International Parkinson and Movement Disorder Society Evidence-Based Medicine Review: Update on Treatments for the Motor Symptoms of Parkinson's Disease

SUPPLEMENTARY TABLES

Supplementary table e1. Definitions for specific recommendations Goetz C. G., et al. Mov Disord (2002)[177]:

Efficacy Conclusions	Definition	Required Evidence
Efficacious	Evidence shows that the intervention has a positive effect on studied outcomes	Supported by data from at least one high-quality (score ≥75%) RCT without conflicting Level-I data
Likely efficacious	Evidence suggests, but is not sufficient to show, that the intervention has a positive effect on studied outcomes	Supported by data from any Level-1 trial without conflicting Level-1 data
Unlikely efficacious	Evidence suggests that the intervention does not have a positive effect on studied outcomes	Supported by data from any Level-1 trial without conflicting Level-1 data
Non-efficacious	Evidence shows that the intervention does not have a positive effect on studied outcomes	Supported by data from at least one high-quality (score ≥75%) RCT without conflicting Level-1 data
Insufficient evidence	There is not enough evidence either for or against efficacy of the intervention in treatment of Parkinson's disease	All the circumstances not covered by the previous statements
Safety		
Acceptable risk without specialized monitoring		
Acceptable risk with specialized monitoring		
Unacceptable risk		
Insufficient evidence to make conclusions on the safety of the intervention		
Implications for Clinical Practice		
Clinically useful	For a given situation, evidence available is sufficient to conclude that the intervention provides clinical benefit	
Possibly useful	For a given situation, evidence available suggests, but is insufficient to conclude that the intervention provides clinical benefit	
Investigational	Available evidence is insufficient to support the use of the intervention in clinical practice, further study may be warranted	
Unlikely useful	Available evidence suggests that the intervention does not provide clinical benefit	
Not useful	For a given situation, available evidence is sufficient to say that the intervention provides no clinical benefit	

Supplementary table e2: Treatments that may delay/prevent disease progression

Intervention	Reference	Investigated population	Sample size	Intervention/comparator	Primary outcome	Main result	Quality score (%)	Comments
Dopamine agonist: pramipexole	**Schapira A. H. Lancet Neurol (2013)[12]**	PD (age 30 – 79 years) diagnosed within 2 years	535	261 were randomized to early start pramipexole (1.5 mg/day) and 274 to placebo with delayed start design (switch to pramipexole at 6 -9 months)	15-month change from baseline in the total UPDRS score	At 15 months (n=411), the adjusted mean change in total UPDRS showed no significant difference between early vs. delayed pramipexole (-0.4 points, 95% CI -2.2 to 1.4, p=0.65)	**90**	Adverse effects occurred in 81% and 84% of patients, respectively (most frequently nausea). 10% patients in the early and 8% in the delayed pramipexole group had serious events, two of which (hallucinations, orthostatic hypotension) were deemed related to the study drug.
Coenzyme Q_{10}	**Shults C. W. Archives of neurology (2002)[17]**	Early (<5 years) untreated PD	80	Randomized to coenzyme Q_{10} (300, 600, and 1200mg/d) or placebo and treated for 16 months or until symptomatic therapy was required	Linear trend between dosages and the mean change in total UPDRS (apparently defined as parts I-III)	Positive (defined as p-value < 0.09)	**74**	Coenzyme Q_{10} was well tolerated.
	Muller T. Neuroscience letters (2003)[16]	Treated and stable PD	28	Coenzyme Q_{10} (360mg/d) vs. placebo for 4 weeks	Not stated	Significant improvement in UPDRS score (not specified) from baseline in the active treatment arm but changes in UPDRS motor and total (not defined) scores were not significantly different between the arms	**62**	Tolerability was stated to be good, but no details were reported
	Storch A. Archives of neurology (2007)[14]	Stable PD	131	Placebo or nanoparticular coenzyme Q_{10} (100 mg 3 times daily) for 3 months	Reduction in UPDRS parts II and III combined	No significant differences between the two treatment arms	**93**	Adverse events were similar in the treatment groups
	Parkinson Study Group Q. E. Investigators JAMA Neurol (2014)[15]	PD since ≤ 5 years; modified H&Y ≤ 2.5; and no anticipated need for dopaminergic therapy within 3 months	600	Placebo, 1200 mg, or 2400 mg/d of coenzyme Q_{10}.; all received 1200 IU/d of vitamin E for 16 months or need for symptomatic treatment	Change in total UPDRS score (Parts I-III) from baseline to final visit.	Mean changes in total UPDRS scores were 6.9 points (placebo), 7.5 points (1200 mg; p = 0.49 relative to placebo), and 8.0 points (2400 mg; p = 0.21 relative to placebo)	**85**	Study was terminated after the pre-specified criterion was reached, showing no evidence of any disease-modifying effect of coenzyme Q_{10}.
Creatine	**Bender A. Neurology (2006)[19]**	PD with average disease duration 2.5 years. H&Y < 2.5; with evidence of dopamine denervation using SPECT.	60	Creatine 20 g daily for 6 days, followed by 2 g/d for 6 months and 4g/d for the remainder, up to 2 years, or placebo	Change in DAT SPECT, evaluated after a 2-week adjustment in PD medications down to baseline level; and motor UPDRS	No significant effects of creatine on any outcome measure, apart from smaller increase needed in dopaminergic medications (2.5-fold increase) vs. placebo group (7.5-fold increase)	**45**	Two further studies evaluating creatine were not scored as they did not fulfill inclusion criteria **NINDS NET-PD Investigators Neurology (2006)[178], and Clin Neuropharmacol (2008)[179]:** One was a futility design Neurology (2006)[178]: and the other Clin Neuropharmacol

