reoperation necessary in n=4 DBS patients. intracerebral abcess or adema n = 2, dislocation of device n=5, impaired wound healing n = 4
Overall Risk of Bias	1. An appropriate method of randomization was used to allocate pts to treatment groups? yes - patient randomized through central centre 2. There was adequate concealment of allocation: yes 3. The groups were comparable at baseline, including all major confounding and prognostic factors? yes 4. Comparison groups received same care apart from interventions: yes 5. Pts receiving care were kept blind to tmt allocation: No - not possible 6. Individuals administering care were kept blind to tmt allocation: No - 7. All groups followed up for an equal length of time: yes 8. Groups

Bibliographic reference	Schüpbach,W., Rau,J., Knudsen,K., Volkmann,J., Krack,P., Timmermann,L., Halbig,T.D., Hesekamp,H., Navarro,S.M., Meier,N., Falk,D., Mehdorn,M., Paschen,S., Maarouf,M., Barbe,M.T., Fink,G.R., Kupsch,A., Gruber,D., Schneider,G.H., Seigneuret,E., Kistner,A., Chaynes,P., Ory-Magne,F., Brefel Courbon,C., Vesper,J., Schnitzler,A., Wojtecki,L., Houeto,J.L., Bataille,B., Maltete,D., Damier,P., Raoul,S., Sixel-Doering,F., Hellwig,D., Gharabaghi,A., Kruger,R., Pinsker,M.O., Amtage,F., Regis,J.M., Witjas,T., Thobois,S., Mertens,P., Kloss,M., Hartmann,A., Oertel,W.H., Post,B., Speelman,H., Agid,Y., Schade-Brittinger,C., Deuschl,G., EARLYSTIM Study Group, Neurostimulation for Parkinson's disease with early motor complications, The New England journal of medicineN Engl J Med, 368, 610-622, 2013
	comparable for treatmen completion? yes 9. Groups were comparable with respect to avalilability of outcome data?yes 10. Study had appropriate length of followup: yes 11. Study used a precise definition of outcome: yes - clearly defined outcomes 12. Valid and reliable method was used to determine the outcome: yes - well-validated measures used 13. Investigators were kept blind to participants exposure to the intervention:yes, blinded assessment 14. Investigators were kept blind to other important confounding and prognostic factors: yes, blinded assessment done

Bibliographic reference	Williams,A., Gill,S., Varma,T., Jenkinson,C., Quinn,N., Mitchell,R., Scott,R., Ives,N., Rick,C., Daniels,J., Patel,S., Wheatley,K., Deep brain stimulation plus best medical therapy versus best medical therapy alone for advanced Parkinson's disease (PD SURG trial): a randomised, open-label trial, The Lancet Neurology.9 (6) (pp 581-591), 2010.Date of Publication: June 2010., 581-591, 2010
Country/ies where the study was carried out	UK
Study type	RCT: BMC vs DBS + BMC Randomized open-label trial
Aim of the study	Aimed to assess whether surgery and best medical therapy improved self-reported QoL more than therapy alone in patient's with advanced PD
Study dates	Between November 2000 and December 2006, study published 2010
Source of funding	Funding from UK medical Research council and Parkinson's UK. Birmingham university clinical trials unit received funding from the UK dept of health to cover some of costs of surgery
Sample size	N = 366, immediate DBS = 183; medical therapy alone = 183
Inclusion criteria	Patient's with PD for whom current medical therapy was not providing adequate symptomatic control were eligible. Inclusion criteria = diagnosis of PD according to UKBB criteria, age-adjusted score of >5 on dementia rating scale II (DRS II) and fitness for surgery
Exclusion criteria	None listed. Unfit for anaesthesia.
Details	Randomization

Bibliographic reference	**Williams,A., Gill,S., Varma,T., Jenkinson,C., Quinn,N., Mitchell,R., Scott,R., Ives,N., Rick,C., Daniels,J., Patel,S., Wheatley,K., Deep brain stimulation plus best medical therapy versus best medical therapy alone for advanced Parkinson's disease (PD SURG trial): a randomised, open-label trial, The Lancet Neurology.9 (6) (pp 581-591), 2010.Date of Publication: June 2010., 581-591, 2010**
	• Patients randomly assigned by telephone call made to central office. Allocation (1:1) to surgery and BMC or BMC alone - done by use of computerised minimisation procedure with following categoriesL age at entry (<60, 60-69, >70), years since diagnosis of PD (<5, 5-9, 10-14, >15); H&Y stage in on state (<2.0, 2.5, 3, >4), reason for considering surgery (tremor, dyskinesia, severe off periods, other reasons); type of surgery (stimulation or lesion), and region to be targeted if allocated to surgery (StN or GP pars interna) and drug therapy to be given if allocated to medical therapy (apomorphine or other std drug tmt for PD). • Pair-wise randomization option available so that centres could enter 2 patients together with one allocated to surgery and one to BMC • Patients and clinicians unmasked to treatment allocation. The local clinician selected surgical techniques and postoperative management of stimulator settings for each patient.
Interventions	DBS • Patients allocated to surgery could receive any std procedure in use at time: either stimulation or lesioning of either the StN or globus pallidus pars interna. • Surgery was to be done within 4 weeks of allocation BMC • Patients in both groups received medical therapy, which could include apomorphine according to local practice, other dopamine agonists, monoamine oxidase type B inhibitors, catechol-O-methyltransferase inhibitors, amantadine, or other drugs for treatment of Parkinson's disease symptoms. • Levodopa equivalents were calculated on the basis of 100 mg/day of standard levodopa being equivalent to the following doses of other drugs: 133 mg controlled-release levodopa; 1 mg pergolide, pramipexole, cabergoline, or rasagiline; 1·25 mg sublingual selegiline; 2 mg benzhexol; 3·3 mg rotigotine; 5 mg ropinirole; 10 mg bromocriptine, oral selegiline, or apomorphine; and 100 mg amantadine. The total levodopa dose was multiplied by 1·33 for entacapone and by 1·5 for tolcapone. • Apart from the random treatment allocation, all other aspects of the management of patients were at the discretion of the local clinicians. Patients in the medical therapy group could cross over to receive surgery after about 1 year. Assessments: • PDQ-39 - primaty outcome of interest Secondary outcomes: • UPDRS in both on and off Neurospsych assessments also done in subset of patients and involved clinical interview and battery of 16 psychometric tests and questionnaires. ** Neuropsych could not be done in all patients because trained examiners were not available in some

<table>
<tr><th>Bibliographic reference</th><td>Williams,A., Gill,S., Varma,T., Jenkinson,C., Quinn,N., Mitchell,R., Scott,R., Ives,N., Rick,C., Daniels,J., Patel,S., Wheatley,K., Deep brain stimulation plus best medical therapy versus best medical therapy alone for advanced Parkinson's disease (PD SURG trial): a randomised, open-label trial, The Lancet Neurology.9 (6) (pp 581-591), 2010.Date of Publication: June 2010., 581-591, 2010</td></tr>
<tr><td></td><td>centres. For centres that did not have trained examiners, a similar method to that used in a previous multicentre randomised controlled trial was adopted, where possible, psychologists (based on oxford) visited centres to complete assessments as required</td></tr>
<tr><td>Results</td><td>366 patients from 13 centres randomly assigned to surgery or BMC. Baseline characteristics similar. 348/366 patients were less 70yrs. 341 patients had PD for at least 5 years (mean duration 11.4 years)
5 patients in surgery group did not have surgery: 3 refused; 1 unfit for anasthesia; 1 died before surgery

<table>
<tr><td>Outcome</td><td>MD</td><td>95%CI_L</td><td>95%CI_U</td></tr>
<tr><td>UPDRS II (on)</td><td>-1</td><td>-2.4</td><td>0.4</td></tr>
<tr><td>UPDRS II off</td><td>-6.3</td><td>-8.2</td><td>-4.4</td></tr>
<tr><td>UPDRS III on</td><td>-4.5</td><td>-6.8</td><td>-2.2</td></tr>
<tr><td>UPDRS III off</td><td>-16.6</td><td>-20.4</td><td>-12.9</td></tr>
<tr><td>UPDRS IV</td><td>-4.6</td><td>-5.4</td><td>-3.7</td></tr>
<tr><td>DRS-II</td><td>0.5</td><td>-0.3</td><td>1.2</td></tr>
<tr><td>PDQ-39 (summ index)</td><td>-5.6</td><td>-8.9</td><td>-2.4</td></tr>
</table>

Adverse events:
Total serious events = 96 (in 65 people) in DBS / 29 (26 people) in BMC
NB** 12 patients in BMC group received DBS surgery between baseline and 1 year follow-up (total N in each group = 183)</td></tr>
<tr><td>Other information</td><td>Bias notes:
• Pair-wise randomization option available so that centres could enter 2 patients together with one allocated to surgery and one to BMC
• Patients and clinicians unmasked to treatment allocation.
• Neuropsych not carried out on all patients
• Targets and methods (stimulation or lesion) left to individual clinician - no control! NB: Authors confirm that all patients had</td></tr>
</table>

Bibliographic reference	**Williams,A., Gill,S., Varma,T., Jenkinson,C., Quinn,N., Mitchell,R., Scott,R., Ives,N., Rick,C., Daniels,J., Patel,S., Wheatley,K., Deep brain stimulation plus best medical therapy versus best medical therapy alone for advanced Parkinson's disease (PD SURG trial): a randomised, open-label trial, The Lancet Neurology.9 (6) (pp 581-591), 2010.Date of Publication: June 2010., 581-591, 2010**
	stimulation - no lesioning was carried out.
Overall Risk of Bias	1. An appropriate method of randomization was used to allocate pts to treatment groups: Yes - Pair-wise randomization option available so that centres could enter two patients together 2. There was adequate concealment of allocation: No 3. The groups were comparable at baseline, including all major confounding and prognostic factors: Yes 4. Comparison groups received same care apart from interventions: No - those in surgical condition attended significantly more follow-up appointments with PD nurses and clinical team than those in medical care 5. Pts receiving care were kept blind to tmt allocation: No - not possible 6. Individuals administering care were kept blind to tmt allocation: No 7. All groups followed up for an equal length of time: Yes 8. Groups comparable for treatment completion: Yes 9. Groups were comparable with respect to avalilability of outcome data: Yes 10. Study had appropriate length of follow-up: Yes 11. Study used a precise definition of outcome: Yes - clearly defined outcomes 12. Valid and reliable method was used to determine the outcome: Yes - well-validated measures used 13. Investigators were kept blind to participants exposure to the intervention: No 14. Investigators were kept blind to other important confounding and prognostic factors:unclear Serious risk of bias: No blinding was carried out, patients in surgical condition recieved significantly more medical attention in the form of clinic and follow-up appointments than those in best medical care arm.

Bibliographic reference	**Charles,David, Konrad,Peter E., Neimat,Joseph S., Molinari,Anna L., Tramontana,Michael G., Finder,Stuart G., Gill,Chandler E., Bliton,Mark J., Kao,Chris C., Phibbs,Fenna T., Hedera,Peter, Salomon,Ronald M., Cannard,Kevin R., Wang,Lily, Song,Yanna, Davis,Thomas L., Subthalamic Nucleus Deep Brain Stimulation in Early Stage ParkinsonGÇÖs Disease, Parkinsonism & related disordersParkinsonism Relat Disord, 20, 731-737, 2014**
Full citation	Charles,David, Konrad,Peter E., Neimat,Joseph S., Molinari,Anna L., Tramontana,Michael G., Finder,Stuart G., Gill,Chandler E., Bliton,Mark J., Kao,Chris C., Phibbs,Fenna T., Hedera,Peter, Salomon,Ronald M., Cannard,Kevin R., Wang,Lily, Song,Yanna, Davis,Thomas L., Subthalamic Nucleus Deep Brain Stimulation in Early Stage ParkinsonGÇÖs Disease, Parkinsonism & related

Bibliographic reference	Charles,David, Konrad,Peter E., Neimat,Joseph S., Molinari,Anna L., Tramontana,Michael G., Finder,Stuart G., Gill,Chandler E., Bliton,Mark J., Kao,Chris C., Phibbs,Fenna T., Hedera,Peter, Salomon,Ronald M., Cannard,Kevin R., Wang,Lily, Song,Yanna, Davis,Thomas L., Subthalamic Nucleus Deep Brain Stimulation in Early Stage ParkinsonGÇÖs Disease, Parkinsonism & related disordersParkinsonism Relat Disord, 20, 731-737, 2014
	disordersParkinsonism Relat Disord, 20, 731-737, 2014
Ref Id	675550
Country/ies where the study was carried out	USA
Study type	Pilot RCT: prospective, randomised, parallel-group, single-blind trial
Aim of the study	To investigate the preliminary safety and tolerability of DBS in early PD
Study dates	August 2006 - April 2009
Source of funding	Medtronic, Inc, National Centre for Advancing Translational Sciences (NCATS), NCATS/NIH award, and by private donations.
Sample size	N=30 (n=15 ODT, n=15 DBS+ODT)
Inclusion criteria	• Idiopathic PD (Hoehn & Yahr Stage II off medication) • Age 50-75 • On medication ≥6 months but <4 years • Absence of motor fluctuations or dyskinesias • MRI within normal range for age • Demonstrated response to dopaminergic therapy
Exclusion criteria	• Subjects younger than 50 years of age • Evidence of an alternative diagnosis or secondary parkinsonism • Uncontrolled medical condition or clinically significant medical disease that would increase the risk of developing pre- or postoperative complications • Evidence of dementia • Major psychiatric disorders • Previous brain operation or injury • Active participation in another clinical trial for the treatment of PD • Patients with demand cardiac pacemakers or medical conditions that require repeat MRI scans

