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	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

<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>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.
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</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</td>
<td>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? 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</td>
</tr>
</table>

Study details	Participants	Methods	Results	Comments
morbo di Parkinson for financial support		body weight). Thus, 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.	<table><tr><td></td><td>Mean</td><td>SD</td><td>Total</td></tr><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>	participant's exposure to the intervention? YES Were investigators kept blind to other important confounding and prognostic factors? UNCLEAR Other information
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	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	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	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	Overall Risk of Bias 1. Has an appropriate method of randomisation been used? YES 2. Was there adequate concealment of allocation? UNCLEAR

<table>
<tr><th>Study details</th><th>Participants</th><th>Methods</th><th>Results</th><th>Comments</th></tr>
<tr>
<td>increases daily energy 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</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>individualised dietary regimen could be 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</td>
<td>Low protein dietary= 4.5 hours

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</td>
<td>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? UNCLEAR
7. Were groups comparable with respect to availability of outcome data and for how many participants</td>
</tr>
</table>

Study details	Participants	Methods	Results	Comments
2006 Source of funding Fondazione Grigioni per il morbo di Parkinson		consumption of protein rich food and not resorting to the usage of any special kind of food.	<table><tr><td></td><td>Mean</td><td>SD</td><td>Total</td></tr><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>	were no 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

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	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,	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))	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

Study details	Participants	Methods	Results	Comments
Aim of the study 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		cholinesterase, CK, 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	Creatine group (n=40) Baseline= 0.8 (1.5) 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)	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 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

Study details	Participants	Methods	Results	Comments
		could be readjusted during the trial.	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)	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 Other information

Study details	Participants	Methods	Results	Comments
			After 2 years patients in the creatine group had a significantly smaller dose 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) | | Mean | SD | Total | | Experimental | 72.00 | 160.65 | 40 | | Control | 129.00 | 166.32 | 20 | Dopamine agonist dose change (mean difference from baseline)	

Study details	Participants	Methods	Results	Comments

	Mean	SD	Total
Experimental	102.00	147.23	40
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)

Study details	Participants	Methods	Results	Comments

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

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)

Study details	Participants	Methods	Results	Comments

	Mean	SD	Total
Experimental	-8.00	21.51	40
Control	-4.00	17.26	20

Total UPDRS score UPDRS, mean 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)

Study details	Participants	Methods	Results	Comments
			<table><tr><td></td><td>Mean</td><td>SD</td><td>Total</td></tr><tr><td>Experimental</td><td>1.40</td><td>4.50</td><td>40</td></tr><tr><td>Control</td><td>0.10</td><td>4.51</td><td>20</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>-0.30</td><td>1.76</td><td>40</td></tr><tr><td>Control</td><td>0.80</td><td>1.66</td><td>20</td></tr></table>	
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	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	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.	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)	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

<table>
<tr><th>Study details</th><th>Participants</th><th>Methods</th><th>Results</th><th>Comments</th></tr>
<tr>
<td>Ref Id
283805
Country/ies where the study was carried out
France
Study type
Randomised controlled trial (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>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, 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>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 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'</td>
<td>*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)
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><td></td><td>Mean</td><td>SD</td><td>Total</td></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><td></td><td>Mean</td><td>SD</td><td>Total</td></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</td>
<td>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 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</td>
</tr>
</table>

Study details	Participants	Methods	Results	Comments
		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 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	<table><tr><td></td><td>Mean</td><td>SD</td><td>Total</td></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>	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 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
		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 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.		

Study details	Participants	Methods	Results	Comments
Full citation Croxson,S., Johnson,B., Millac,P., Pye,I., 19911031, Dietary modification of Parkinson's disease, European Journal of Clinical 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	Sample size 8 participants enrolled Inclusion criteria Idiopathic Parkinson's disease Daily on/off phenomenon Exclusion criteria None stated Characteristics Average age: 63 years (range 56-70) Average duration of disease: 12 years	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 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.	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 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.	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 treatment allocation?YES Were the individuals

<table>
<tr><th>Study details</th><th>Participants</th><th>Methods</th><th>Results</th><th>Comments</th></tr>
<tr>
<td>Published 1991

Source of funding
Not stated</td>
<td></td>
<td>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 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.</td>
<td>Total "off" time
<table><tr><td></td><td>Mean</td><td>SD</td><td>Total</td></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>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 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</td>
</tr>
</table>