Intervention	Reference	Investigated population	Sample size	Intervention/comparator	Primary outcome	Main result	Quality score (%)	Comments
								(2008)[179]: was an extension study only. Safety measures were reviewed and no additional issues noted
	Kieburtz K. JAMA (2015)[18]	Early PD (1.5-1.6 years duration since diagnosis	1741	Creatine 1g/d vs. placebo	A global statistical test (GST) comprising 5 validated measures of motor and activities of daily living (ADL) and quality of life over 8 years	Interim analysis (in 955 subjects) after 5 years reported no significant changes between groups and the study was stopped.	**95**	There were no significant differences in adverse events (AEs)
Vitamin D	**Suzuki M. The American journal of clinical nutrition (2013)[20]**	Treated PD (mean age 72±7 years; disease duration range 2 – 60 months; baseline H&Y median 2.0 [range 1-5] and on levodopa average dose 150 – 600 mg/day)	114	Vitamin D3 supplements (1200 IU/d) or placebo for 12 months	Clinical changes from baseline and the percentage of patients who showed no worsening of the modified H&Y stage and UPDRS	Vitamin D3 prevented the deterioration of H&Y (mean change ±SD vitamin D3 group +0.02±0.62 vs. placebo +0.33±0.70; p=0.005; RR 2.37 [95% CI, 1.06 to 5.31]).	**76**	The study population was heterogeneous with subjects recruited having variable disease duration and severity, thus the benefit in early or advanced disease, and the biological significance are not clear.
Exercise	**Park A. Parkinsonism Relat Disord (2014)[21]**	Relatively early-stage PD (within 3 years of diagnosis, H & Y < 3 and on dopaminergic treatment)	31	Early-start group (ESG) or a delayed-start group (DSG) exercise program; The ESG underwent a rigorous formal group exercise program for 1 hour three days/week for 48 weeks, while the DSG participated in this identical exercise program from weeks 24-48.	Change in UPDRS, with additional analysis of the get-up-and-go walking test, the Tinetti Mobility test, and the PDQ-39	At week 48, there was no significant improvement in primary or secondary outcomes, with the mean change from baseline total UPDRS score (the primary outcome measure) of 6.3 in the ESG vs. 5.1 in the DSG (P=0.58; 95% CI not reported)	**64**	The study is limited by lack of measures of activity in the delayed-start group, small sample size, and single-blinding.
	Frazzitta G. Neurorehabilitation and neural repair (2015)[22]	Newly diagnosed PD on rasagiline	40	2 groups: an "MIRT" group (two 28-day multidisciplinary intensive rehabilitation treatments, at 1-year intervals) and a control group (only drug)	UPDRS II, UPDRS III, 6-minute walking test (6MWT), Timed Up-and-Go test (TUG), PD Disability Scale (PDDS), and levodopa equivalents at baseline, 6 months, 1 year, 18 months, and 2 years later.	Over 2 years, UPDRS II, UPDRS III, TUG, and PDDS differentially progressed in the 2 groups: in the MIRT group, all scores at 2-year follow-up were better than at baseline (all p<0.03). No changes were noted in the control group. Levodopa equivalent dosages increased significantly in the control group (p=0.0015).	**70**	

Supplementary table e3: Treatments For Symptomatic Monotherapy

Intervention class	Reference	Investigated population	Sample size	Intervention/comparator	Primary outcome	Main result	Quality score (%)	Comments
Dopamine agonist: pramipexole IR	**Kieburtz K. Mov Disord (2011)[23]**	Early PD	311	Twice daily vs. three times daily pramipexole immediate release 0.5 mg BID, 0.75 mg BID, 0.5 mg TID	Change from baseline at week 12 in UPDRS I-III	Change in UPDRS I-III was significantly better with pramipexole (vs. placebo) was 4.4 (2.3 – 6.5) (0.5 BID) ($p < 0.0001$); 4.7 (2.5-6.9) (0.75mg BID) ($p <0.0001$) and 4.4 (2.3 – 6.5) (0.5 mg TID) ($p < 0.0001$). No difference between pramipexole groups. Sleepiness was reported in 22% of 0.75mg BID vs. placebo but no different to 0.5 mg TID group (25%)	**95**	
Dopamine agonist: pramipexole ER	**Poewe W. Neurology (2011)[24]**	Early PD	523	Pramipexole ER vs. IR over 33 weeks	UPDRS II and III	Adjusted mean change (pramipexole vs. placebo) – 8.2 (-9.5 to 6.9) for ER ($p < 0.0001$); -8.7 (-10.1 to -7.4) for IR ($p < 0.0001$) and -1.2 (-3.1 to 0.6) for placebo	**97**	**Hauser R. A. European journal of neurology (2014)[25]:** (No QS as Extension Study) reported on an open label extension of 3 RCTs: 2 in early and 1 in advanced PD over 80 weeks (Pramipexole ER 0.375 0 4.5mg/d) n = 590 with no issues on long-term safety and maintained efficacy of pramipexole ER in early and advanced PD. Reported AEs (≥10.0%) were somnolence (15.1%), peripheral edema (11.7%) and back pain (10.6%) in early-PD and dyskinesia (27.4%) and somnolence (13.6%) in advanced PD. Impulse control disorders were identified by semi-structured interview in 13 subjects (1.4% of 902)
Dopamine agonist: rotigotine	**Mizuno Y. Mov Disord (2013)[26]**	Early PD patients in Japan (mean H&Y 2, range 1-3)	172	Rotigotine (mean dose 12.8 mg, up to 16 mg/24 hours; or placebo for 12 weeks	UPDRS part II & III sum score	Mean improvement in UPDRS part II & III sum score (the primary endpoint) was 8.4 in the rotigotine group vs. 4.1 in the placebo group ($p=0.002$; 95% CI, -7.0 to -1.7)	**89**	**Hauser R. A. BMC neurology (2016)[27]:** evaluated rotigotine for PD apathy (early and advanced); not rated as motor was not primary outcome; No new safety concerns: adverse events in rotigotine-treated patients were application site reactions, somnolence, and nausea.
Prolonged-release levodopa	**Pahwa R. Parkinsonism Relat Disord**	Levodopa-naive PD	381	Placebo vs. IPX066 containing 145, 245 or 390 mg of levodopa administered three times daily	Change from baseline in UPDRS (Part II) and III), at 30 weeks	Mean improvement in UPDRS II + III was 11.7, 12.9, and 14.9 points for the three dosages and 0.6 points for placebo ($p<0.0001$, all dosages). PDQ-39 total scores improved with	**93**	Most common AEs with IPX066 included nausea, dizziness, and headache IPX066 145 mg TID appeared to provide the best overall balance between efficacy and safety