<table>
<tr><th>Bibliographic reference</th><th>Charles,David, Konrad,Peter E., Neimat,Joseph S., Molinari,Anna L., Tramontana,Michael G., Finder,Stuart G., Gill,Chandler E., Bliton,Mark J., Kao,Chris C., Phibbs,Fenna T., Hedera,Peter, Salomon,Ronald M., Cannard,Kevin R., Wang,Lily, Song,Yanna, Davis,Thomas L., Subthalamic Nucleus Deep Brain Stimulation in Early Stage ParkinsonGÇÖs Disease, Parkinsonism & related disordersParkinsonism Relat Disord, 20, 731-737, 2014</th></tr>
<tr><td></td><td>• Evidence of existing dyskinesias or motor fluctuations</td></tr>
<tr><td>Details</td><td>Prior to randomisation, included patients were scheduled for an 8 day inpatient baseline assessment, which included a 7 day medication washout. Details on the method of randomisation were reported elsewhere.</td></tr>
<tr><td>Interventions</td><td>All subjects randomised to DBS+ODT were implanted in three stages using the same methodology used as standard of care at Vanderbilt University Medical Centre
Four weeks after lead implantation, subjects presented off medication for at least 36 hours for evaluation of the clinical response to stimulation
Programming was performed in a standardised fashion using the same methods used for patients with advanced PD
Pulse width was fixed at 60µsec and frequency at 130 Hz.
Modest stimulation increases were performed over three subsequent visits within 6 months based on clinical response.
Primary endpoint was the time to reach a 4-point worsening from baseline in the UPDRS III following a one week treatment washout</td></tr>
<tr><td>Results</td><td>Baseline characteristics did not differ between treatment groups.
In total 30 patients were included in the study, 1 withdrew from the ODT group after baseline due to family and financial circumstances and was therefore not included in the final analysis.
Two SAEs were reported in the DBS+ODT group: 1 patient suffered from perioperative stroke and 1 suffered from lead infection and the device was subsequently removed.
Mean change scores from baseline to 24 months (ODT n=14, DBS+ODT n=15). All on assessments were completed on Day 1 of the washout with subjects on medicine and stimulation, if applicable. All off assessments were completed on Day 8 with subjects off medicine and stimulation if applicable:
<table>
<tr><td>Outcome</td><td>MD (95% CI)</td></tr>
<tr><td>UPDRS II on</td><td>1.8 (-3.1 to 6.7)</td></tr>
<tr><td>UPDRS II off</td><td>-1.2 (-6.1 to 3.7)</td></tr>
<tr><td>UPDRS III* on</td><td>-3.4 (-12.1 to 5.4)</td></tr>
<tr><td>UPDRS III* off</td><td>-1.37 (-9.6 to 6.9)</td></tr>
<tr><td>UPDRS IV</td><td>-1.59 (-3.7 to 0.5)</td></tr>
</table></td></tr>
</table>

Bibliographic reference	**Charles,David, Konrad,Peter E., Neimat,Joseph S., Molinari,Anna L., Tramontana,Michael G., Finder,Stuart G., Gill,Chandler E., Bliton,Mark J., Kao,Chris C., Phibbs,Fenna T., Hedera,Peter, Salomon,Ronald M., Cannard,Kevin R., Wang,Lily, Song,Yanna, Davis,Thomas L., Subthalamic Nucleus Deep Brain Stimulation in Early Stage ParkinsonGÇÖs Disease, Parkinsonism & related disordersParkinsonism Relat Disord, 20, 731-737, 2014**
	UPDRS Total* | -2.7 (-14.7 to 9.3) *Rigidity was not included in the UPDRS III scores
Overall Risk of Bias	1. An appropriate method of randomization was used to allocate pts to treatment groups? Unclear 2. There was adequate concealment of allocation: Unclear 3. The groups were comparable at baseline, including all major confounding and prognostic factors? Yes 4. Comparison groups received same care apart from interventions: Yes 5. Pts receiving care were kept blind to tmt allocation: No - not possible 6. Individuals administering care were kept blind to tmt allocation: No 7. All groups followed up for an equal length of time: Yes 8. Groups comparable for treatment completion? Yes 9. Groups were comparable with respect to availability of outcome data? Yes 10. Study had appropriate length of followup: Yes 11. Study used a precise definition of outcome: yes - clearly defined outcomes 12. Valid and reliable method was used to determine the outcome: yes - well-validated measures used 13. Investigators were kept blind to participants exposure to the intervention: Rater blinded to UPDRS III outcome only 14. Investigators were kept blind to other important confounding and prognostic factors: Unclear

D.7 Managing and monitoring impulse control disorder as an adverse effect of dopaminergic treatment

D.7.1 Predictors for the development of impulse control disorders

Study details	Participants	Methods	Results	Comments
Full citation Auyeung,M., Tsoi,T.H., Tang,W.K., Cheung,C.M., Lee,C.N., Li,R., Yeung,E., 20120618, Impulse control disorders in Chinese Parkinson's disease patients: the effect of ergot derived dopamine agonist, Parkinsonism & Related Disorders, 17, 635-637, 2011 Ref Id 306788 Country/ies where the study was carried out China Study type cohort study Aim of the study The Authors studies the prevalence and related risk factors of ICD's in Chinese PD patients	Sample size N=213 Inclusion criteria prospectively entered all PD patients who presented to clinic from 1999 onwards into a PD databank. Dementia was screened and anly patient with an MMSE of <26 would be sent to a cognitive neurologist for demenita assessment. From aug 1999 to aug 2010 authors screened all non-demented PD patients diagnosed by brain bank criteria who attended the PD clinic and had thier information entered into the databank. Exclusion criteria	Details pre-designed structured screening questionnaire for ICD was constructed by combining both questionnaires for the QUIP and the hedonistic homeostatic dysregulation screening conducted by a well-trained RA who was blinded to medications patient was taking both patients and carers interviewed as far as possible patients who gave at least 1 positive answer to the questionnaire were seen by a neurologist and a diagnosis of ICD was made according to previously defined criteria those patients who were still sufering from an ICD were labelled as active ICD and those who had a previous ICD were regarded as prior ICD	Results demographic mean age at onset 58 (11.1) mean age 67.5 (9.9) 127 male duration of disease 9.3 (5.0) 113/213 DA exposure Dode DA LLED (mg) 98.7 (113.7) total LLED mg 674.9 (387.5) HY 2.3 (0.9) UPDRS 28.1 (17.4) young onset (<50 years) 57/213 findings identified 15/213 (7%) subjects with ICD multivariate analysis revealed following factors to be significantly predictive of IC: young age onset OR = 4.1 (95% CI: 1.1 to 15.9) subjects with anxiety or depression: OR = 10.0 (95% CI:2.0 to 50.8) dose of dopamine agonist /100mg 2.4 (95% CI:1.2 to 4.3)	Overall Risk of Bias CASP quality appraisal checklist 1. Did study address on clearly focused issue? yes 2. Was cohort recruited in acceptable way? yes 3. Was exposure accurately measured to minimise bias? yes 4. Was outcome accurately measured to minimise bias? yes, however PD patients asked to recall symptoms and medications, details etc at that time. Prone to significant recall bias 5. Have authors identified all important confounding factors and taken account of these in design/analysis? yes 6. Was follow-up of subjects complete/long enough? NA 7. What are results? significant predictive factors of ICD reported 8. How precise are results?precise 9. Are results believable? yes

<table>
<tr><th>Study details</th><th>Participants</th><th>Methods</th><th>Results</th><th>Comments</th></tr>
<tr><td>Study dates
Received 4t Feb 2011, revised 25th May, Accepted 2nd June

Source of funding
Not listed</td><td>Patients with a diagnosis of dementia</td><td>patients
clinical and demographic data was collected , including medication information, UPDRS, and depression

Interventions
NA</td><td></td><td>10. Can results be applied to local population? yes 11. Do results fit with other available evidence? yes

low risk of bias</td></tr>
<tr><td>Full citation
Giladi,N., Weitzman,N., Schreiber,S., Shabtai,H., Peretz,C., 20071004, New onset heightened interest or drive for gambling, shopping, eating or sexual activity in patients with Parkinson's disease: the role of dopamine agonist treatment and age at motor symptoms onset, Journal of Psychopharmacology, 21, 501-506, 2007
Ref Id
307571
Country/ies where the study was carried out
Israel
Study type
case-control study</td><td>Sample size
N=203 consecutive PD patients and 190 age and gender matched healthy individuals

Inclusion criteria
Consecutive patients diagnosed with PD according to UK brain bank criteria and being treated at tge Movement disorders unit and national parkinson's disease centre of tertiary care

Exclusion criteria
the following groups of patients were excluded:
Patients with</td><td>Details
Patients underwent cognitive screening during neurological interview. Medical, medical history, ADL H&Y stage, UPDRS, disease duration and treatments were all recorded.
Behavioural aspects of patients and controls were assessed by a personal interview that included general personal and medical history. New onset of gambling, shopping, eating, or sexual behaviour (GSES) were assessed by direct questions to both the patient and the spouse or immediate caregiver.
A heightened interest or</td><td>Results
demographics
mean age = 67.5 (10.9) for PD and 66.7 (11.6) for control
mean age at time of diagnosis = 57.7 years (12.2)
122/193 (63%) were male
27/193 (14%) of patients were found to have new onset heightened interest or drive in GSES which had developed after onset of PD motor symptoms.
behavior:
gambling n=6 (3.1%);
shopping n=6 (3.1%);
eating n=7 (3.6%);
sexual n=17 (8.8%);
number of patients with >1 GSES n=10 (5.0%).

characteristic comparisons

<table><tr><td>male (%)</td><td>78</td><td>56</td><td>p = 0.09</td></tr><tr><td>age of motor symptom onset</td><td>51.5 (12.2)</td><td>58.7 &12.1)</td><td>p=0.006</td></tr></table></td><td>Overall Risk of Bias
No quantification of how diagnosis of ICD was made. only behavioral interview. Adjusted odds ratio not clear on what is adjusted for. Also not clear at all why healthy control population was recruited?

1. Did study address on clearly focused issue? yes 2. Was cohort recruited in acceptable way? yes, consecutive recruitment 3. Was exposure accurately measured to minimise bias? NO - only GSES behavioural interview 4. Was outcome accurately measured to minimise bias? NO- ICD diagnosis not formally made. behaviours only</td></tr>
</table>

<table>
<tr><th>Study details</th><th>Participants</th><th>Methods</th><th>Results</th><th>Comments</th></tr>
<tr>
<td>Aim of the study
To examine the prevalence and risk factors for new onset heightened interest or drive in gambling, shopping, eating, or sexual activity in patients with Parkinson's disease.

Study dates
Published 2007; no other information reported

Source of funding
None acknowledged</td>
<td>dementia according to DSM IV criteria or if their MMSE was <25.
Patients with a psychiatric illness that required psychotropic medication prior to the onset of PD.
Patients with diaganosed and treated OCD</td>
<td>drive in GSES was diagnosed if:
patient was frequently (>1x p/w) involved in shoppping or buying merchandise or gifts that both patients and caregiver agreed were unnecessary
patient was involved in active gambling and was attracted to gambling several times per week
the patient developed compulsive, uncontrolled eating habits
the patient and the spouse or caregiver reported heightened sexual drive and freuquent sexual thoughts coupled with demanding behaviour or the amount of time a patient spent engaging with pornographic material

Interventions
na</td>
<td>
<table>
<tr><td>disease duration</td><td>10.3 (4.9)</td><td>9.7 (6.6)</td><td>0.667</td></tr>
<tr><td>Patients on DA</td><td>70</td><td>58</td><td>0.24</td></tr>
<tr><td>mean duration of DA</td><td>4.4 (2.4)</td><td>3.7 &3.1)</td><td>0.324</td></tr>
<tr><td>n on ropinerole (%)</td><td>48.2</td><td>31.3</td><td>0.09</td></tr>
<tr><td>n on pergolide (%)</td><td>22.2</td><td>5.3</td><td>0.737</td></tr>
<tr><td>n on apomorphine (%)</td><td>22.2</td><td>4.2</td><td>p=0.009</td></tr>
<tr><td>n on amantadine (%)</td><td>63</td><td>51.2</td><td>0.25</td></tr>
<tr><td>n on selegeline (%)</td><td>29.7</td><td>25.9</td><td>0.68</td></tr>
</table>

new behavioural change n=27, no behavioural change n=166

Risk factors for development of new heightened interests of drive in GSES among all PD patients.
Multivariate logistic regression:
<table>
<tr><td></td><td>adj OR</td><td></td></tr>
<tr><td>age at PD symptoms onset</td><td>0.99</td><td>95%CI: 0.99 to 1.00</td></tr>
<tr><td>gender male</td><td>1.10</td><td>95%CI:1.00 to 1.22</td></tr>
</table>
</td>
<td>recorded via interview, no diganostic criteria used. 5. Have authors identified all important confounding factors and taken account of these in design/analysis? yes 6. Was follow-up of subjects complete/long enough? na 7. What are results? risk factors for development of ICD reported 8. How precise are results? unclear- very tight confidence intervals in multivariate analysis, but not clear what OR's are adjusted for/ Control data collected in methods, however not reported. Unclear why collected control data or how it was used? 9. Are results believable? unclear 10. Can results be applied to local population? yes 11. Do results fit with other available evidence? results report lower OR than other studies within the clinical area 12. What are implications for practice? some factors may be associated with increased likelihood of ICD in PD

serious risk of bias.</td>
</tr>
</table>

Study details	Participants	Methods	Results	Comments
			duration of treatment with DA <2 years | 0.95 | 95%CI:0.84 to 1.08 duration of treatment with DA <2 years | 1.04 | 95%CI: 0.91 to 1.18 duration of treatment with DA <2 years | 1.18 | 95%CI: 1.00 to 1.39	
Full citation Imamura,A., Geda,Y.E., Slowinski,J., Wszolek,Z.K., Brown,L.A., Uitti,R.J., Medications used to treat Parkinson's disease and the risk of gambling, European Journal of Neurology.15 (4) (pp 350-354), 2008.Date of Publication: April 2008., 350-354, 2008 Ref Id 307832 Country/ies where the study was carried out	Sample size 11 PD patients who developed onset of PG between 1995 and 2006; 37 age and sex matched ontrols; N=48 Inclusion criteria cases = diagnosis of PD by a neurologist; no history of PG; new onset of G in period between 1995 and 2006 controls = patient with PD but did not have PG	Details Cases and controls recruited from hospital database which records information on all PD patients. Every case who met inclusion criteria considerd for study. All potential controls selected randomly from among patients fullfilling age and sex match criteria IV in this study was presence of PG in a patients with PD. Exposure ascertainment done by neurologist who was uninformed of case	Results 11 cases identified. Matched with 37 controls median age at onset PD 61 years (48-72); 100% males; PD duration 9.6 years (5.2) cases; 7.8 years (5.3) controls total LEDD (mg/day) case = 574 (548); control = 879 (558) (NS difference) pramixepole (mg/day)dose case = 4.3 (2.1), control 2.8 (2.2) (significantly higher dose in cases, p<0.0001) - patients who took premixepole were 3.65 times more likely to develop PG compared to patients who do not take it pramixepole used more frequently in cases vs control, trend t/w significant; OR = 3.65, 95%CI: 0.89 to 14.9 ropinerole and entacapone more common in cases than controls however numbers taking this were small (1 case 3 controls); OR = 1.13, 95%CI: 0.11 to 12.3 for both levodopa use not significantly different between cases	Overall Risk of Bias **NICE case-control study checklist:** 1. The study addresses an appropriate and clearly focused question? yes 2. Cases and controls from comparable populations? yes - well matched 3. Same exclusion criteria used for both cases and controls? yes 4. What was participation rate for each group? Cases: controls: NA - data used from database