Study details	Participants	Methods	Results	Comments
				exposure to the intervention? YES Were investigators kept blind to other important confounding and prognostic factors? UNCLEAR 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.,	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	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	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	Overall Risk of Bias Has an appropriate method of randomisation been used? YES Was there adequate concealment of

Study details	Participants	Methods	Results	Comments
Garcia-Vieitez,J.J., 20141023, A randomised clinical trial to evaluate the effects of Plantago ovata husk in Parkinson patients: changes in 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	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 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	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 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,	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 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	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? UNCLEAR Were groups comparable with respect to availability of outcome data and for how

<table>
<tr><th>Study details</th><th>Participants</th><th>Methods</th><th>Results</th><th>Comments</th></tr>
<tr>
<td>fibre on several biochemical parameters including levodopa absorption.

Study dates
Published 2014
Between April 2006 and November 2006

Source of funding
Unclear. Authors declare no competing interests. Collaboration with Rottapharm.</td>
<td></td>
<td>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 days, the other treatment (A or B) as given.</td>
<td>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

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>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)
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</td>
</tr>
</table>

Study details	Participants	Methods	Results	Comments
				Other information
Full citation Hass,C.J., Collins,M.A., Juncos,J.L., 20070418, Resistance training with 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	Sample size Randomised =20 patients Creatine group= 10 patients Placebo group= 10 patients Inclusion criteria 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	Details Randomised double blind placebo controlled trial for 12 weeks Data collection began with a 2-week 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	Results Hoehn & Yahr Baseline Placebo group (n=10)= 2.2 ± 0.2 Creatine resistance (n=10)= 2.1 ± 0.2 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	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

<table>
<tr><th>Study details</th><th>Participants</th><th>Methods</th><th>Results</th><th>Comments</th></tr>
<tr>
<td>To test the efficacy of resistance training with creatine monohydrate in Parkinson's disease patients

Study dates
Published 2007

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>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</td>
<td>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 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.</td>
<td>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
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><th></th><th>Mean</th><th>SD</th><th>Total</th></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>
</td>
<td>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? 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</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>The placebo group consumed lactose monohydrate using an identical dosing scheme.</td>
<td>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>
<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)</td>
<td>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>
</table>

Study details	Participants	Methods	Results	Comments
			<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>	
Full citation Nathan,J., Panjwani,S., Mohan,V., Joshi,V., Thakurdesai,P.A., Efficacy and 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	Sample size Randomised= 50 IBHB group= 23 Placebo group= 19 Inclusion criteria 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	Details A randomised, double blind, placebo controlled trial over 6 months. Randomised in a 1:1 ratio according to a 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	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 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)	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 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

Study details	Participants	Methods	Results	Comments
India Study type Randomised controlled trial Aim of the study To find the efficacy and 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 Study dates Published 2013 Source of funding Indus Biotech Private Limited	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) 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)	and 1 hour before evening tea) Placebo group recieved matching capsules of di-calcium phosphate.	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 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)	treatment allocation?YES Were the individuals administering care kept blind to treatment allocation? UNCLEAR (but double blind) Were groups comparable 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

<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>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.

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></table></td><td>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>
</table>

Study details	Participants	Methods	Results	Comments

Control	3	19	

Total UPDRS score UPDRS, mean difference from baseline)

	Mean	SD	Total
Experimental	0.43	0.50	23
Control	5.79	18.55	19

UPDRS (motor) mean difference from baseline)

	Mean	SD	Total
Experimental	0.92	10.55	23
Control	5.68	12.43	19

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

	Mean	SD	Total
Experimental	-0.09	6.17	23
Control	-0.16	6.10	19

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

	Mean	SD	Total
Experimental	-0.39	2.13	23
Control	0.26	2.39	19

Study details	Participants	Methods	Results	Comments
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., 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	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 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	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 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	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 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	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 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

Study details	Participants	Methods	Results	Comments
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 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)	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) 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)		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 (%): 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 (%)	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 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

Study details	Participants	Methods	Results	Comments
	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) 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.		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 UPDRS Combined ADL/motor scores (mean difference from baseline) | | Mean | SD | Total | | Experimental | -2.10 | 8.81 | 64 | | Control | -4.25 | 10.02 | 64 |	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 Some data was extracted from a combination of data provided in baseline characteristics table and read from a graph

Study details	Participants	Methods	Results	Comments
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 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	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 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)	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 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	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) 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)	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 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

Study details	Participants	Methods	Results	Comments
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 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.	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): 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)		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 (%) 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)	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 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