Intervention class	Reference	Investigated population	Sample size	Intervention/comparator	Primary outcome	Main result	Quality score (%)	Comments
IPX066	**(2014)[29]**					IPX066 (p≤0.034, all dosages)		The area under the curve levodopa dose-equivalence for the 390mg TID dose of IPX066 is approximately 800mg/d, which is considered high for early PD and not usual in clinical practice
Levodopa IR, dopamine agonists, monoamine oxidase type B inhibitors (MAOB-I)	**Gray R. Lancet (2014)[28]**	Early PD	1620	Levodopa, or 'levodopa-sparing' therapy including dopamine agonists, or monoamine oxidase type B inhibitors (MAOBI) for up to 7 years	Mobility dimension on the PDQ-39	With 3-year median follow-up, PDQ-39 mobility scores averaged 1.8 points (95% CI 0.5-3.0) better in patients randomly assigned to levodopa than those assigned to levodopa-sparing therapy, with no increase or attrition of benefit during 7 years' observation. PDQ-39 mobility scores were 1.4 points (95% CI 0.0-2.9) better in patients allocated MAOBI than in those allocated dopamine agonists	**76**	The study showed very small but persistent benefits for patient-rated mobility scores when treatment is initiated with levodopa compared with levodopa-sparing therapy However the 'pragmatic' study design (which permitted omission of the levodopa or the MAOBI arm) may potentially have introduced some bias
Selective adenosine A_{2A} receptor antagonist: istradefylline	**Fernandez H. H. Parkinsonism Relat Disord (2010)[30]**	Untreated PD	176	Istradefylline (40mg/d) as monotherapy vs. placebo for 12 weeks	UPDRS III	No significant change vs. placebo	90	AEs were similar in each group. The investigators questioned if the study was underpowered as the power analysis was based on advanced PD patients in previous istradefylline trials

SYMPTOMATIC ADJUNCT THERAPY

Supplementary table e4: Symptomatic adjunct therapy for early or stable PD

Intervention class	Reference	Investigated population	Sample size	Intervention/comparator	Primary outcome	Main result	Quality score (%)	Comments
Dopamine agonist: pramipexole ER	**Mizuno Y. Clin Neuropharmacol (2012)[31]**	Advanced and levodopa 'undertreated' PD group (not well defined)	112	Pramipexole ER (average 3.36mg/d) and IR (3.54 mg/d) over 12 weeks	Not predefined	Change in UPDRS II (average ON/OFF) + III (ON) was ER -13.6, IR -13.3 (both significant from baseline)	**85**	The mean levodopa doses were low e.g. 299.1mg/d in the ER group and 270.5 mg/d in the IR group
MAO B inhibitor: rasagiline	**Hauser R. A. Mov Disord (2014)[32]**	Early PD not adequately controlled on current medication	321	Rasagiline vs. placebo as an add-on to DA therapy (pramipexole or ropinirole) over 18 weeks	Change in total UPDRS (I, II, and III) from baseline to week 18	Significantly greater improvement in total UPDRS scores with rasagiline compared to placebo, regardless of the DA patients were taking (least squares mean difference – 2.4 ± 0.95 (SE); 95% CI, -4.3, - 0.5 (p = 0.012). Differences between groups were not statistical significant	**93**	Rasagiline was well tolerated It is not reported whether there was a difference in the outcomes between the patients who were included in the trial judged not optimally controlled on DA therapy and did not report a history of dose limiting AEs (42.7%) and those patients (57.3%) who were judged not optimally controlled on DA therapy but had previous dose limiting AEs
MAOB-inhibitor and channel blocker: Safinamide	**Stocchi F. Mov Disord (2012)[33]**	Early PD (< 5 years)	269	Safinamide 100mg/d, 200mg/d vs. placebo	Hierarchical and first comparison was change in UPDRS III after 24 w using safinamide 200mg	Primary endpoint not met, but 100mg safinamide showed significant change vs. placebo: -6.0 vs. -3.6; point estimate: -1.9; (95% CI: -3.7 to- 0.1; P 0.0419).	**85**	The lack of dose effect in efficacy, the small change in UPDRS III and overall high loss of subjects in 200mg group (21% of safinamide 200mg group withdrew from study vs. 10% from 100mg and placebo) reduces quality score
Surgery: subthalamic nucleus deep brain stimulation (STN DBS)	**Charles D. Parkinsonism Relat Disord (2014)[34]**	Very early-stage PD (treated with antiparkinsonian medications for >6 months, but ≤4 years; mean 2.2 years) without motor response complications	**30**	Optimal Drug Therapy (ODT) vs. ODT and subthalamic nucleus deep brain stimulation (STN DBS)	OFF-medication UPDRS III	At two years, the DBS group did not experience worsening of motor function compared to the ODT group (OFF-medication UPDRS III scores worsening by 8.2 vs. 9.6 points [p=0.74] in the DBS vs. ODT group, and ON-medication UPDRS III scores worsening by 0.1 vs. 3.4 points [p=0.45], respectively).	**74**	There were 2 serious AEs in the DBS group; stroke with permanent cognitive impairment and head injury with secondary hardware infection