Study details	Participants	Methods	Results	Comments
USA Study type case control Aim of the study To assess whether dopamine agonist therapy is associated with pathological gambling in patients with PD Study dates received 26th Jan 2007, accepted December 2007 Source of funding Partially supported by Morris K Udall PD research center of excellence awarded to Mayo clinic Jacksonville. Y>E>G supported in part by National institute of health/National institute of mental health grant	Exclusion criteria secondary causes of Parkinsonism and record of unresponsiveness to levodopa. controls excluded in presence of previous history of PG	control status information on antiPD meds was extracted on de-indentified records Interventions NA	and controls OR = 0.27 (0.05 to 1.29) combination therapy including levodopa and pramipexole not signif different, OR = 1.96 (0.3 to 8.79)	5. Participants and non-participants are compared to establish their similarities or differences? yes 6. Cases are clearly defined and differentiated from controls s 7. It is clearly established that controls are not cases? yes 8. Measures were taken to prevent knowledge of primary exposure from influencing case ascertainment? yes - blinded 9. Exposure status is measured in a standard, valid, and reliable way? yes - exposure ascertainment done clearly differentiated in terms of behaviour, however no diagnostic criteria for pathological gambling provided 10. Main potential confounders are identified and taken into account in the design and analysis yes 11. Have confidence intervals been provided? yes
Full citation	Sample size	Details	Results	**Overall Risk of Bias**

Study details	Participants	Methods	Results	Comments
Joutsa,J., Martikainen,K., Vahlberg,T., Kaasinen,V., Effects of dopamine agonist dose and gender on the prognosis of impulse control disorders in Parkinson's disease, Parkinsonism and Related Disorders.18 (10) (pp 1079-1083), 2012.Date of Publication: December 2012., 1079-1083, 2012 Ref Id 307925 Country/ies where the study was carried out Finland Study type Cohort study Aim of the study to conduct a large-sclae prospective study to investigate the predictive and prognostic factors of ICD's in patients with PD Study dates received March 2012	N=290 patients with PD Inclusion criteria urbey sent to 1000 patients on PD database. 575 responded and second survey sent to these, of these 290 responded in full to second dataset and were included. No further information; authors refer to another previous publication Joutsa et al., 2012 Exclusion criteria no information provided authors refer to another previous publication Joutsa et al., 2012 ;	surveys sent out included demographic dta, including year of diagnosis, alcohol consumption, caffeine, smoking. medical treatments and symptom profile information also collected. Levodopa equivalent daily dose (LEDD) calculated. ICD's and related behaviours assessed using the QUIP and depression with Beck depression inventory. Interventions	demographics 181/290 = male median follow up time 449 days (440 - 456) multiariate analyses for icd at baseline male gender OR = 6.10, 95%CI: 2.16 to 17.18 higher dopamine LEDD at baseline, for 100mg increase OR = 2.25, 95%CI 1.29 to 3.91 No differences in ICD outcomes between patients treated with pramipexole or ropinerole in patients with no ICD at baseline, increase in BDI score between baseline and follow up was only factor associated with ICD at follow up (OR = 1.095, 95%CI: 1.004 to 1.195) no differences in aseline BDI scores between patients who developed novel ICD's compared to patients without ICD's at neither time point medication or demographic factors were not associated with novel ICD's in univariate analysis at both time points patients with ICD's had higher BDI scores compared to patients without ICD	1. Did study address on clearly focused issue? Yes 2. Was cohort recruited in acceptable way? yes - survey mail out to whole database 3. Was exposure accurately measured to minimise bias? yes, although self reported so potentially open to fabrication 4. Was outcome accurately measured to minimise bias? Yes - QUIP used to inform ICD diagnosis 5. Have authors identified all important confounding factors and taken account of these in design/analysis? yes 6. Was follow-up of subjects complete/long enough? yes - 15 months 7. What are results? reports on prdictive factors of ICD 8. How precise are results? imprecise - quite wide CI's 9. Are results believable? yes 10. Can results be applied to local population? yes 11. Do results fit with other available evidence? yes 12. What are implications for practice? inform patients of increased risk of ICD's, especially in light of

Study details	Participants	Methods	Results	Comments
revised and published June 2012 Source of funding This work was supported by the Finish Alcohol research foundation, the Finnish medical foundation, the Turku university hospital funds, Turku university hospital foundation,the Paulo foundaton, and the Finnish Parkinson's foundation				highlighted predictive factors
Full citation Lee,J.Y., Kim,J.M., Kim,J.W., Cho,J., Lee,W.Y., Kim,H.J., Jeon,B.S., 20100524, Association between the dose of dopaminergic medication and the behavioral disturbances in Parkinson disease, Parkinsonism & Related Disorders, 16, 202-207, 2010 Ref Id 308116 Country/ies where the	Sample size N=1167 Inclusion criteria consecutive patients who visited movement disorder clinics at 6 referral hospitals between March and July 2008 were recruited inclusion criteria were: 1) ideopathic PD diagnosis as defined by UKBB criteria 2) having been taking stable DRT	Details subjects assessed for current symptoms suggestive of an ICD using modification of Minnesota impulsive disorders interview (MIDI) data also collected on all demographic, cognitive, PD symptoms, medications, and presence of motor complications of DRTi.e. fluctuations and dyskinesia questionnaires used to assess symptoms was a	Results demographics 57.3% women age 64.9 (9.8) years age at PD onset 58.3 (10.5) disease duration 6.6 (4.3) durtion of DRT 5.0 (3.8) total LLED = 657.5 (387.1) mg/day prevalence ICD 118/1167 (10.1%) patients had ICD punding most common 4.3% eating 3.4% sex 2.8% buying 2.5% gambling 1.3% of those 118 patients, 34 (28.8%) had symptoms of 2	**Overall Risk of Bias** CASP quality appraisal checklist 1. Did study address on clearly focused issue? yes 2. Was cohort recruited in acceptable way? yes - consecutive reruitment 3. Was exposure accurately measured to minimise bias? yes 4. Was outcome accurately measured to minimise bias? yes - using Minesota impulsive disorders interview 5. Have authors identified all important confounding

<table>
<tr><th>Study details</th><th>Participants</th><th>Methods</th><th>Results</th><th>Comments</th></tr>
<tr>
<td>study was carried out
South Korea
Study type
cross sectional survey

Aim of the study
To survey the point prevalence of impulse control disorder and repetitive behaviour disorders in patients with PD and to determine the relationship between PD medication dose and risk of ICD's

Study dates
received July 2009, revised November, published December 2009

Source of funding
Korea health research project grant</td>
<td>for at least 3 months

Exclusion criteria
patients who were unable to complete questionnaires due to cognitive impairment</td>
<td>modified version of MIDI and was comprised of 5 ICD modules: compulsive buying, gambling, eating, sexual behaviour, and punding behaviour
presence of an ICD was defined as answering in the affirmative to one or more of the remaining questions on the ICD module. In the interview, current symptoms of an ICD that commenced after begginning the DRT were considered to be positive.</td>
<td>or more ICDs
factors contributing to development of ICD
NB: OR's are adjusted for age at PD onset, gender, and PD duration Agonist LLED mg/d
<table>
<tr><td>risk factor</td><td>ICD (buy, gam, sex)</td><td>Eating</td><td>Punding</td></tr>
<tr><td>agonist LLED 60 - 160 mg/d</td><td>3.3 (1.3 - 9.1)</td><td>1.1 (0.4 - 2.8</td><td>1.1 (0.5 - 2.4)</td></tr>
<tr><td>>160 mg/d</td><td>4.3 (1.6 - 11.9)</td><td>1.0 (0.3 - 2.8)</td><td>0.6 (0.2 - 1.7)</td></tr>
<tr><td>daily dose l-dopa 450 - 750</td><td>0.8 (0.4 - 1.6)</td><td>0.9 (0.4 - 2.1)</td><td>2.2 (1.0 - 5.1)</td></tr>
<tr><td>>750</td><td>1.0 (0.5 - 2.1)</td><td>1.8 (0.8 - 4.1)</td><td>3.5 (1.5 - 8.2)</td></tr>
</table>
</td>
<td>factors and taken account of these in design/analysis? yes 6. Was follow-up of subjects complete/long enough? NA - no follow up 7. What are results? predictive factors of ICD reported 8. How precise are results?precise - tight CI's in OR model 9. Are results believable? yes 10. Can results be applied to local population? yes 11. Do results fit with other available evidence? yes 12. What are implications for practice? patients taking DA therapy be advised of risk of developing ICD</td>
</tr>
<tr>
<td>Full citation
Pontone,G., Williams,J.R., Bassett,S.S., Marsh,L., 20061108, Clinical features associated with impulse control</td>
<td>Sample size
N=100; n with ICD = 9, n without ICD = 91

Inclusion criteria</td>
<td>Details
individuals were recruited as above. Participants received a clinical interview, with current and past psychiatric diagnoses established</td>
<td>Results
Psychiatric interviews revealed ICD's in 6 men and 3 women, yeilding a prevalence of 9% for the three types of ICD's: hypersexuality PG, and excessive spending.
No significant differences in PD-related or demographic variables.</td>
<td>Overall Risk of Bias
recruitement strategy unclear: unclear if consecutive recruitment; unclear exclusion criteria. Non demented was</td>
</tr>
</table>

Study details	Participants	Methods	Results	Comments
disorders in Parkinson disease, Neurology, 67, 1258-1261, 2006 Ref Id 308671 Country/ies where the study was carried out USA Study type Retrospective cohort study Aim of the study To identify factors associated with the development of ICD's. In particular, the paper investigated the association of non-pharmacologic clinical features of patients with PD with the presence of ICD's. Study dates Study dates not listed. Published 2006. Source of funding Not listed	n=66 men and n=34 women with ideopathic PD, based on UK brain bank criteria, recruited from outpatient clinics, ongoing research programs, and community outreach to participate. Individuals were 65 years or younger, non demented, and had no evidence of a current substance abuse or psychotic disorder, or a history of neurosurgical treatment for PD. Exclusion criteria None listed	according to the clinical interview and diagnosis (SCID) for DSM IV and supplemental question regarding axis 1: disorders not in the SCID i.e ICD. the neuropsychiatric inventory (NPI) was administered directly to the patient, and was used to rate individual psychiatric phenomena. Participants rated according to UPDRS and H&Y staging system, and MMSE. Interventions NA	demographics mean age ICD = 48.9 (10.0), non ICD = 55.1 (7.4) mean age on set PD ICD = 44.3 (9.0), no IVD = 48.6 (9.0) mean duration PD ICD = 4.6 (2.2), no ICD = 6.5 (5.5) psychiatric comorbidities comorbid anxiety disorder ICD n = 5/9; non ICD n = 30/91 comorbid depressive disorder ICD n = 3/9, no ICD n = 20/91 comorbid psychotic symptoms ICD n = 5/9; no ICD = 27/91 NPI depression ICD mean score = 4.3 (5.0), no ICD = 1.1 (2.5) NPI anxiety mean score ICD = 3.4 |(4.6), non ICD = 1.3 (2.8) NPI total mean score ICD = 19.7(17.6), no ICD = 8.1 (9.2) medication regimen association All patients with ICD taking a DA and at time of ICD onset used combined L-dopa/DA therapy. in non ICD group 71/91 taking L-dopa, 56/91 used DA (pramixepole n=36; ropinerole n=11; pergolide n=6; bromocriptine n=2; sumanirole n=1) and 35 were taking DA + L-dopa. Only DA were associated with ICD as a class: OR = 11.9 95%CI: 3.93 to 51.4 Associated found for pramipexole OR = 5.35 (95%CI: 1.05 to 27.2)	inclusion criteria, however one subject in ICD group had MMSE of 22. N very small for ICD group. <u>CASP quality appraisal checklist</u> 1. Did study address on clearly focused issue? yes 2. Was cohort recruited in acceptable way? No - recruitment stretegy unclear 3. Was exposure accurately measured to minimise bias? yes 4. Was outcome accurately measured to minimise bias? yes 5. Have authors identified all important confounding factors and taken account of these in design/analysis? yes 6. Was follow-up of subjects complete/long enough? NA =- no follow up 7. What are results? number of predictive factors for ICD listed 8. How precise are results? Not precise - no CI's listed 9. Are results believable? yes 10. Can results be applied to local population? yes 11. Do results fit with other

<table>
<tr><th>Study details</th><th>Participants</th><th>Methods</th><th>Results</th><th>Comments</th></tr>
<tr><td></td><td></td><td></td><td></td><td>available evidence? yes</td></tr>
<tr><td>Full citation
Voon,V., Thomsen,T., Miyasaki,J.M., de,Souza M., Shafro,A., Fox,S.H., Duff-Canning,S., Lang,A.E., Zurowski,M., Factors associated with dopaminergic drug-related pathological gambling in Parkinson disease, Archives of Neurology.64 (2) (pp 212-216), 2007.Date of Publication: February 2007., 212-216, 2007
Ref Id
309316
Country/ies where the study was carried out
Canada
Study type
Case-control

Aim of the study
To evaluate factors associated with pathological gambling in PD

Study dates</td><td>Sample size
21 patients with PD and PG identified ; patients with PDPG compared to 286 patients with PD and no PG (previously described in Von et al., 2006)

Inclusion criteria
Inclusion criteria included: PG diagnosis according to DSM IV and ideopathic PD diagnosis according to UKBB criteria