Study details	Participants	Methods	Results	Comments
	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 (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)		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) 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)	kept blind to participant's exposure to the intervention? YES Were investigators kept blind to other important confounding and prognostic factors? UNCLEAR Other information

Study details	Participants	Methods	Results	Comments
	Vitamin D3 group (n=56)= 61.3 (17.1) Placebo group (n=58)= 60.4 (16.8)		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) 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)	

Study details	Participants	Methods	Results	Comments
			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 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)	

<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>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)
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
<table><tr><td></td><td>Mean</td><td>SD</td><td>Total</td></tr><tr><td>Experimental</td><td>0.01</td><td>0.20</td><td>55</td></tr><tr><td>Control</td><td>-0.04</td><td>0.31</td><td>57</td></tr></table></td><td></td></tr>
</table>

Study details	Participants	Methods	Results	Comments
			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 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	

Study details	Participants	Methods	Results	Comments
			PDQ39 communication (mean difference from baseline) <table><tr><td></td><td>Mean</td><td>SD</td><td>Total</td></tr><tr><td>Experimental</td><td>-5.73</td><td>18.81</td><td>55</td></tr><tr><td>Control</td><td>-3.56</td><td>21.80</td><td>57</td></tr></table> PDQ39 stigma (mean difference from baseline) <table><tr><td></td><td>Mean</td><td>SD</td><td>Total</td></tr><tr><td>Experimental</td><td>0.30</td><td>23.90</td><td>55</td></tr><tr><td>Control</td><td>-5.45</td><td>16.50</td><td>57</td></tr></table> PDQ39 emotional well being (mean difference from baseline) <table><tr><td></td><td>Mean</td><td>SD</td><td>Total</td></tr><tr><td>Experimental</td><td>-5.27</td><td>22.60</td><td>55</td></tr><tr><td>Control</td><td>-3.56</td><td>21.80</td><td>57</td></tr></table> PDQ39 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>-2.47</td><td>23.90</td><td>55</td></tr><tr><td>Control</td><td>-0.83</td><td>24.70</td><td>57</td></tr></table> PDQ39 Mobility (mean difference from baseline)	

Study details	Participants	Methods	Results	Comments

	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

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)

<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></td><td>Mean</td><td>SD</td><td>Total</td></tr>
<tr><td>Experimental</td><td>0.35</td><td>1.54</td><td>55</td></tr>
<tr><td>Control</td><td>0.44</td><td>1.32</td><td>57</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>-1.05</td><td>10.00</td><td>55</td></tr>
<tr><td>Control</td><td>1.05</td><td>9.09</td><td>57</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>-0.87</td><td>12.80</td><td>55</td></tr>
<tr><td>Control</td><td>4.37</td><td>14.60</td><td>57</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>0.11</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.,</td><td>Sample size
10 participants

Inclusion criteria
Idiopathic Parkinson's disease</td><td>Details
Double blind, crossover, randomised controlled study over 2 weeks</td><td>Results
Modified Columbia Scores
Low protein diet (n=10) = 17.85 ± 12.21
High protein diet (n=10) = 21.83 ± 12.52</td><td>Overall Risk of Bias
Has an appropriate method of</td></tr>
</table>

<table>
<tr><th>Study details</th><th>Participants</th><th>Methods</th><th>Results</th><th>Comments</th></tr>
<tr>
<td>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
To compare the effect of high and low protein diets on the efficacy of l-dopa

Study dates
Published 1989</td>
<td>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>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 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.</td>
<td>*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
<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>
</table>
</td>
<td>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 treatment allocation?YES
Were the individuals administering care kept blind to treatment allocation? YES</td>
</tr>
</table>

Study details	Participants	Methods	Results	Comments
Source of funding None stated		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>Control</td><td>59.95</td><td>19.70</td><td>10</td></tr></table>	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) Was a valid and reliable method used to determine that outcome? YES (only on/off self reported) Were investigators kept blind to

<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>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 acid supplementation in l-dopa treated Parkinson's disease patients, Clin Nutr, 34, 1189-1194, 2015
Ref Id</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

Exclusion criteria
- Diabetes, kidney failure, heart failure, liver cirrhosis or any other relevant systemic comorbidity.