Supplementary table e5: Adjunct Therapies For specific or general Motor Symptoms in PD subjects on optimized treatment

Intervention class	Reference	Investigated population	Sample size	Intervention/comparator	Primary outcome	Main result	Quality score (%)	Comments
Cholinesterase inhibitor: donepezil	**Chung K. A. Neurology (2010)[35]**	Advanced PD with falls (> 2 /week); (6 had received prior STN DBS surgery	23	Donepezil (5mg/day for 3 weeks then 10mg/day for another 3 weeks) - crossover study	Falls per day as assessed using weekly home-completed diaries	Falls significantly decreased to 0.13 (± 0.03)/ d with donepezil vs. 0.25(±0.08) /day with placebo ($p < 0.05$); absolute risk reduction: 0.12 falls/d (CI -0.09 – 0.33). No change in near-falls frequency.	**62**	The baseline mean number of falls per day was not clear and the primary outcome has not been validated, thus precluding determining if the outcome was clinically relevant The frequency of overall side effects was 35% on donepezil but relative frequencies were not stated
Cholinesterase inhibitor: Rivastigmine	**Henderson E. J. Lancet Neurol (2016)[36]**	Advanced PD who had fallen at least once in the year before enrolment (range 2-12 falls), were able to walk 18 meters without an aid, had no previous exposure to an acetylcholinesterase inhibitor, and did not have dementia	130	Rivastigmine titrated from 3 mg to the target dose of 12 mg/d over 12 weeks vs. placebo	Difference in step time variability between the groups at 32 weeks, adjusted for baseline age, cognition, step time variability, and number of falls in the previous year	At week 32, patients on rivastigmine (assessed: 55) had improved step time variability for normal walking (ratio of geometric means 0·72, 95% CI 0·58–0·88; p=0·002) and the simple dual task (0·79; 0·62–0·99; p=0·045) compared with placebo (59 assessed). Improvements in the complex dual task did not differ between groups (0·81, 0·60–1·09; p=0·17)	**84**	Gastrointestinal side effects were more common with rivastigmine than with placebo (p<0·0001); nausea: 20 (31%) patients in the rivastigmine group vs. three (5%) in the placebo group; vomiting: 15 (17%) vs. three (5%) placebo
Stimulants: methylphenidate	**Espay A. J. Neurology (2011)[38]**	PD with moderate gait impairment (mean disease duration 10.9 years)	23	Methylphenidate (maximum 80 mg/day, mean 64 mg/day) or placebo for 12 weeks, and crossed over after a three-week washout	Change in a gait composite score of stride length and velocity	Non-significant	**64**	Dropout rate of 26% Side-effects included hypersexual, manic, irritability, sweating" symptoms; and were more frequent in methylphenidate-treated patients vs. placebo (5 vs. 0)
	Moreau C. Lancet Neurol (2012)[37]	Advanced PD (median disease duration 17 years, median duration of bilateral STN DBS 5-6 years)	69	Methylphenidate (1 mg/kg/day [mean 71 mg] in three divided doses) or placebo for 90 days	Number of steps taken during the stand-walk-sit (SWS) test OFF-medication	Number of steps during the SWS OFF-medication, improved significantly in the methylphenidate group vs. placebo (median 31 vs. 33 steps; p = 0.017, adjusted effect size 0.61)	**91**	There was no difference in ON state thus clinical importance is unclear Methylphenidate was well tolerated and there were no serious AEs, but treated patients had increased heart rate (mean 3.6 beats per minute) and decreased

Intervention class	Reference	Investigated population	Sample size	Intervention/comparator	Primary outcome	Main result	Quality score (%)	Comments
								weight (mean 2.2 kg) compared with the placebo group; upper gastrointestinal symptoms were also more frequent Methylphenidate improved daytime somnolence and apathy
N-methyl-D-Aspartate (NMDA) antagonist: memantine	**Moreau C. Journal of neurology, neurosurgery, and psychiatry (2013)**[39]	Advanced PD with gait disorder (≥ 2 on UPDRS part III item 29 subscore and abnormal forward stance). Sixteen subjects (8 per group) had prior STN DBS surgery.	25	Memantine vs. placebo for 30 days titration up to 20 mg/d, then continued for 60 days	Change in stride length, 'ON' levodopa using gait analysis	No change in either group pre- and post-treatment ($F_{(1,21)}$=0.27; p = 0.61 adjusted effect size covariance analysis (-0.2).	**73**	Dyskinesia was significantly less with memantine (dyskinesia rating score mean reduction 2 vs. 0 with placebo, p<0.001) There were no significant AEs but data were sparse
Cannabinoids: cannabidiol	**Chagas M. H. J Psychopharmacol (2014)**[40]	Moderately disabled PD subjects with 6 – 8 years disease duration	21	Cannabidiol, 75mg or 300mg/d vs. placebo	Change from baseline of the 'ON' medication UPDRS scores vs. placebo	No significant difference	**60**	Statistical issues including lack of clarity of number of patients evaluated at end of study and lack of intention-to-treat design and likely under-powering reduces quality score