Exclusion criteria
DSM IV-defined dementia diagnosis</td><td>Details
All patients with PD and PG onset after iitiation of receiving dopaminergic medications were ID through movement disorders clinic at Toronto western hospital through clinical presentation or through 3 month prevalence screening 297 patients with PD.
For controls, sequential patients with PD attending follow-up appointments at the movement disorders clinic.
patients and controls completed patient-rated scales and were assessed by neurologist and a psychiatrist - clinical information was collected including age at onset, current medications, MMSE, motor features UPDRS, frontal assessment battery, depression inventory.
Pathological gambling, compulsive shopping,</td><td>Results
21 patients with PDPG identified. 1 patient PG onset after DBS to STN; separate analyses excluding this patient did not alter results.
76 potential controls contacted.
Patients with PG compared to 42 controls with PD without compulsive behaviors and with 286 patients with PD but without PG previously.
<table>
<tr><td>characteristic</td><td>PD PG N=21</td><td>PD controls N=42</td><td>MD (95%CI)</td></tr>
<tr><td>age at PD onset</td><td>50.9 (8.8)</td><td>58.4 (10.1)</td><td></td></tr>
<tr><td>PD duration</td><td>9.2 (5.2)</td><td>6.9 (4.2)</td><td></td></tr>
<tr><td>DA LEDD</td><td>268.3 (194.3)</td><td>192.1(105.3)</td><td></td></tr>
<tr><td>Left hemisphere onset PD, N</td><td>16</td><td>15</td><td>OR =</td></tr>
<tr><td>Beck depression inventory</td><td>12.4 (6.0)</td><td>10.3 (7.9)</td><td></td></tr>
<tr><td>family hist alcohol use disorder, N</td><td>12</td><td>8</td><td>OR =</td></tr>
<tr><td>Barratt impulsivity (total)</td><td>65.2 (12.2)</td><td>54.1 (10.1)</td><td></td></tr>
</table></td><td>Overall Risk of Bias

NICE case-control checklist
1. The study addresses an appropriate and clearly focused question? yes
2. Cases and controls from comparable populations? yes 3. Same exclusion criteria used for both cases and controls? yes
4. What was participation rate for each group? Cases: controls: full participation
5. Participants and non-participants are compared to establish their similarities or differences? yes 6. Cases are clearly defined and differentiated from controls yes 7. It is clearly established that controls are not cases? yes 8. Measures were taken to prevent knowledge of primary exposure from influencing case ascertainment? yes 9. Exposure status is measured in a standard, valid, and reliable way? yes 10. Main potential</td></tr>
</table>

Study details	Participants	Methods	Results	Comments
patients recruited between June 2003 and June 2005, study published February 2007 Source of funding No financial disclosure reported		hypersexuality, and compulsive medication use were diagnosed. Past and present mood disorders, anxiety, substance abuse disorders were diagnosed via clinical interview using structured clinical interview DSM IV axis. impulsivity measures Barratt impulsivity score which assesses planning, attention, and motor factors. Novelty seeking and harm avoidance were assessed using the temperament character inventory. Interventions NA	Novelty seeking score: 20.3 (6.6) | 10.9 (4.2) | N recieving DA adjunctive therapy. N: 20 | 30 | OR =	confounders are identified and taken into account in the design and analysis: yes 11. Have confidence intervals been provided? yes **no serious risk of bias**
Full citation Weintraub,D., Siderowf,A.D., Potenza,M.N., Goveas,J., Morales,K.H., Duda,J.E., Moberg,P.J., Stern,M.B., 20060807, Association of dopamine agonist use with impulse control	Sample size N=272 Inclusion criteria Outpatients diagnosed with ideopathic PD, predominantly of mild to moderate severity, confirmed by movement	Details 2 trained research assistants administered the screening battery, which included open ended questions about the existance(lifetime, anytime during PD, and currently) of recurrent compulsive buying, gambling, or sexual behaviours.	Results demographic age rage 35 - 91 years 137/272 (50.4%) participants taking a DA at screening For patients taking DA, no difference between both groups in LEDD 21/272 patient positive for ICD - 2 did not meet MIDI criteria and one was lost to follow up so final N ICD = 18 compulsive sexual behaviour as common as compulsive gambling, both N = 7 , compulsive buying	Overall Risk of Bias For subjects who had experienced and ICD at any stage of their PD, were asked to recall symptoms and medications, details etc at that time. Prone to significant recall bias. CASP quality appraisal checklist

Study details	Participants	Methods	Results	Comments
disorders in Parkinson disease, Archives of Neurology, 63, 969-973, 2006 Ref Id 309365 Country/ies where the study was carried out USA Study type cohort study - unstructured screening interview for ICD's followed by telephone administered structured interview for screen positive patients Aim of the study To determine the frequency and correlates of ICD's in PD Study dates Patients screened between July 2004 and June 2005. Paper published July 2006 Source of funding study supported by grant from NIMH and by mental illness	disorders specialist. Subjects were established patients of one of two movement disorder clinics and were thought to represent a cross-section of the clinic's populations Exclusion criteria Patients unable to provide written consent due to cognitive impairment	Subjects also administered the 15 item geriatric depresion scale and MMSE as part of screening. Those who screened positive for ICD during course of their PD were contacted by phone and administered a modified MIDI, which includes queries for the presence of clinically-significant compulsive gambling, sexual, and buying behaviours Patients were instructed to answer questions based on based on their state at the time they were symptomatic ICD's defined as answering in the affirmative to 1 (compulsive sexual behaviour and compulsive shopping) or 2 (compulsive gambling) gateway questions plus 1+ affirmative answer to remianing ICD questions PI reviewed medical charts of all patients to verify answers LEDD's calculated for DA's and DA +L-dopa	N = 4 (all for anytime during PD) results On univariate analysis, younger age, longer PD duration, history of ICD symptomology prior to PD, and use of DA or amantadine were associated with presence of an ICD, with suggestion of higher LEDD all 11 active ICD cases were taking a DA all 18 ICD cases (any time) were taking DA at time of symptoms 7 became unsymptomatic; 4 = discontinuation of DA, 2 = reduction in DA , 1 = counselling In multivariate model taking all significant univarate factors into account, dopamine agonist use and history of ICD behaviour/symptomology prior to PD were the only significant factors predictive of an ICD : prior ICD symptoms, OR = 15.54, unadjusted 95%CI: 2.83, 76.16 DA use, OR = 16.27, unadjusted 95%CI: 2.61, upper limit approaches infinity) No significant differences between the 3 DA's and incidence of ICD; in patients who had experienced an ICD, ropinerole = 8, pramipexole =7, pergolide = 3 DA dosage In patients currently taking a DA, ICD's were associated with exposure to higher daily doses of pergolide (T13 = -3.38, p=0.05), but not pramipexole (t 71 = -2.14, p=0.06), or ropinerole (t47 = -0.81, p=0.4) Using LEDD's and examining the 3 dopamine agonists as a class, treatment with higher doses was associated with the presence of an ICD (t135 = -4.06, p=0.001).	1. Did study address on clearly focused issue? yes 2. Was cohort recruited in acceptable way? yes 3. Was exposure accurately measured to minimise bias? yes 4. Was outcome accurately measured to minimise bias? yes, however PD patients asked to recall symptoms and medications, details etc at that time. Prone to significant recall bias 5. Have authors identified all important confounding factors and taken account of these in design/analysis? yes 6. Was follow-up of subjects complete/long enough? NA 7. What are results? significant predictive factors of ICD reported 8. How precise are results?precise 9. Are results believable? yes 10. Can results be applied to local population? yes 11. Do results fit with other available evidence? yes **low risk of bias**

<table>
<tr><th>Study details</th><th>Participants</th><th>Methods</th><th>Results</th><th>Comments</th></tr>
<tr>
<td>research, education,and clinical centers at the Philadelphia and West Haven veterans affairs medical centers</td>
<td></td>
<td>(total LEDD)
to probe for possible risk factors in development of ICD in PD, data obtained for factors that have been previously reported as associated with ICD's in PD i.e. type and ose of dopaminergic therapy, disease duration, age, and sex) or were factors of interest (history of ICD, cognition, education, marital status).

Interventions
NA</td>
<td>
<table>
<tr><td>Variable</td><td>No active ICD (261)</td><td>Active ICD (11)</td><td>Odds ratio (95%CI) or MD (95% CI)**Calculated from raw data</td></tr>
<tr><td>age</td><td>68.6 (10.2)</td><td>59.5 (9.4)</td><td></td></tr>
<tr><td>male, N</td><td>182 (69.7)</td><td>10 (90.9%)</td><td>OR =4.34 (0.5463 to 34.4871)</td></tr>
<tr><td>L-dopa mg/d</td><td>448.1 (335.2)</td><td>543.6 (453.5)</td><td></td></tr>
<tr><td>total LEDD mg/d</td><td>5699.3 (369.1)</td><td>925.5 (534.9)</td><td></td></tr>
<tr><td>DA use, N</td><td>126 (48.3)</td><td>11 (100%)</td><td>OR =24.6 (1.4 to 422.44)</td></tr>
<tr><td>amantadine use, N</td><td>49(18.8)</td><td>6 (54.5%)</td><td></td></tr>
<tr><td>PD duration, years</td><td>6.9 (5.8)</td><td>11.2 (7.5)</td><td></td></tr>
<tr><td>GDS</td><td>4.0 (3.8)</td><td>6.0 (5.5)</td><td></td></tr>
<tr><td>prior ICD behaviour, N</td><td>9 (3.5)</td><td>4 (36.4)</td><td>OR =16 (3.957 to 64.68)</td></tr>
</table>
</td>
<td></td>
</tr>
<tr><td>Full citation</td><td>Sample size</td><td>Details</td><td>Results</td><td>CASP quality appraisal checklist</td></tr>
</table>

Study details	Participants	Methods	Results	Comments
Weintraub,D., Koester,J., Potenza,M.N., Siderowf,A.D., Stacy,M., Voon,V., Whetteckey,J., Wunderlich,G.R., Lang,A.E., 20100701, Impulse control disorders in Parkinson disease: a cross-sectional study of 3090 patients, Archives of Neurology, 67, 589-595, 2010 Ref Id 309372 Country/ies where the study was carried out USA and Canada Study type Cross sectional cohort study Aim of the study To ascertain point prevalence estimates of 4 ICD's in PD and examine their associations with dopamine-replacement therapies and other clinical characteristics Study dates	N=3090 patients with PD Inclusion criteria Subjects diagnosed as having ideopathic PD by a movement disorder specialist, aged 30 - 75 years, recruited from 46 movement disorder clinics in US and canada. Inclusion criteria required patients had treatment with a PD medication for at least 1 year with demonstrated response Exclusion criteria Dopamine agonist treatment could not be initiated or terminated in the 6 months prior to evaluation	Semi structred interview using formal diagnostic criteria assessed current frequency of 4 different ICD's: pathological gambling compulsive sexual behaviour compulsive buying binge eating All participants informed primary purpose of study was to study ICD and the association with PD medication Participants answered atudy questions individually but corroborative evidence was taken from informant where available. Patients recruited regularly during clinic visits based on set selection process such that every third patient on given clinicl day was assessed for suitability by researcher with no knowledge of patient's ICD status and PD medication. The following semi-structure diagnostic instruments were administered by trained research staff to capture	3030/3091 taking either levodopa or a DA 2040/2090 taking 1 or more DA's 2682/2090 were taking levodopa, including the 991 not taking a DA 59 patients taking neither ICD prevalence at leas one active ICD identified in 13.6% of patients 3.9% experienced 2 or more ICD's clinical characteristics by ICD: Those with ICD more likely to be Young. age <65 v > 65 = 302/420 (ICD) vs 1322/2670 (no ICD) OR = 2.5 (1.98 to 3.15) currently smoke = 28/420 vs 90/2670 - OR = 1.70 (1.07 to 2.70) report familial gambling = 30/420 vs 94/2670 - OR = 2.08 (1.33 to 3.25) not married vs married - OR = 1.48 (1.16 to 1.89 dopamine agonist treatment - OR = 2.72 (2.07 to 3.57) levodopa treatment - OR = 1.51 (1.09 to 2.09) men more likely women to have compulsive sexual behaviour - OR = 11.98, 95%CI: 4.87 to 29.48 men less likely compulsive buying - OR = 0.55; 95%CI: 0.40 to 0.74 men less likely binge eating disorder - OR = 0.57, 95%CI: 0.4 to 0 patients with history of gambling problems had higher rate of: problem gambling- OR = 2.97, 95%CI: 1.71 to 5.17 compulsive buying OR = 1.97, 95%CI: 1.08 to 3.58 binge eating OR =2.49, 95%CI:1.43 to 4.64 ICD frequency in those with and without DA's. No DA vs DA	1. Did study address on clearly focused issue? yes 2. Was cohort recruited in acceptable way? yes 3. Was exposure accurately measured to minimise bias? yes 4. Was outcome accurately measured to minimise bias? yes, however PD patients asked to recall symptoms and medications, details etc at that time. Prone to significant recall bias 5. Have authors identified all important confounding factors and taken account of these in design/analysis? yes 6. Was follow-up of subjects complete/long enough? NA 7. What are results? significant predictive factors of ICD reported 8. How precise are results?precise 9. Are results believable? yes 10. Can results be applied to local population? yes 11. Do results fit with other available evidence? yes **low risk of bias**

Study details	Participants	Methods	Results	Comments
published May 2010 Source of funding study funded by and designed by jointly by Boehringer Ingleheim and the scientific advisory board (consisting of Drs Weintraub, Potenza, Siderowf, Stacy, Voon, and Lang)		clinically significant symptoms: Massachusetts gambling screen , ≥ 5 endorsed for pathological gambling, 3 - 4 endorsed for problem gambling Minessota Impulsive Disorders interview for compulsive buying and sexual behaviour - both disorders positive response to gateway question plus ≥ 1 secondary question for that sub section DSM IV proposed research criteria for binge-eating disorder. Positive response to gateway question plus ≥ 3 secondary questions Interventions N/A	Patients treated with DA had higher frequency iof ICD compared to those not taking DA - OR 2.72 (2.08 to 3.54) problem gambling: OR = 2.82 (1.81 to 4.39) pathological gambling - OR = 2.15 (1.26 to 3.66) compulsive sexual behaviour - OR = 2.59 (1.55 to 4.33) compulsive buying - OR = 2.53 (1.69 to 3.78) binge eating - OR = 3.34 (2.01 to 5.53) Examining only patients on DA (n=2040) no dopamine agonist dosage effect any levodopa use and higher levodopa use assocuated with current ICD - OR = 1.43 (95% CI: 1.03 to 2)	
Full citation Weintraub,D., Sohr,M., Potenza,M.N., Siderowf,A.D., Stacy,M., Voon,V., Whetteckey,J., Wunderlich,G.R., Lang,A.E., Amantadine use associated with	Sample size (see Weintraub et al., 2010a) Inclusion criteria (see Weintraub et al., 2010a)	Details (see Weintraub et al., 2010a) Interventions NA	Results see (see Weintraub et al., 2010a) for demographic details results At least 1 active ICD identified in 17.6% amantadine users compared with 12.4% of patients not taking amantadine (p = 0.0001) (see table below)	CASP quality appraisal checklist 1. Did study address on clearly focused issue? yes 2. Was cohort recruited in acceptable way? yes 3. Was exposure accurately measured to minimise bias? yes 4. Was outcome accurately