Characteristics</td><td>Details
This is a monocentric, prospective, randomised, double-blind study on two groups PD-affected, protein-restricted, patients

Interventions
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</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 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>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/pro</td></tr>
</table>

Study details	Participants	Methods	Results	Comments
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 Source of funding No funding reported	Number Sex (F/M) Age (y) BMI (kg/m2) Waist circumference (cm) Disease duration (y)	administration. Every administration of AA mixture corresponds to 28g of proteins. Control group: Placebo tablets		gnostic 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 outcome data and for how many participants were no outcome data available? YES Did the study have an

Study details	Participants	Methods	Results	Comments
				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 Serious risk of bias
Full citation	Sample size 5 RCTs (981 patients)	Details	Results UPDRS total: MD -0.05 [-0.25, 0.15]	Overall Risk of Bias

Study details	Participants	Methods	Results	Comments
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 review and meta-analysis Aim of the study To synthesize evidence from published RCTs	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 Study / Intervention / Population QE3 investigators 2014 / 1200 mg/d or 2400mg/d of CoQ10 vs placebo / Patients with idiopathic PD diagnosed within the past 5 years	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 England score, UPDRS score and its subscales. The search strategy retrieved 1251 unique citations, 20 full texts were retrieved and reviewed and 5 met	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]	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."

Study details	Participants			Methods	Results	Comments
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)	NINDS NET-PD 2007	2400mg/d of CoQ10 or 4000mg GPI-1485 vs placebo	patients who had a diagnosis with PD and not requring any medication for their symptoms	the inclusion criteria and were included in this review. Interventions Coenzyme Q10 (all doses from 300mg to 2400mg/d) vs. placebo		
	Storch et al 2007	300mg/d nanoparticular CoQ10 vs placebo	PD patients without fluctuations and on a stable anti-PD treatment			
	Muller et al 2003	360mg/d of CoQ10 vs placebo	PD patients on stable anti-PD treatment			
	Shults et al 2002	300mg/d, 600mg/d or 2400mg/d of CoQ10 vs placebo	Patients with idiopathic PD diagnosed within the past 5 years			

Study details	Participants	Methods	Results	Comments
Kieburtz K et al. Effect of creatine monohydrate on clinical progression in patients with Parkinson's disese, JAMA 2015 Feb 10; 303(6): 584-593 Aim of the study: To determine whether creating monohydrate was more effective than placebo in slowing long-term clinical decline in participants with Parkinson's disease. Study dates: March 2007 to September 2013. Source of funding: National Institute of Neurological	<table><tr><td></td><td>Intervention</td><td>Control</td></tr><tr><td>Participants</td><td colspan="2">Early PD patients</td></tr><tr><td>Number randomised</td><td>874</td><td>867</td></tr><tr><td>Mean (SD) age (years)</td><td>62.1(9.7)</td><td>61.5(9.6)</td></tr><tr><td>Number of males (n (%))</td><td>569(65)</td><td>554(64)</td></tr><tr><td>Mean (SD) duration of PD (years)</td><td>1.5(1.1)</td><td>1.6(1.1)</td></tr></table>	Details: A multicentre, double-blind, parallel-group, placebo-controlled, 1:1 randomised efficacy trial. Participants were recruited from 45 investigative sites in the United States and Canada and included 1741 men and women with early (within 5 years of diagnosis) and treated (receiving dopaminergic therapy) PD. Intervention: Creatine (10g/d) monohydrate for minimum of 5 years (maximum follow-up, 8 years).	<table><tr><td></td><td>No.</td><td>Intervention</td><td>No.</td><td>Control</td></tr><tr><td>UPDRS Total</td><td>330</td><td>11.3(15.3)</td><td>336</td><td>10.4(13.8)</td></tr><tr><td>UPDRS Mental</td><td>333</td><td>1.2(1.9)</td><td>339</td><td>1.1(1.8)</td></tr><tr><td>UPDRS ADL</td><td>333</td><td>4.5(5.7)</td><td>339</td><td>4.0(5.1)</td></tr><tr><td>UPDRS Motor</td><td>330</td><td>5.6(10.2)</td><td>336</td><td>5.3(9.8)</td></tr><tr><td>EQ-5D</td><td>334</td><td>-0.1(0.2)</td><td>342</td><td>-0.1(0.2)</td></tr><tr><td>PDQ-39 Summary index</td><td>447</td><td>14.2(23.5)</td><td>478</td><td>13(23.2)</td></tr><tr><td>BMI, mean change</td><td>338</td><td>-0.1(2.9)</td><td>341</td><td>-0.4(3.3)</td></tr></table>	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 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

Study details	Participants	Methods	Results	Comments
Disorders and Stroke (NINDS)				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? UNCLEAR Overall, low risk of bias.

Study details	Participants	Methods	Results	Comments