Supplementary table e6: Physiotherapy

Intervention class	Reference	Investigated population	Sample size	Intervention/comparator	Primary outcome	Main result	Quality score (%)	Comments
Physiotherapy	**Canning C. G. Clin Rehabil (2012)[49]**	PD H&Y 1-2	20	6 weeks of semi-supervised treadmill training 30-40 minutes, four times a week) followed by a further 6 weeks follow-up vs. usual physical activities	Walking capacity (6-minute timed walk)	N.S. difference between the two groups (36m vs. 41.5m)	**67**	Study was not fully powered as 140 participants were required but only 20 were recruited due to funding issues
	Frazzitta G. Neurorehabilitation and neural repair (2012)[44]	PD H&Y 2	50	4 weeks of intensive rehab therapy (IRT) consisting of 3 x 1h daily sessions; repeated at 12 months vs. a control group assigned general home exercises with no specific intervention specified	UPDRS (total and II+III)	IRT group had no change in total and UPDRS II and III at 1 year vs. baseline; the control group significantly worsened in all UPDRS scores vs. baseline. At 12-months, UPDRS III was 21 $\pm$ 6 in the IRT group vs. 28.7 $\pm$ 7 in controls. The benefit of the second IRT treatment was similar to the first treatment. The IRT group was on less levodopa equivalents at 12 months (mean -52mg) ($p = 0.04$) while the control group increased levodopa equivalent by + 30mg ($p = 0.015$)	**65**	Limited interpretation is due to lack of statistical comparisons between IRT and control groups
	Schenkman M. Physical therapy (2012)[50]	PD H&Y 1-3	121	3 modes of exercise therapy for 16 months: A) FBF (flexibility, balance, function) program (i.e., individualized spinal and extremity flexibility exercises followed by group balance/functional training) supervised by a physical therapist; B) Aerobic endurance) program (i.e., using treadmill, bike, or elliptical) supervised by an exercise trainer, or C) Home exercises (Fitness Counts program) with only one supervised session per month	Physical Activity measure: Continuous Scale-Physical Functional Performance [CS-PFP]), Balance: (Functional Reach Test [FRT])	Primary and secondary outcomes (including UPDRS) were similar between all groups with the exception of superior walking economy in the aerobic endurance group up to the 16-month measurements. Overall physical function was better in the FBF group at 4 months but not at other time points in the study	**69**	Relevance of primary outcome to PD unclear Statistical analysis was a one-way analysis of variance instead of a two-way, and it was unclear whether the sample size was calculated to compare both active interventions to control therapy or to compare active interventions against each other
	Bello O. Gait Posture (2013)[52]	PD (mean disease duration 4.95 y; H&Y 1-3.	22	Individually adjusted treadmill training vs. overground walking for 5 weeks, 3 sessions per week, of increasing duration (up to 20 minutes)	Gait kinematics during walking at preferred and maximal speed; Timed Up and Go (TUG); static posturography using a stabilometric platform, and knee extensors	Preferred speed walking improved from baseline in both groups. The treadmill training program, but not the overground training, led to improvements in stride length at preferred (from 1.27±0.08 to 1.33±0.07m) and maximal (from 1.44±0.09 to	**53**	Conclusions are limited by the small sample size, lack of clear blinding; the fact that multiple comparisons were carried out without reporting of significance data, and

Intervention class	Reference	Investigated population	Sample size	Intervention/comparator	Primary outcome	Main result	Quality score (%)	Comments
					strength, assessed on an isometric knee extensor machine.	1.49±0.09m) walking speed, in TUG (total time: from 12.87±1.73 to 11.26±0.09 m/s) and some subscores of static posturography.		the lack of a 1-month assessment in the control group
	Cholewa J. Neurologia i neurochirurgia polska (2013)[66]	PD; H&Y 3; disease duration 7-8 years	70	Physiotherapy was carried out for 60 minutes, twice a week for 12 weeks vs. no exercise	UPDRS II and III	UPDRS Parts III and II scores improved significantly in the intervention group after treatment (by 19.0% and 22.2% respectively) vs. non-significant changes in the control group (95% CI values not reported)	**51**	Lack of active intervention in the control group and no information on patient follow up after randomization resulted in lower QS. There was also no mention of blinding in this study
	Combs S. A. NeuroRehabilita (2013)[51]	PD H&Y 2-3	31	Group Boxing training vs. traditional exercise for 24–36 sessions, each lasting 90 minutes, over 12 weeks	Multiple Outcomes included the BBS, Activities-specific Balance Confidence Scale (ABC), Timed Up and Go (TUG), Dual-task Timed Up and Go (dTUG), gait velocity, 6-Minute Walk Test (6MWT), and Parkinson's disease Quality of Life scale (PDQL).	Both groups demonstrated improvements in most outcome measures. The traditional exercise group improved more on the ABC (from 85.0% to 93.3% vs. 83.1% to 85.3%; p=0.015; 95% CI not reported)	**51**	There was a dropout rate of 29%.
	Corcos D. M. Mov Disord (2013)[43]	PD (50 – 65 years), mean disease duration 6.5 years	48	Progressive resistance exercise (PRE) vs. modified fitness counts (mFC) for 24 months	Change in OFF UPDRS III at 24 months compared to baseline	UPDRS III OFF better in both groups; but significantly improved by -7.3 points (95% CI -11.3 to -3.6) in PRE vs. mFC (p>0.001)	**82**	Lack of benefit in ON reduces the clinical relevance of the interventions One subject developed wrist pain directly related to the mFC and 7 possibly related serious AEs involving back, hip and knee surgery were reported in both
	Poliakoff E. NeuroRehabilita (2013)[67]	Mild to moderate PD subjects not currently exercising formally	32	Immediate 20-week biweekly gym-training program vs. a 10-week program starting 10 weeks later	UPDRS III, PDQ39	UPDRS III score, PDQ-39 did not change over time	**44**	There was greater disease duration in the active group (7.4 years) compared to controls (4.7 years); Timing of assessments in relation to ON/OFF drug status is not stated. A formal