<table>
<tr><th>Study details</th><th>Participants</th><th>Methods</th><th>Results</th><th>Comments</th></tr>
<tr>
<td>impulse control disorders in Parkinson disease in cross-sectional study, Annals of Neurology.68 (6) (pp 963-968), 2010.Date of Publication: December 2010., 963-968, 2010
Ref Id
309373
Country/ies where the study was carried out
USA
Study type
cross section study - See Weintraub et al., 2010a

Aim of the study
secondary analysis of the DOMINION data (see Weintraub et al., 2010a) to determine the frequency of ICD's in patients treated with amantadine

Study dates
published July 2010 - (see Weintraub et al., 2010a)

Source of funding
Boehringer Ingelheim</td>
<td>Exclusion criteria (see Weintraub et al., 2010a)</td>
<td></td>
<td>
<table>
<tr><td>Any ICD</td><td>OR = 1.49 (95%CI: 1.19 to 1.87)</td></tr>
<tr><td>PG</td><td>OR = 1.78 (95%CI: 1.27 to 2.50)</td></tr>
<tr><td>compulsive sexual</td><td>OR = 1.70 (95%CI:1.13 to 2.56)</td></tr>
<tr><td>compulsive buying</td><td>OR = 1.60 (95%CI:1.15 to 2.22)</td></tr>
<tr><td>binge eating disorder</td><td>OR = 1.03 (95%CI: 0.68 to 1.54)</td></tr>
</table>
Patients treated with amantadine compared with those who no amantadine use were: younger, had longer PD duration, more sever PD based on H&Y, more likely to have undergone DBS, had more formal education, were likely to be treated with a DA and were taking higher levodopa dosage. see below:
<table>
<tr><td>variable</td><td>amantadine use (n=728)</td><td>no amantadine use (n=2357)</td><td>p value</td></tr>
<tr><td>gender, male</td><td>463 (63.6)</td><td>1515 (64.3)</td><td>0.69</td></tr>
<tr><td>age <65 years</td><td>446 (61.3)</td><td>1177 (49.9)</td><td>na</td></tr>
<tr><td>PD duration, median yrs</td><td>10.0 (6.4-14.0)</td><td>5.7 (3.3 - 9.2)</td><td>0.0001</td></tr>
<tr><td>H&Y</td><td>n=724</td><td>n=2354</td><td>0.0001</td></tr>
</table>
</td>
<td>measured to minimise bias? yes, however PD patients asked to recall symptoms and medications, details etc at that time. Prone to significant recall bias 5. Have authors identified all important confounding factors and taken account of these in design/analysis? yes 6. Was follow-up of subjects complete/long enough? NA 7. What are results? significant predictive factors of ICD reported 8. How precise are results?precise 9. Are results believable? yes 10. Can results be applied to local population? yes 11. Do results fit with other available evidence? yes

low risk of bias</td>
</tr>
</table>

Study details	Participants	Methods	Results	Comments

stage			
current smoking, Y	n=33	n=85	0.2
curent alcohol, Y	n=281	n=990	0.1
fam hist gambling, Y	n=32	n=94	0.6
fam hist alcohol abuse, Y	n=155	n=571	
DA use, Y Levodopa LEDD, median mg/d	n=521 468.75	1517 450	0.0003 0.0001

Multiple logistic model stepwise selection of ICD correlates

1	age (<65 v > 65)	OR = 2.40 (95%CI: 1.91 to 3.02)	p < 0.0001
2	DA use (Y v N)	OR = 2.64 (95%CI: 2.01 to 3.46)	p < 0.0001
3	L-dopa LEDD	OR = 1.50 (95%CI: 1.21	p = 0.0002

Study details	Participants	Methods	Results	Comments
			<table><tr><td></td><td>(median > 450 mg/d)</td><td>to 1.86)</td><td></td></tr><tr><td>4</td><td>amantadine use (YvN)</td><td>OR = 1.29 (95%CI: 1.02 to 1.63)</td><td>p = 0.0342</td></tr></table>	
Full citation Sharma,A., Goyal,V., Behari,M., Srivastva,A., Shukla,G., Vibha,D., 20150306, Impulse control disorders and related behaviours (ICD-RBs) in Parkinson's disease patients: Assessment using "Questionnaire for impulsive-compulsive disorders in Parkinson's disease" (QUIP), Annals of Indian Academy of Neurology, 18, 49-59, 2015 **Ref Id** 371219 **Country/ies where the study was carried out** India **Study type** cross-sectional study **Aim of the study**	**Sample size** N=299 consecutive patients with PD **Inclusion criteria** patients with ideopathic PD according to UKBB criteria aged 30 - 75 years on treatment with DRT for >1 year with documented response and whose treatment was not modified based on prior reporting of ICD RB's **Exclusion criteria** patient not consenting for study cognitive abnormaility of MMSE <24	**Details** participants and their spouses asked to fill out QUIP based on behaviours that ocurred anytime during PD that lasted at least 4 consecutive weeks. following cut offs used to represent a poaitive screen based on QUIP validation study data: compulsive gambling = 2/5 items, sexual behaviour = 1/5, buying = 1/5, eating = 2/5, plus other compulsive behaviours i.e. hobbyism, punding demographic details collected along with UPDRS motor score in 'on' state, H&Y score in on state, and details of antiparkinsonian medication regimen **Interventions** NA	**Results** demographics: age = 57.7 (11.4) disease duration = 6.9 (4.7) males = 74.9% females = 25.1% 296/299 taking LD or DA N=245 on a DA At least one ID RB present in 93 (31.1%) of patients frequency of ICD RB in subjects exposed only to LD (20.3%) was lower than those on DA monotherapy (24.2%) which was lower than those on both (55.5%) Bivariate and multivariate analysis results taken here only from ICD (NOT ICDRB) dataset independent predictors of ICD after multivariate analysis were younger age at onset, being unmarried, smoking and higher DA and total LEDD **MULTIVARIATE** analysis controlling for age of onset, being unmarried, smoking, disease duration, Ldopa LEDD, DA LEDD, total LEDD (positive factors from univariate analyses) <table><tr><td></td><td>OR</td><td>95%CI low</td><td>95%CI high</td></tr><tr><td>age onset <40 vs >40</td><td>0.96</td><td>0.93</td><td>0.99</td></tr><tr><td>unmarried</td><td>6.92</td><td>1.84</td><td>25.94</td></tr><tr><td>smoker</td><td>7.67</td><td>3.28</td><td>17.93</td></tr></table>	**Overall Risk of Bias** CASP quality appraisal checklist 1. Did study address on clearly focused issue? yes 2. Was cohort recruited in acceptable way? yes 3. Was exposure accurately measured to minimise bias? yes 4. Was outcome accurately measured to minimise bias? yes 5. Have authors identified all important confounding factors and taken account of these in design/analysis? yes 6. Was follow-up of subjects complete/long enough? NA 7. What are results? significant predictive factors of ICD reported in univariate and multivariate anayses 8. How precise are results? precise 9. Are results believable? yes 10. Can results be applied to local population? yes - although this cohort is

<table>
<tr><th>Study details</th><th>Participants</th><th>Methods</th><th>Results</th><th>Comments</th></tr>
<tr>
<td>ascertain prevalence of ICDRB's and association of these behaviours with dopamine replacement therapy

Study dates
study conducted from March 2012 to May 2013

Source of funding</td>
<td></td>
<td></td>
<td>
<table>
<tr><td>disease duration</td><td>NA</td><td></td><td></td></tr>
<tr><td>L-dopa</td><td>NA</td><td></td><td></td></tr>
<tr><td>DA LEDD 150 - 300mg
DA LEDD >300 mg</td><td>4.52
4.53</td><td>1.6
2.26</td><td>12.5
13.06</td></tr>
<tr><td>total LEDD 400 - 800mg
total LEDD >800mg</td><td>1.38
4.41</td><td>0.5
1.62</td><td>3.82
11.98</td></tr>
</table>
UNIVARIATE ANALYSES
<table>
<tr><td>variables</td><td>OR</td><td>95%CI LOW</td><td>95%CI HIGH</td></tr>
<tr><td>pramipexole use</td><td>3.03</td><td>1.73</td><td>5.30</td></tr>
<tr><td>entacapone</td><td>1.47</td><td>0.75</td><td>2.9</td></tr>
<tr><td>rasagaline</td><td>0.98</td><td>0.5</td><td>1.9</td></tr>
<tr><td>amantadine</td><td>3.48</td><td>2.02</td><td>6.01</td></tr>
<tr><td>unmarried</td><td>9.6</td><td>2.9</td><td>31.3</td></tr>
<tr><td>smoker</td><td>7.5</td><td>3.5</td><td>16.15</td></tr>
<tr><td>alcohol intake</td><td>4.0</td><td>2.0</td><td>8.05</td></tr>
<tr><td></td><td></td><td></td><td></td></tr>
</table>
</td>
<td>from India, unknown how comparable this PD population is to UK PD population and relevance of predictive factors i.e. smoking, alcohol intake, and marital status, which are culturally-dependent variables
11. Do results fit with other available evidence?
yes</td>
</tr>
</table>

<table>
<tr><th>Study details</th><th>Participants</th><th>Methods</th><th>Results</th><th>Comments</th></tr>
<tr><td></td><td></td><td></td><td></td><td></td></tr>
<tr><td>Full citation
Rizos,A., Sauerbier,A., Antonini,A., Weintraub,D., Martinez-Martin,P., Kessel,B., Henriksen,T., Falup-Pecurariu,C., Silverdale,M., Durner,G., Rokenes,Karlsen K., Grilo,M., Odin,P., Chaudhuri,K.R., A European multicentre survey of impulse control behaviours in Parkinson's disease patients treated with short- and long-acting dopamine agonists, Eur J Neurol, 23, 1255-1261, 2016
Ref Id
675546

Country/ies where the study was carried out
UK, Spain, Denmark and Romania

Study type
A retrospective and</td><td>Sample size
425

Inclusion criteria
PD patients diagnosed according to the UK Brain Bank criteria
Data from patients already taking ropinirole-IR/XL, pramipexole-IR/PR and rotigotine, as well as those initiating treatment with these DAs

Exclusion criteria
Patients who had dementia or parkinsonism not due to idiopathic PD</td><td>Details
This medical record survey was registered as an audit and the prospective component was part of a longitudinal study of motor and non-motor symptoms in PD and the impact of PD treatments. Assessment was based on established clinical records and chart review.

Interventions
N/A</td><td>Results
Main demographic and PD historical characteristics:<table><tr><td>Demographic characteristics</td><td>All cases (n=425)</td><td>ICD cases (n=57)</td></tr><tr><td>Male gender (%)</td><td>259(60.9)</td><td>45(78.9)</td></tr><tr><td>Mean age in years (range)</td><td>68.3(37-90)</td><td>62.7(42-85)</td></tr><tr><td>Mean duration of PD in years (range)</td><td>7.5(0-37)</td><td>7.0(0-24)</td></tr><tr><td>Median H&Y stage (range)</td><td>2.5(1.0-5.0)</td><td>3.0(1.0-5.0)</td></tr></table>ICD rates on immediate- and extended release DAs:
Pramipexole pooled (IR+PR): 13.8%
Pramipexole-IR: 19%
Pramipexole-PR: 6.6%
Ropinirole pooled (IR+XL): 13.9%
Ropinirole-IR: 14%
Ropinirole-XL: 13.9%
Rotigotine: 4.9%</td><td>Overall Risk of Bias
CASP quality appraisal checklist
1. Did study address on clearly focused issue? Yes. 2. Was cohort recruited in acceptable way? Yes. 3. Was exposure accurately measured to minimise bias?
Unclear. 4. Was outcome accurately measured to minimise bias? Yes. 5. Have authors identified all important confounding factors and taken account of these in design/analysis?
Unclear. 6. Was follow-up of subjects complete/long enough?
NA - no follow up
7. What are results? Incidence of ICD in PD patients treated with short- or long-acting DAs. 8. How precise are results?
Precise. 9. Are results believable?
Yes. 10. Can results be applied to local population? yes 11. Do results fit with other available evidence?</td></tr>
</table>

<table>
<tr><th>Study details</th><th>Participants</th><th>Methods</th><th>Results</th><th>Comments</th></tr>
<tr>
<td>prospective survey based on medical records and clinical interviews

Aim of the study
To assess the occurrence of ICDs in PD patients across several European centres treated with short- or long-acting (ropinirole; pramipexole) and transdermal (rotigotine skin patch) DAs, based on clinical survey as part of routine clinical care.