Intervention class	Reference	Investigated population	Sample size	Intervention/comparator	Primary outcome	Main result	Quality score (%)	Comments
								statistical comparison of the two treatment groups was not performed
	Shulman L. M. JAMA Neurol (2013)[42]	PD H&Y 1-3	80	3 exercise arms: A) High intensity treadmill (30 minutes at 70-80% heart rate); B) Low intensity treadmill (30 minutes at 40-50% heart rate); C) Stretching/resistance (sets of leg exercises) All groups participated in their exercise treatments three times a week for 3 months	Three motor tests: Gait speed (6 minute walk), cardiovascular fitness, and muscle strength	All three groups improved their gait distance. Both treadmill groups improved cardiovascular fitness, but this was better in the lower speed group. The stretching/resistance group achieved better muscle strength.	**76**	
	Ganesan M. Pm r (2014)[45]	PD (mean age <60 years) mean disease duration (5-6 years), H&Y <2.5	60	Partial (20% unloaded) body weight–supported treadmill gait training (PWSTT), to allow faster walking, vs. conventional gait training (CGT) (both interventions involving walking and balance strategy training) 30 min/day over 4 days total 16 sessions in 4 weeks vs. no intervention on balance	UPDRS III	After 4 weeks, UPDRS III was significantly better in PWSTT vs. baseline and vs. the two other groups (mean ON UPDRS III score from PWSTT reduced from 31 to 25 after 4 weeks). CGT was better than baseline but not the control group. POMA gait score and balance posturography measures similarly improved in PWSTT vs. CGT, while the Berg balance improved vs. baseline but not with the intervention	**63**	The relevance of the intervention in PD subjects with falls despite optimal medication is hard to assess as all participants were relatively mild and specific balance scores that indicated no major issues with balance in the participants
	Harro C. C. NeuroRehabilitation (2014)[54]	PD H & Y 1-3; mean disease duration 4.1 years	20	Speed-dependent treadmill training (SDTT) vs. rhythmic auditory-cued (RAC) over ground walking	Comfortable gait speed (CGS) and fast gait speed (FGS) measured on the 10-meter walk test, the 6-minute walk test (6MWT) and the Functional Gait Assessment (FGA)	SDTT significantly improved the mean FGS between baseline and post-training ($p = 0.012$), whereas RAC significantly improved mean CGS from baseline to post-training ($p = 0.013$). These improvements were retained at 3 months The 6MWT and the FGA also significantly improved in both groups from baseline to post-training. The improvement in FGA was retained in both groups at 3 months while the 6MWT was retained in the RAC group. No statistically significant differences between the 2 groups in any of the dependent gait measures from baseline to post-training, or from baseline to 3	**69.5**	Reduced quality score as statistically under-powered

Intervention class	Reference	Investigated population	Sample size	Intervention/comparator	Primary outcome	Main result	Quality score (%)	Comments
						months.		
	Nadeau A. Med Sci Sports Ex (2014)[53]	PD H&Y 1.5 or 2	93	Speed Treadmill Training (TT) vs. Mixed TT vs. controls The interventions consisted of 72 one-hour exercise sessions over 24 weeks	MDS-UPDRS, PDQ-39, spatiotemporal parameters of gait and 6-minute walking distance at baseline, 12 weeks, and after 24 weeks	Changes on the MDS-UPDRS and total PDQ-39 did not differ between groups (95% CI not stated). Both TT groups improved in terms of speed, cadence, and stride length during self-selected walking conditions at the study endpoint Both groups also showed improvements in distance traveled	**62**	Only 34 out of 93 subjects were available for analysis
	Paul S. S. Clin Rehabil (2014)[56]	PD; mean disease duration7-8 years	40	Power training using pneumatic variable resistance equipment versus "sham exercise" (low-intensity unmonitored exercise at home) groups for 12 weeks	Peak power of the four leg muscle groups	The power training group had significantly improved leg muscle power in leg extensors, knee flexors, hip flexors and hip abductors, as well as the secondary measures of the Timed Up and Go Test, choice stepping reaction time	**60**	The relevance of the conclusions was limited due to lack of description of blinding and lack of clinically relevant outcomes
	Uc E. Y. Neurology (2014)[55]	Mild-to-moderate PD	60	Aerobic walking (3 times a week, for six months	Multiple end points: Effect on motor function UPDRS III, cognition, and quality of life	ON UPDRS III improved from 18.8 to 15.9 ($p<0.05$). Other measures of aerobic fitness, fatigue, mood, and cognition (executive function) all improved	**61.4**	The initial study design had to be modified in response to recruitment difficulties In addition safety concerns were raised about interval training, thus all participants in the latter part of the study were assigned to the continuous arm
	Volpe D. Clin Rehabil (2014)[46]	PD patients (H&Y 2.5-3)	34	Hydrotherapy treatment vs. land-based rehabilitation treatment; 60 minutes, 5 days a week for 2 months	Center of the pressure sway area recorded with open and closed eyes, using a stabilometric platform	Greater improvement with hydrotherapy than with land-based therapy in these variables: center of pressure sway area closed eyes (mean change: 45.4 +/- 64.9 vs. 6.9 +/- 45.3, p = 0.05), Berg Balance Scale (51.2 +/- 3.1 vs. 6.0 +/- 3.1, p = 0.005), Activities-specific Balance Confidence Scale (16.8 +/- 10.6 vs. 4.1 +/- 5.4, p = 0.0001), Falls Efficacy Scale (-5.9 +/- 4.8 vs. -1.9 +/- 1.4, p = 0.003), PDQ-39 (-18.4 +/- 12.9 vs. -8.0 +/- 7.0, p = 0.006) and falls diary (-2.4 +/- 2.2 vs. -0.4 +/- 0.5, p = 0.001)	**67**	The clinical relevance of the primary outcome is unclear and the authors based their sample size calculation on a secondary outcome measure (Berg Balance Scale)

Intervention class	Reference	Investigated population	Sample size	Intervention/comparator	Primary outcome	Main result	Quality score (%)	Comments
	Carvalho A. Clin Interv Aging (2015)[57]	PD H&Y 1-3; Disease duration 4 -6 years	22	Strength training (ST) using repetitive weights (80% of one repetition maximum vs. aerobic training (AT) on treadmill (defined at 70% of maximum HR) vs. group physical therapy consisting of calisthenics and stretching and gait training. Interventions were 2 days a week for 12 weeks	Effect size of UPDRS III change	Effect size of UPDRS III change significantly improved from baseline in the ST group by 27.5% and AT by 35.% vs. 2.5% for physiotherapy group, as a control group. No statistical significance between-group differences	**60**	The subjects in the physical therapy group had lower DA use. The number of subjects per group was small and probably underpowered statistical analysis motor fluctuations were not taken into account
	Dibble L. E. J Neurol Phys Th (2015)[59]	PD H&Y 2-3	41	High intensity eccentric resistance exercise program (Resistance Exercise using Negative Eccentric Work [RENEW]) vs. an active control group	Quadriceps force production determined via a maximum voluntary isometric contraction (MVIC)	In both groups, exercise and medication resulted in improvements in muscle force and mobility. No direct comparison between groups was reported	**70**	Groups were not balanced regarding age of patients and duration of disease at baseline; 8.00 (4.48) years in RENEW v 5.70 (4.23) years in controls
	King L. A., et al. Parkinsons Dis (2013)[180]	PD H&Y 1-3	39	Agility Boot Camp (ABC) vs. Treadmill training for 4 weeks	1) Effects of the interventions for improving mobility, measuring multiple variables; 2) exploring which of five outcome measures was most sensitive to exercise intervention	Both groups improved in numerous mobility measures similarly. The conclusions of best outcome measures pointed more to the "body structure and function level" of the ICF model (International classification of functioning, disability and health)	**65**	The study was self-admittedly underpowered and exploratory to test for any different effects between exercise groups
	King L. A. J Neurol Phys Ther (2015)[47]	PD H&Y 2-3;	58	Exercise by individualized physical therapy vs. group class or home exercise, 3 times a week for four weeks	7-item Physical Performance Test	Only the individual group significantly improved in the 7-item Physical Performance Test. The home exercise program improved the least across all outcomes, particularly in patients with more advanced disease and comorbidities such as cognitive impairment.	**65**	
	Monticone M. Mov Disord (2015)[41]	PD mean disease duration 15 ± 3 years, H&Y 2.5-4	70	Multidisciplinary inpatient rehabilitative care and control group (general physiotherapy) for 8 weeks	MDS-UPDRS Part III at 8 weeks and then 12 months after end of treatment	MDS-UPDRS Part III between-group difference in favor of the experimental group of 25 points after training, which was maintained at follow-up at 12 m	**77**	The large reported treatment effects in this study warrant a study to confirm the results
	Trigueiro L. C. Am J Phys Med Rehabil (2015)[60]	Moderate PD; H&Y 2-3; mean disease duration 4.5 years	35	Treadmill training using 5% or 10% added weight (using belt) or no weights for 4 weeks of 3 x 30 min sessions	Objective gait analysis	Improvement in all groups before and after in gait speed; stride length and step length but no intergroup effect	**49**	There was a large drop out 7/35 subjects, and the effects of baseline PD medications was unclear
	Agosti V. Neurol Sci	PD mean	20	Global postural reeducation (GPR)	Kinematic gait	At the end of the GPR program (4	**59**	The relevance of the