Study dates
Not reported

Source of funding
No funding</td>
<td></td>
<td></td>
<td></td>
<td>Unclear. 12. What are implications for practice? patients taking DA therapy be advised of risk of developing ICD

Overall risk of bias: Low.</td>
</tr>
<tr>
<td>Full citation
Wang,X.P., Wei,M., Xiao,Q., A survey of impulse control disorders in Parkinson's disease patients in Shanghai area and literature review, Transl</td>
<td>Sample size
217

Inclusion criteria
Idiopathic PD patients, based on UK Brain Bank clinical diagnostic</td>
<td>Details
The modified version of Minnesota Impulsive Disorders Interview (Chinese version) was used to assess gambling, compulsive shopping, hypersexuality, binge eating, and punding.</td>
<td>Results
Comparison between patients with and without ICD behaviours (mean±SD, n, %, p):
<table>
<tr><td></td><td>Non-ICD</td><td>ICD</td></tr>
<tr><td>Number of case</td><td>208</td><td>9</td></tr>
<tr><td>Age, yr</td><td>67.25±8.82</td><td>63.67±10.55</td></tr>
</table>
</td>
<td>Overall Risk of Bias
CASP quality appraisal checklist
1. Did study address on clearly focused issue? Yes. 2. Was cohort recruited in acceptable way? Yes. 3. Was exposure accurately</td>
</tr>
</table>

Study details	Participants	Methods	Results			Comments
Neurodegener., 5, 4-, 2016 Ref Id 675547 Country/ies where the study was carried out Shanghai Study type Survey Aim of the study To investigate the incidence of ICD in Chinese PD patients from Shanghai area, explore the association of ICD with dopamine replacement therapy. Study dates March to October 2013 Source of funding National Natural Science Foundation of China and the Natural Science Foundation of Shanghai	criteria Exclusion criteria Atypical parkinsonism secondary parkinsonism cognitive abnormality that might have problem in understanding and giving feedback of questionnaire	Interventions N/A	Male, n(%)	114(54.8%)	6(66.7%)	measured to minimise bias? Yes. 4. Was outcome accurately measured to minimise bias? Yes. 5. Have authors identified all important confounding factors and taken account of these in design/analysis? Yes. 6. Was follow-up of subjects complete/long enough? NA - no follow up 7. What are results? Incidence of ICD in PD patients treated with dopamine replacement therapy. 8. How precise are results? Imprecise – only 9/208 had ICD. 9. Are results believable? Unclear. 10. Can results be applied to local population? Unclear. 11. Do results fit with other available evidence? Unclear. 12. What are implications for practice? patients taking DA therapy be advised of risk of developing ICD. Overall risk of bias: Low to moderate.
			Disease duration, yr	5.76±4.38	6.44±3.17	
			Dose of l-dopa (mg/d)	425±327.26	791.67±802.73	
			DA-LED (mg/d)	60.5±80.5	119.4±86.4	
			TLED (mg/d)	503.78±359.13	912.81±878.73	
			H&Y stage	1.41±0.52	2.33±0.87	
			Use of agonists, n(%)	94(45.2%)	7(77.8%)	

D.7.2 Managing dopaminergic treatment in people who have developed impulse control disorder

Study details	Participants	Methods	Results	Comments
Full citation Okai,D., Askey-Jones,S., Samuel,M., O'Sullivan,S.S., Chaudhuri,K.R., Martin,A., Mack,R.J., Brown,R.G., David,A.S., Trial of CBT for impulse control behaviors affecting Parkinson patients and their caregivers, Neurology.80 (9) (pp 792-799), 2013.Date of Publication: 26 Feb 2013., 792-799, 2013 Ref Id 308530 Country/ies where the study was carried out UK Study type RCT of CBT Aim of the study to test the effects of a novel CBT-based intervention delivered by a nurse therapist to patients with PD with clinically significant impulse control behaviours	Sample size N= 45 diagnosis of PD ; treatment n=28; waitlist n=16 Inclusion criteria diagnosis of PD according to UKBB criteria and associated ICB which had failed to remit despite measures taken by treating neurologist, including medication changes Exclusion criteria participants were excluded if did not meet inclusion criteria (n=11). standardized MMSE score <24, non english seakers, those without n identifiable carer able to participate in the trial	Details ICB screened using QUIP. following screening, ICD confirmed by clinical interview which made us of DSM IV criteria for pathological gambing, along with other criteri for the ICB Eligible consenting participants were randomly assigned to immediate treatment or 6 month waiting list randomization via random number tables held independently of those performnig the initial clinical assessment those randomized to treatment started immediate;y with intention to see people weekly for 12 sessions of treatment patients nd rather were aware of location following randomization Interventions treatment - CBT treatment manual was compiled during the pilot phase of the trial and informed by currently published treatment of ICDin general population adapted for a PD population, with additional components of communication and interpersonal relationships	Results demographics mean age; treatment = 59.3 years (8.1), control = 57.9 (9.5) male sex 19; treatment (67.9%), control 12 (70%) duration of PD; treatment 10.5 (6.0), control 8.8 (5.6) duration of ICB; treatment 4.4 (3.2), control 3.8 (4.6) Study data all patients completed t least one session in group and were completed in the analysis; 58% completed all and 88% completed at least 6 sessions No significant differences between groups based on demogrpahic and clinical characteristics, nor was there a difference in use of dopamine agonists or ledd. Total UPDRS scores were similar across treatment groups and remained stable over the course of treatment There was a significant effect with regard to changes in global levels of symptom severity using CGI as continuous measure with reduction in tmt group. 75% improved in treatment group compared to 29% in waitlist group The frequency and impact of ICB was significantly reduced over time in the treatment group. additionally there was an improvement in anxiety and depression in treatment group. GHQ-28 scores were significantly better in tmt gropou. GRIMS indicated no treatment effect on	**Overall Risk of Bias** 1. An appropriate method of randomization was used to allocate pts to treatment groups? yes - via independent random number table 2. There was adequate concealment of allocation no - not possible. patient, nurse, clinician qnd family all informed of allocation. The groups were comparable at baseline, including all major confounding and prognostic factors? yes 4. Comparison groups received same care apart from interventions. waitlist control received no care 5. Pts receiving care were kept blind to tmt allocation no - not possible 6. Individuals administering care were kept blind to tmt allocation no not

Study details	Participants	Methods	Results	Comments
Study dates published feb 2013 Source of funding Parkinson's UK		in relation to carers, executive dysfunction, and elements of case management. therapy was given by the same therapist supervied by a consultaant clinical psychologist. individual therapy supervision was provided once every 4 weeks amd included review to ensure manual adherence, fidelity, and quality therapy usually took place in patient' s homes although some sessions were done in clinic. notes were made on themes discussed in every session along with a record of number of treatment sessions attended, active withdrawals from treatment, and follow-up standard medical care all pts received information leaflets about treatments in PD and potental adverse effects those randomised to wait list recieived SMC and waited for 6 months before recieving intervention (results not reported here) SMC included ongoing review by patients treating physician, specialist nurse access, and potential referral to geriatrician	carers perception of the quality of their relationship with mean scores consistently rated as poor. No serious adverse outcomes were reported. Mean change (95% CI) scores are as follows: patient CGI: -0.8 (-1.2 to -0.5) NPI: -4.7 (-9.1 to -0.3) carer NPI distress: -3.0 (-5.6 to -0.3) patient: impulse behavioural scale: 4.7 (-5.8 to -2.5) work social adjustment scale: -3.6 (-6 to -1.3) GRIMS martital state questionnaire: 0.05 (-4 to 4.1) general health (GHQ): -3.8 (-5.6 to -2.0) BDI: -3.5 (-6.6 to 0.4) BAI: -1.8 (-5.4 to 1.8) carer GHQ: -1.5 (3.2 to 0.1) GRIMS: -2.3 (-5.7 to 1.3)	possible 7. All groups followed up for an equal length of time yes 8. Groups comparable for treatmen completion? yes 9. Grops were comparable with respect to avalilability of outcome data? yes 10. Study had appropriate length of followup: yes 11. Study used a precise definition of outcome: yes 12. Valid and reliable method was used to determine the outcome: yes well validated clinically meaningful outcome measures 13. Inves tigators were kept blind to participants exposure to the intervention yes 14. Investigator s were kept blind to other important confounding and prognostic factors: unclear **no serious risk of bias**

Study details	Participants	Methods	Results	Comments
		or neurologist if necessary. SMC did not preclude clinically necessary adjustment to medications		
Full citation Papay,K., Xie,S.X., Stern,M., Hurtig,H., Siderowf,A., Duda,J.E., Minger,J., Weintraub,D., 20141211, Naltrexone for impulse control disorders in Parkinson disease: a placebo-controlled study, Neurology, 83, 826-833, 2014 Ref Id 308584 Country/ies where the study was carried out USA Study type double-blind placebo controlled RCT Aim of the study To determine the efficacy and tolerability of naltrexone, an opioid antagonist, for the treatment of ICD's in	Sample size N=50 randomised, N=45 completed study; n=26 received naltrexone; n=24 received placebo Inclusion criteria Participants aged 18 - 85 years with a diagnosis of ideopathic PD and compulsive gabling, sexual behaviours, or eating were enrolled into the study. ICD symptoms had to have begun after 1) PD onset and 2) initiation of DA treatment. Participants required to have been taking their current DA (ropinerole or pramexipole in all cases)for >6 months and on a stable dose for >1 month. Exclusion criteria Montreal cognitive	Details Following diagnostic criteria for ICD's was applied: DSM IV for PG; McElroy criteria for compulsive buying; Voon criteria for compulsive sexual behavior; DSM IV for compulsive binge eating disorder Study design: single-site 8 week 1:1 randomized double blind placebo controlled flexible dose 50-100mg/d participants randomly assigned via computer-generated variable block sizes (2 or 4 participants per block) with numbers sealed in opaque envelopes evaluated at baseline, week 2, week 4, week 6, week 8 at end of study baseline, week 4, week 8 visits in person, week 2 and week 6 conducted via telephone outcomes of interest: unstructured, clinician-completed CGIC chosen as primary outcome measure of change (range 1 - 7; 1 indicates very much improved, 7 indicates very	Results 45 patients completed study (90%): n=4 lost in naltrexone group, n = 1 lost after week 2 in placebo group demographics sex male % naltrexone =61.5, placebo 75 age yrs naltrexone = 61.3 (9.0) ; placebo 61.8 (8.2) MoCA naltrexone =26.9 (2.1); placebo 27.58(1.7) PD duration y naltrexone =7.35 (6.0); placebo 9.5 (7.2) Levodopa LEDD mg/d naltrexone 559.2 (410.7); placebo 594.7 (411.9) DA LEDD mg.d naltrexone 247.6 (130.9); placebo 330 (313.4) UPDRS motor naltrexone 19.5 (9.5); placebo 24.9 (10.7) baseline QUIP ICD core naltrexone 35.4 (17.9); placebo 30 (17.6) between group differences found in frequency of comorbid ICD's (50% in naltrexone vs 21% in placebo) and hisory of DBS (0% in naltrexone vs 17% in placebo): these variables entered as covariates in mixed effects model CGI-C no between-group difference for response with estimated response of 54,4% in naltrexone vs 33.1% in placebo: OR = 1.57, 95%CI: 0.47 to 5.23) at week 8	Overall Risk of Bias Other information findings of this study were negative for efficacy of naltrexone for treatment of ICD's using CGIC study lacked statistical precision to exclude important difference in response rates between naltresone and placebo using patient rated PD specific assessment of ICD - naltrexone treatment was associated with a decrease in ICD symptoms compared with placebo - may be easier to detect change in rating scale than in dichotomous measure of change

Study details	Participants	Methods	Results	Comments
patients with PD Study dates Study dates not listed, published August 2014 Source of funding Study funded by clinical intervention award from the Michael J Fox foundation for Parkinson's research	assessment (MoCA) score of <20, active suicide ideation, history of DBS within the past year or onset of ICD symptoms temporarily related to DBS, active liver disease, alcohol or opiate dependence, overlapping psychiatric diagnoses, use of opiods for pain management,	much worse; score of 1 or 2 taken as reponsive, all other scores taken to be non responsive for this study) before study initiation, participants completed QUIP Parkinson's disease rating scale (QUIP-RS): score 0 -0 16 for each item (total of 0 - 64) where higher score = greater severity other items collected = geriatric depression inventory beck hopelessness scale Barratt impulsivity scale and tridimensional personality scales included as exploratory measures Interventions intervention = naltrexone: a competitive, nonselective opioid receptor antagonist. Currently efficacious in treatment of alcohol and opioid dependence . study details: For 1st 4 weeks, all participants administered naltrexone at 50 mg/d (or matching placebo). participants not in response (defined as a score of 1 or 2 on CGIC) at week 4 were increased to 100mg/d naltrexone or matching placebo for final 4 weeks	QUIP naltrexone led to greater decrease in QUIP ICD score over time compared to placebo at week 8 mean change naltrexone = (MC=14.92, 95%CI: 9.89 to 19.96); placebo group (MC= 7.55, 95%CI: 2.45 to 12.66); between group difference MD = -7.37 95%CI: 2.45 to 12.66 (nb 4 patients modified DA treatment during study period in naltrexone group - results still significant when these people removed from analysis at p<0.04) MID nominated as 7 points (0.5 SD) of change in the QUIP score over time in study completers:60% of naltrexone completers met this criteria clinical data no change in geriatric depression inventory (p=0.88) beck hopelessness (p=0.70) Baratt impulsivity scale (p=0.60) UPDRS motor scores changed from mean score of 19.5 (9.5) to 18.1 (8.6) in naltrexone and 24.9 (10.7) to 21.8 (11.1) in placebo group no between-group differences for change in UPDRS motor score over time adverse events 48 patients reported adverse events new onset nausea was common in naltrexone group (29.2% vs 0%, Fishers exact text p=0.0009) reported as mild to moderate intensity in all cases not associated with vomiting and did not lead to study discontinuation in any participants 5 participants discontinued (4 naltrexone 1	because continuous measure provides more information and therefore better power to detect change

Study details	Participants	Methods	Results	Comments
		at study completion or termination, all study participants offered routine clinical care, including the option to take naltrexone	placebo). None of these patients reported nausea or experienced any other adverse event likely to be due to study treatment other adverse events that occurred in >5% of patients that were more common in naltrexone group were dizziness (16.7% vs 4.2%) abd headaches (20.8% vs 16.7%) increase or decrease in blood pressure more common in placebo group (41.7& vs 25%)	
Full citation Thomas,A., Bonanni,L., Gambi,F., Di,Iorio A., Onofrj,M., 20100924, Pathological gambling in Parkinson disease is reduced by amantadine, Annals of Neurology, 68, 400-404, 2010 Ref Id 309188 Country/ies where the study was carried out Italy Study type double blind placebo-controlled crossover open extension study Aim of the study to investigate the	Sample size N=17 Inclusion criteria patients with PD according to UKBB criteria with severe PG in the last 10 months that was no decreased by DA reduction or withdrawal or behavioural strategies. 17 patients were selected from a cohort of 1096 patients. PG identified according to DSM IV manual and south oaks gambling scale criteria. Exclusion criteria Patients affected by manic episodes or bipolar disorder and patients receiving	Details PD symptoms evaluated with UPDRS, PD stage with H&Y scale, cognition with MMSE, and behavioural and mental functions with the NPI study design: 17 week double blind placebo controlled crossover 4 weeks baseline and 8 weeks amantadine/placebo crossover with 1 week washout and 4 weeks follow up PG was quantified by blind raters with gambling symptom assessment scale and the Yale-Brown Obsessive Compulsive scale for PG daily diaries assessed the time spent gambling and gambling cost in each day of the week. patients reports were double-checked with caregivers assessments were performed twice during baseline period of 4	Results demographics 13 male 2 female mean age 61.0 yrs (1.6) disease duration 52.4 months (7.8) H&Y stage 1.9 (0.2) LEDD (DA) mg, 1.2 (0.4) L-dopa dose 223.5 (49.2) duration of PG 7.1 months (0.4) results 5 patients dropped out because of side effect: confusion, orthostatic hypotension, insomnia (2 patients), and visual hallucinations. All were on amantadine branch. amantadine abolished daily expenditure, resolving PG in 7 patients and in 5 patients amantadine reduced Gambling on symptom assessment scale and yale brown obsessive compulsive scale, daily expenditure by 75%-90%, and time spent gambling amantadine effective in number of assessments, placebo was not effective in any area comparison between amantadine and placebo revealed effect in favor of amantadine for G-	**Overall Risk of Bias** 1. An appropriate method of randomization was used to allocate pts to treatment groups? NO: randomisation not clear 2. There was adequate concealment of allocation yes - double blind design 3. The groups were comparable at baseline, including all major confounding and prognostic factors? same groups 4. Comparison groups received same care apart from interventions yes 5. Pts receiving care were kept blind to tmt allocation yes

<table>
<tr><th>Study details</th><th>Participants</th><th>Methods</th><th>Results</th><th>Comments</th></tr>
<tr>
<td>possible efficacy of amantadine in the control of pathological gambling associated with PD

Study dates
Received Jan 2010, revised March, published March 2010

Source of funding
None listed</td>
<td>antipsychotics or anticholinergics or previously exposed to amantadine were excluded from the study</td>
<td>weeks (T1 and T2) and twice during follow up perdiod of 4 weeks, where only 12 patients recieved amantadine (T6, T7).
randomization at end of baseline period (T2) assigened amantadine/placebo with ratio 1:1
during crossover period, assessment done at T3 after 2 weeks of treatment,

Interventions
amantadine was administered as an add-on to the current antiparkinsonian medications, consisting of DA monotherapy, l-dopa monotherapy, L-dopa and DA therapy, entacapone, and rasagiline, unmodified throughout the study.
amantadine tablets were triturated and inserted into polymadine capsules; identical capsues containing agar gel were used as placebo
amantadine or placebo administered by a nurse unaware of patients assignments, with a titration schedule of 50mg twice daily fir 2 days and 100mg in the following 2 weeks., and was withdrawn in 2 days (50mg) during period T4
all patients had 24hr access to</td>
<td>SAS, Y-BOCS, and total gambling espentidute
G-SAS and Y-BOCS scores after 2 weeks of amantadine treatmen were reduced by 80% compared to baseline, whereas no changes occurred during the placebo treatment
differences between treatments in crossover study were statistically significant (G-SAS, F=522.9, p<0.0001; Y-BOCS, F=698.2, p<0001), regardless of whether dropped out patients were included
no carryover effect was observed (GSAS F=0.17, Y-BOCS F=1.59, both p>0.05)
no patient had side effects because of amantadine withdrawal.

<table>
<tr><td>% of salary expenditure</td><td>B</td><td>2.0 (0.2)</td></tr>
<tr><td></td><td>A</td><td>0.01 (0.1)</td></tr>
<tr><td>SAS</td><td>B</td><td>30.9 (0.7)</td></tr>
<tr><td></td><td>P</td><td>31.2 (0.2)</td></tr>
<tr><td></td><td>A</td><td>21.6 (0.9)</td></tr>
<tr><td>Y-BOCS</td><td>B</td><td>28.0 (0.6)</td></tr>
<tr><td></td><td>P</td><td>28.0 (0.1)</td></tr>
<tr><td></td><td>A</td><td>17.3 (0.7)</td></tr>
<tr><td>UPDRS -IV items 32-33 (complications of therapy)</td><td>B
P
A</td><td>4.2 (1.5)
4.1 (1.6)
2.2 (0.4)</td></tr>
</table>
</td>
<td>6. Individuals administering care were kept blind to tmt allocation yes
7. All groups followed up for an equal length of time yes 8. Groups comparable for treatment completion? yes 9. Groups were comparable with respect to avalilability of outcome data? yes 10. Study had appropriate length of followup:
yes 11. Study used a precise definition of outcome:
yes 12. Valid and reliable method was used to determine the outcome:
yes 13. Investigators were kept blind to participants exposure to the intervention:
yes 14. Investigators were kept blind to other important confounding and prognostic factors: unclear

serious risk of bias: unclear how patients were randomised and whether any cross-over effect. Data not separated for different</td>
</tr>
</table>

Study details	Participants	Methods	Results	Comments
		clinicians to inform about effects of treatment or of withdrawals		arms **Other information** present report showed PG culd be supressed in 2 to 3 days by amantadine and that amanadine withdrawal induced, in a few days, resurgence of the disorder.

Full citation Bastiaens,J., Dorfman,B.J., Christos,P.J., Nirenberg,M.J., Prospective cohort study of impulse control disorders in Parkinson's disease, Movement Disorders.28 (3) (pp 327-333), 2013.Date of Publication: March 2013., 327-333, 2013 Ref Id 306844 Country/ies where the study was carried out USA Study type prospective cohort study	Sample size N=164 outpatients with PD and no previous history of ICD Inclusion criteria nondemented outpatients with PD who presented to a tertiary movement disorders clinic between June 2008 and November 2010. Inclusion criteria were ideopathic PD by UKBB criteria, capacity to provide writeen informed consent and ability to complete a series of research questionnaires	Details Subjects followed under routine clinical care and followed prospectively until they reached first of the following pre determined end points: new onset of ICD discontinuation of DAA therapy death or loss to follow up June 30, 2011 Only those who received a predefined minimum exposure to DAA after study enrollment (at least 50 L-dopa equivalent daily dose (LEDD) of DAA for 3 months or more consecutive months) were included within the analysis. at baseline all subjects	Results frequency and characteristics of ICD 164 patients enrolled in study, of whom 46 subsequently treated with minimum dosage and duration of DAA therapy for inclusion in analysis of these 46, 18 (50% female) developed ICD's after mean duration 21.0 months 6 subjects with ICD lost to follow up mean ICD-free survival time was 68 months (95% CI: 34.8 to 101.2) most common ICD compulsive eating (16/18); 6/18 hyersexuality; 5 compulsive shopping/buying, 1 compulsive gambling concomittent punding present in 12/18 no ICD (-) patients reportd punding behaviours time of onset ICD highly variable (range 3 months 10 years, median 23 months) after initiation of DAA therapy and 1 to 19 years after PD onset diagnosis delayed from between 0 - 15 months afer ICD onset (median 4 months) in 4 subjects (22.2%), incidence of ICD elucidated only through 66.7%)of caregiver or other outside observer	**Overall Risk of Bias** 1. Did study address on clearly focused issue? yes 2. Was cohort recruited in acceptable way?yes - consecutive 3. Was exposure accurately measured to minimise bias? yes 4. Was outcome accurately measured to minimise bias? yes 5. Have authors identified all important confounding factors and taken account of these in design/analysis? yes 6. Was follow-up of subjects complete/long enough? yes - follow up until reach one of pre-defined end points 7. What are results?

Study details	Participants	Methods	Results	Comments
Aim of the study To study prospective incidence time course and risk factors of ICD's Study dates received 9th augus 2012, revised Oct, published Jan 2013 Source of funding The study was supported by a centre grant from the PD foundation	Exclusion criteria Previous history of ICD, atypical clinical features, MMSE score of <25, clinical diagnosis of dementia, life expectancy of <12 months use of dopaminergic receptor blocking agent, or previous PD neurosurgery	avaluated by movement diorder neurologist who completed series of assessments including UPDRS, ADL, MMSE, depression inventory, medication and family history assessment for presence of ICD and punding behaviours occurred at baseline visit and each subsequent visit using semistructured interview involving the subject and all available caregivers interview included broad questions to identify symptoms suggestive of an ICD. If a subject endorsed one or more repetitive behaviours then follow-up questions were asked to determine the scope and consequences of these behaviours . Behaviours classified as ICD's if they disrupted normal work, family, or social interaction or casued negative medical or psychiological consequences. ICD status determined at time of each visit, and	risk factors/baseline characteristics baseline demographic characteristics similar between both groups ICD+ grop had significantyly higher prevalence of smoking (44.4% vs 14.3%) and also higher caffeine use (100% vs 66.7%) previous alcoholism rare and same across both groups (88.9% vs 64.3%) at baseline ICD group greater prevalence of motor complications (61.1% vs 25.0%) in contrast, no significant differenes in UPDRS quantitative and qualitiative use of dopaminergic medication same across both groups as was antidepressant and benzodiapepine use trand toward greater familyh istory of depression in ICD group (^1.1%vs 32.1%) endpoint characteristics at endppoint major difference between ICD+/- groups was higher peak DAA dosage in ICD+ grop (median 300 vs 165 LEDD) disease duration. DAA treatment duration, cumulative DAA exposure, specific DAA used, concomittant L-dopa, total LEDD and durattion of dopaminergic therapy were comparable between groups Outcomes in ICD + subjects. ICD resolved in: 10/10 subjects discontinued DAA usage 3/5 reduced DAA dosage 0/3 who continued same dosage concomittent punding occured in 12/18 patients with ICD and resolved in: 5/5 who discontinued DAA therapy 2/4 who reduced DAA dose 0/3 who continued same dose dopamine agonst withdrawal syndrome (DAWS)	study found number of predictive factors for ICD's in prospective cohort 8. How precise are results? only raw data and p- vlaues given. OR's calculated where possible. 9. Are results believable? yes 10. Can results be applied to local population? yes , however all subjects were taking DA. May not be appropriate for patients not taking DA 11. Do results fit with other available evidence? yes 12. What are implications for practice? advise patients taking DA of increased risk of ICD **low risk of bias**

Study details	Participants	Methods	Results	Comments
		data on medication usage, caffiene consumption and cigarette smoking behaviours also recorded. Interventions NA	occurred in: 6 of ICD subjects; 4 who discontinued use; 1 who reduced dose; 1 who was unable to decrease DAA dose because of severity of DAWS symptoms 4/5 subjects with DAWS developed DDS as they self adjusted l-dopa in unsuccessful attempt to alleviate DAWS symptoms	

D.8 Palliative Care

Study details	Participants	Methods	Results	Comments
Full citation Kwak,J., Wallendal,M.S., Fritsch,T., Leo,G., Hyde,T., Advance care planning and proxy decision making for patients with advanced Parkinson disease, Southern Medical Journal.107 (3) (pp 178-185), 2014.Date of Publication: March 2014., 178-185, 2014 Country/ies where the study was carried out USA Study type cross-sectional survey Aim of the study to examine advance care directives and proxy decision making by family healthcare proxies for patients with advanced PD Study dates Published Sept 2013 Source of funding partnership and innovations grant program of Parkinson's research Institute of Wisconsin Parkinson association	Sample size N = 64 spouses and adult children of patients with PD Inclusion criteria Patient eligible to participate if patient was at least 60 years old, diagnosed with having ideopathic PD or parkinsonism for at least 5 years, diagnosed by a neurologist or movement disorders specialist consultant according to PD UK brain bank criteria. Patients considered to be at advanced stage of disease, which requires substantial caregiver involvement if the patients had dementia or scored <70% on Schwab and England ADL scale, indicating lack of full independence; >20 on UPDRS part II (functional impairment); or >40 on part III of UPDRS (motor impairments) family members eligible to participate if they were the patient's spouse/partner or adult child and designated healthcare proxy.	Details patients demographic and clinical data obtained from regional PD centre electronic patient register proxies provided info re education living arrangements and frequency of falls and general health of patient. proxies asked whether the patients had ever completed will or durable power of attorney for healthcare, and whether they had communicated to their physicican preferences regarding CPR, ventilator, feeding tube, and hospice care proxies presented with hypothetical EOL scenario and asked to chosse a goal of care and treatment option if their relative with PD were in the situation. Initial scenario and EOL care goals and treatment choices adapted from theliteratures (Volandes et al,). reviewed and modified for patients with PD and palliation needs specific to this population. EOL scenarios described symptoms likely to occur in end-stage PD, i.e. dementia,	Results 70% proxies female patient mean age 75 yrs (6.8) mean UPDRS function 21.5 (7.6) mean UPDRS motor 31.1 (12.3) Schwab and England ADL score 53.4% (21.1) 31% diagnosed with dementia Advanced care planning - patients 60 (93.7%) completed will; 58 (90.6)%) shared copy with proxy; 24 (37.5%) shared copy with physician EOL treatments - patients 29 (45.3%) yes CPR, 13 (20.3%) DK; 13 (20.3%) Yes feed tube, 12 (18.8%) DK; 10 (15.6%) yes ventilator, 17 (26.6%) DK; 18 (28.1%) yes to hospice care, 46 (71.9) DK Goal of care, treatment, decision-making processes - proxies EOL care goal: 53% chose comfort care only; 38% limited care; 6% life-prolonging care treatment options: 72% pain and symptom control only;	**Overall serious risk of bias:** Methodology not clear, not clear whether all survey material was standardised or validated. **Other information:** Study only focuses on end of life care in advanced patients. NOTE: 30% of respondents had dementia diagnosis, which could skew preferences in current state from pre-dementia state and therefore not provide true representation of patient preferences from earlier stages of disease and pre-dementia manifestation.

Study details	Participants	Methods	Results	Comments
	Exclusion criteria none listed	inability to independently ambuilate etc Goal of care questionnaire included 3 options: life-prolonging care, limited care, and comfort only care Following goal of care questionnaire, proxies asked to choose among 3 sets of tmt options: perform everything that a modern hospital can offer; perform everything except for CPR or procedures used in ICU; and perform only procedures for pain and symptom control, but not hospitalization, CPR, feeding tube, ventilator, or other procedures common in ICU. Proxies also asked to choose from following options for how EOL decisions for patient should be made: one person decides alone, several people decide together, and several people talk, but one person makes final decision. Asked to indicate who should be involved in decision making Interventions data analysis: descriptive stats used to characterize patients' EOL preference, care preference, documentation and	16% chose everything except CPR or procedures in ICU; 9% chose performance of everything approx 70% chose treatment options consistent with goals of care. Proxy's EOL care choices for the patient were not generally consistent with patients choices for life support How should decisions for patients be made - proxy 53% several discuss but one person decides; 28% one person decides alone; 14% severl people decide together. 92% proxy should be involved; 72% other family members; 70% physicians should be involved; 52% think all 3 should be involved.	

Study details	Participants	Methods	Results	Comments
		communication, and proxy's choice of EOL care for patient		
Full citation Hasson,F., Kernohan,W.G., McLaughlin,M., Waldron,M., McLaughlin,D., Chambers,H., Cochrane,B., An exploration into the palliative and end-of-life experiences of carers of people with Parkinson's disease, Palliative Medicine.24 (7) (pp 731-736), 2010.Date of Publication: October 2010., 731-736, 2010 Country/ies where the study was carried out Northern Ireland, UK Study type Qualitative: semi-structured interview Aim of the study to explore former carer's lived experiences of palliative and end of life care Study dates 2010 Source of funding Parkinson's disease society UK	Sample size N = 15 11 males, 4 females. age > 55 years Inclusion criteria Carers of someone with PD who had been bereaved between 6 months and 2 years. Had to be > 18 years of age, not chronically ill, and have no serious communication issues. All had been carers of someone with PD. all participants were immediate family members of the person they cared for. Exclusion criteria none listed	Details Exploratory descriptive design used. Qualitative semi-structured interview used to explore palliative and end of life care experiences of former carers of people with PD. Interview themes were: history of family members illness carers info and educational needs caring role impact on social, physical, and financial needs psychosocial impact of caring in the advanced stage spiritual support caregiving experience at advanced stage experiences of health and social services accessed experience of palliative care services accessed bereavement support accessed/needs Sensitive 1-1 interview conducted Participants recruited via poster in local GP and libraries, and PD support groups. interview approach allowed for	Results 4 themes identified: Carer's role and burden All spoke of gradual adjustment to carer role with adoption of multiple roles as disease progressed. Most provided care without any guidance from health professionals psychological impact of disease difficult: feeling of helplessness; lack of control; physical deterioration unpredictability of illness meant future plans could not be made many postponed their own needs ie. psych support, in order to meet patient's needs. carers found it difficult to deal with patients mood changes and anger and being physically and emotionally hurt by patient " there was one night he really, really was getting to me... i was going to life my hand at him. Thank God i didn't". Respite opportunities were viewed as essential to health and wellbeing of carer, however	Overall serious risk of bias: The study was retrospective and open to memory bias.

Study details	Participants	Methods	Results	Comments
		probing and clarification of responses, thus helping to ensure the correct understanding was obtained, All but one interview recorded and transcribed verbatim. Each interview subject to content analysis by 2 separate authors to allow for comparison and enhance inter-rater reliability. common and consistent themes drawn together in analysis Interventions N/A	accessing these was cited as very difficult. Palliative care watching physical and psychological deterioration of patient was most distressing to all caregivers most carers knew death was inevitable, there was an implicit aim of keeping the patient at home for as long as possible "Not that i was great at looking after him, but that's what I wanted to do anyway, I wanted him to be at home'. However this goal was prevented by a lack of access to domiciliary palliative care services such as hospice care. Few carers were fully aware of these services, with many viewing them as predominantly for patients with cancer at end of life. Some patients had died in hospital and nursing homes, not in own home. Many carers surprised at the speed at which advanced stage was reached and found patients' decline very sudden. They were unaware that death was imminent. Others wanted a quick painless death for the patient. Many spoke of	

Study details	Participants	Methods	Results	Comments
			feelings of relief at the patient's death, finding comfort that they were no longer suffering. All former carers advocated need to be better prepared for advancement of disease " I must say, I thank god he was taken that day". "I knew he was deteriorating but i didn't expect him to die so soon" " I feel maybe it's hard to say but i knew the end would come and really it was a release not only for me but for X, I knew it was because it was very hard to watch him" Bereavement note: not relevant to review question Access to health and social care services findings revealed access to palliative care and clinical services was uncoordinated and patchy, with carers explaining that they had accessed them on an ad-hoc basis. carers had to actively seek out info and access services on patient's behalf. All were frustrated that professional care was not in	

Study details	Participants	Methods	Results	Comments
			place for patients and carers at the start of the disease trajectory. In addition, some carers were confused over the boundaries and duties of the health and social care professionals involved. One carer recommended an MDT be established to deal with neurological illness "There seems to be a vague boundary between the responsibilities that one person has and the responsibilities another has. They just don't seem to work as a team or have any team effort as such. You are nearly taking pot luck with each one in turn" lack of signposting to services resulted in some patients not obtaining help from allied professionals such as physiotherapists, OT, or SLT, even though careres felt that this would have been beneficial. Carers spoke of MDT involved in care i//e/ PDNS, neurologist, GP. All appreciated support, however highlighted that accessing specialists was very difficult and lengthy waiting times.	

Study details	Participants	Methods	Results	Comments
			Quality of interaction between specialist, patient and carer was variable with meetings brief, focusing on medication, little or no psych support or signposting to other or no psychological support or signposting to other types of services. All carers advocated the need for regular surveillance of the patient's needs by specialists “the neurologist saw him every 6 months and agreed the tablets; they didn't have a lot of time. She (PDNS) would have helped explain things afterwards to you if you didn't pick it up at the consultation itself. Many carers relied on GP for help. some gave examples of lack of knowledge of the disease by GP's and social care professionals. All carers advocated need for adequately trained staff to care for PD patients. " The psychiatrist thought she was faking all her symptoms and that she hadn't PD at all, and took her off all of her medication" some felt lack of communication between primary and specialist health	

Study details	Participants	Methods	Results	Comments
			care providers with carer having to act as go-between " it was very frustrating because you were the liaison...you were at them to constantly go back and say this isn't working" All carers agreed should have been provided with a more integrated care package, regular access to specialist practitioner with clear signposting to other services and information. Carers wanted information to help them fulfil their caring role, with specific advice and training available.	
Full citation Kristjanson,L.J., Aoun,S.M., Oldham,L., 20061120, Palliative care and support for people with neurodegenerative conditions and their carers, International Journal of Palliative Nursing, 12, 368-377, 2006 Country/ies where the study was carried out Australia Study type Survey data	Sample size PD patient N = 174 PD carer N = 141 Inclusion criteria Self-administered questionnaires mailed to individuals with the 4 degenerative illnesses. Surveys distributed through the associations for these conditions. Exclusion criteria Anyone who had recently	Details service use and support needs component of survey developed using data from semi-structured interview with patients carers and HCP's. Interviews coded using content analysis to identify themes and these cross-references to the literature. data collection protocol designed to allow participants 30 mins to complete survey. patients and carers completed: demographic service use	Results >66% carers were female. mean age carers and patients 60 years 33% patients female. support needs and services patients and carers rated the amount of assistance needed to undertake several daily activities using Likert scale 1 (no help) - 4 (help needed all the time). Those items rated as >2.5 (leaning towards help most to all of the time) were:	Overall Risk of Bias: Serious. Methodology not clear, not clear whether all survey material was standardised or validated. Other information exclusion criteria that were imposed have determined the profile of disability and service use respondents - level of bias

Study details	Participants	Methods	Results	Comments
Aim of the study to identify and compare needs for supportive care/palliative care services of people in Australia with MND, MS, HD, and PD, and the needs of the carers. (NB only PD data presented here) Study dates conducted 2003 - published 2006 Source of funding National health and medical research council, Australia	been diagnosed or those who were too sick or disabled to answer.	support needs 2 item QoL index (Graham and Longham 1987) symptoms assessment scale (patients) hospital anxiety and depression scale (patients) patient satisfaction questionnaire (patients) general health questionnaire (carers FAMCARE scale (carers) content validity tested by pilot testing new protocol with 87 patients and carers internal consistency of instruments estimated using Cronbach's alpha. All had >0.70 high internal consistency Interventions NA	patients: information about disease (3.5); equipment for daily living (2.62) carers: information about how to provide care (3.31); reliable, ongoing, dependable support workers (2.84); financial assistance for care (2.72); flexible home support program access (2.52) QoL Asked to rate QoL on scale: 0 indicates very poor QoL to 10 - indicating excellent QoL PD patient rating of QoL = 6.87 (2.29; carer 6.59 (2.27) satisfaction with QoL patient 5.55 (2.68; carer 6.35 (2.58) Family satisfaction with care (FAMCARE): [5 point Likert scale] information giving 3.75 (0.74) physical patient care: 3.96 (0.70) psychosocial care : 3.70 (0.75) availability of care: 3.87 (0.67) HADS anxiety and depression 30% PD patients suffered moderate to severe depression; 20% anxiety	

Study details	Participants	Methods	Results	Comments
			Family carer's health score 19% carers experience overall dysfunction in anxiety and depression mean SAS symptom assessment scale for patient groups; highest scoring symptoms (i.e. >3.5): (0 = no problem, 10 = worst possible problem) fatigue and tiredness 5.1(2.9) concentration 3.9 (3.1) sleeping 4.1 (3.3)	
Full citation Giles,S., Miyasaki,J., Palliative stage Parkinson's disease: Patient and family experiences of health-care services, Palliative Medicine.23 (2) (pp 120-125), 2009.Date of Publication: 2009., 120-125, 2009 Country/ies where the study was carried out Canada Study type semi-structured in depth interview	Sample size N = 3 x family groupings ; total N = 7 (2 x carer patient 1; 2 x carer patient 3, and 3 x carer patient 2) Inclusion criteria participants received care at tertiary referral centre. Patients had been previously diagnosed with palliative stage PD (H&Y stage 2.5 - 5). Participants were purposefully selected by their neurologist for the	Details Analysis employed the interpretive phenomenological approach where the goal is to understand the meaning of the participant's experiences - relies on considerable self-reflection and interpretation skills of the researcher. Each interview read and reread in its entirety one interview at a time. Manuscripts then analysed as a unit together to reflect and maintain contextual aspects of their shared and divergent	Results Key themes: missing information lack of information received regarding prognosis, diagnosis, and homecare services, and not knowing or being able to ask for what is missing. Many wished they had been given more information " I didn't get the brochures or anything from the doctors... There's not really much help" " that (home care services) is	Overall Risk of Bias very poor study - very serious level of bias in terms of how participants were recruited, information was collected, interpreted, small sample size, and lack of detail in how information was interpreted. Text written in highly emotive and sensationalist way. Other information by study's own admission: methodology relies on

Study details	Participants	Methods	Results	Comments
Aim of the study to understand participant's lived health-care experiences and the needs flowing from them. Interviews followed the question: What are the lived experiences of the health-care system for persons and their family members, who have lived with the palliative stages of PD. Study dates 2009 Source of funding National Parkinson's foundation	ability to verbally discuss their experiences in detail. Exclusion criteria case 2 patient had sever dementia and could not participate, however his family were included in the study.	experiences. This allowed for comparison and/or contrast between interpretations of their experiences. Text interrogated and reflected upon to reveal deep and multiple meanings. During each interview clarification sought from participants to attempt to ensure correct meaning understood. Interviews recorded and then transcribed Interventions NA	something that you know somebody should tell those people" power imbalance between doctor and patient - "I'm the type of woman, I'm afraid to ask too many questions because sometimes I feel like they would say, like you're asking too many questions, just take the pills" Being on your own people gave up waiting for govt funded homecare support and expended a great deal of effort trying to obtain private home care "they (govt homecare) still haven't called us ... so we're lucky that, yuo know, we finally made the decision to move on. Because I don't know what we would have done because I don't think my mom would have lasted" participants found it difficult to judge quality of homecare "I was like, this one's got three like little gold medal things so maybe I'll go with this one"... "super expensive" "and the people they send were just, we went through a whole slew	interpretation skills of the researcher.

Study details	Participants	Methods	Results	Comments
			of people" finding a neurologist was challenging: "a friend of ours... offered to talk (to a friend) for us, to see if a doctor could see my husband and that's how I got our neurologist" due to a lack of information, one family turned to the internet for help. they were "shocked" "you have to be prepared and understand it's just kind of a shocker and no one really explained to us what all of this meant" Patients and carers wanted a multidisciplinary (MDT) team to make care affordable, less time consuming, and credible. "that would be amazing if we didn't have to call 50 million different places and like try and figure out if they're able to do it and care for the people".. "for the clinicians to look at the whole person, not just questions about Parkinson's. To integrate the physiotherapy (into routine care)". wanting and not wanting A nurse caregiver was clear about roles that HCP should fulfil " to help the family or as	

Study details	Participants	Methods	Results	Comments
			a group decide what would be the best care situation for the person, and you know what to expect"	
Full citation Tuck,K.K., Brod,L., Nutt,J., Fromme,E.K., Preferences of patients with Parkinson's disease for communication about advanced care planning, American Journal of Hospice & Palliative Medicine, 32, 68-77, 2015 Country/ies where the study was carried out USA Study type Survey study Aim of the study To determine preferences of patients with PD for timing and initiation of discussions regarding treatment, prognosis, advanced care planning, and end-of-life care options such as hospice. Study dates Not reported Source of funding	Sample size 267 out of 585 surveys were returned Inclusion criteria Age between 18 and 85 with a diagnosis of idiopathic PD confirmed by a movement disorders specialist Patients must have been visited at least twice in Oregon Health and Science University's Movement Disorders Clinic and must have received a diagnosis of PD at least 6 months prior to inclusion Patients could be in any stage of disease and be receiving any form of treatment Exclusion criteria - Patients with a known diagnosis of dementia, drug-induced parkinsonism, or atypical parkinsonism	Details Survey questions addressed patient preferences about prognostic and end-of-life discussions as well as basic demographic and disease-stage information. It also included the Patient Health Questionnaire Depression screen and the 7-item binary "information" subscale of the Krantz Health Opinion Survey to assess the degree that patients wished to be active in their own care. Interventions N/A	Results - Most patients felt responsible to bring up issues of life expectancy, end-of-life care planning, and end-of-life care options such as hospice. However, about half felt these topics should be raised by their neurologist. A very small number felt end-of-life issues should never be discussed. - Almost all patients wanted to discuss PD symptoms along with treatment goals, options, and side effects early (at the time of diagnosis or during the next few visits). The majority also wanted their family involved in discussing their disease early, and about half wanted to discuss advanced care documents early. Some patients even wanted early discussions about life expectancy, end-of-life care planning, end-of-life care options such as hospice or to encourage family communication about end- of-life care, although it was more	Overall Risk of Bias: Likely high risk of bias Not clear whether the questionnaire was standardised or validated and lack of detail in how information was interpreted.

Study details	Participants	Methods	Results	Comments
No funding received			common for patients to want to discuss these issues when their disease worsened. - Majority of patients (183 of 267, 68.5%) reported having some kind of advance care planning document.	