Intervention class	Reference	Investigated population	Sample size	Intervention/comparator	Primary outcome	Main result	Quality score (%)	Comments
	(2016)[58]	disease duration 6 years		program, three times a week, for 40-min individual sessions vs. control (physiotherapy treatment or intervention) for 12 weeks	parameters of thigh (T), knee (K) and ankle (A)	weeks) there was an improvement of the kinematic gait pattern with increased flexion amplitudes of knee and thigh. There was a significant interaction between time and groups was observed (F = 5.557, p <0.001) for UPDRS-III score (F = 131.581, p < 0.001)		conclusions was limited due to lack of clinically relevant primary outcomes
	Cheng F. Y. Sci Rep (2016)[64]	PD H&Y 1-3	36	Three groups: Balance and strengthening training vs. turning-based treadmill training (12x 30-min training sessions followed by 10 min of turning training on a level surface) vs. general exercise training for 6 weeks	Turning performance	Specific exercise and the turning-based training group experienced improved turning performance, vs. controls (specific exercise, 33% change, p = 0.016; turning-based training, 35% change, p = 0.021)	**73**	
	Ni M. Parkinsonism Relat Disord (2016)[69]	PD H&Y 1-3	26	Power-based resistance training (PWT) two sessions/ week of high-speed resistance training combined balance and agility drills vs. controls (One-hour/month of non-exercise, health education classes, for 3 months	Outcome measures included upper and lower limb bradykinesia scores, other outcomes: one repetition maximums (1RM) and peak powers on biceps curl, chest press, leg press, hip abduction and seated calf, and quality of life (PDQ-39).	The PWT group produced significant improvement in both upper and lower limbs bradykinesia scores, 1RM and muscle peak power ($p < 0.05$), which surpassed the control group except for power during the seated calf exercise No significant correlations between changes in clinical measure of bradykinesia and muscle peak power were observed after training	**63**	
	Ridgel A. L. Journal of science and medicine in sport (2016)[63]	PD (with depression)	30	Enhanced (EXCEED) exercise therapy (included psychoeducation, peer education/support and manualized group exercise) vs. self-guided therapy (self-paced exercises following a written manual) 12 weeks	Number of exercise sessions attended and an International Physical Activity Questionnaire (IPAQ) score at 12 and 24 weeks	Both groups attended similar number of exercise sessions (average 56%) and Physical activity (IPAQ) level was not significantly different between the two groups after the 12-week intervention During the post intervention (weeks 12 - 24), there was a significant increase in the amount of physical activity in the EXCEED (+ 34%) and a decrease in the self-guided therapy group (- 32%)	**55**	There were baseline differences in the 2 groups; with significantly higher levodopa equivalent dosages in the EXCEED group and it was unclear if any changes in drug therapy for PD occurred during the study
	Silva-Batista C. Med Sci Sports Exerc (2016)[61]	PD H&Y II-III, average 10 years	39	Resistance training (RT) - exercises with increasing resistance leg /chest presses and squats vs. RT -Instability	Timed-up and go test (TUG)	TUG significantly improved in RTI but not RT or control groups from baseline; there was no	**73**	Lack of statistical validity reduced quality of the study

Intervention class	Reference	Investigated population	Sample size	Intervention/comparator	Primary outcome	Main result	Quality score (%)	Comments
		duration		(RTI) with additional "unstable" devices (e.g., BOSU) that was progressively increased 1 hour x 2 days over 3 months 1 hour twice a week over 3 months vs. control (social activities but no exercise (1 day a week for 3 months)		significant difference between the two intervention groups Secondary outcome was ON UPDRS III that significantly improved from baseline in the RTI (- 4.5 score RTI) but not in PT (- 1.1 score) or control (+1.6 score) but with no significant difference between groups		
	Stozek J. Aging clinical and experimental research (2016)[68]	PD H&Y 1.5-3	61	Rehabilitation-training program in small groups (2-3 people) focused on mobility, balance and gait exercises, consisting of 28 sessions vs. controls (medication only) for 4 weeks	Balance (tandem stance and the Pastor test (shoulder tug). Gait (10 meter walk at preferred speed and 360-degree turn). Physical Performance Test (PPT) and timed motor activities at 4 weeks and 4 weeks post intervention	The rehabilitation group significantly improved in balance and gait outcomes, Physical Performance Test (PPT) score, and timed activities both improved in comparison to the control group and baseline	**62**	Study limitations include lack of an active control group, lack of rater blinding, and a short duration of follow-up (one month post-end of treatment only)
	Collett J. Journal of neurology, neurosurgery, and psychiatry (2017)[65]	PD; mean disease duration 4.8/5.3 years	105	Minimally supervised program: Workbook-based exercise program consisting of 30 minutes of aerobic and 30 minutes of resistance exercise vs. handwriting and hand exercises	2-minute walk test	No significant differences between groups in any outcomes although the effect sizes were greater in the exercise group	**74**	Only 70% of subjects adhered to the recommended exercise. It was not designed primarily as an efficacy study
	Santos S. M. European journal of physical and rehabilitation medicine (2017)[48]	PD; H&Y ≤3; mean disease duration 5.4 - 5.6 years	40	Balance training (BT) focusing on functional independence and gait, or to resistance training (RT) focusing on lower limbs and trunk, both supervised by trained physiotherapists The 60-minute sessions were held twice a week, 24 sessions in total	Balance assessed on force platform with center of pressure sway measures in different balance conditions	Significant improvement ($p<0.02$) was reported in favor of BT for one-legged standing on force platform, with 36% improvement for BT compared with 0.07% for RT	**72**	Limitations include a high number of early terminations, including due to falls during therapy in both groups (>3 falls in 8 patients, 1 fall in 1 patient). It is not clear whether corrections for multiple comparisons were applied
	Volpe D. Clin Rehabil (2017)[62]	PD with postural deformities	30	A water-based physiotherapy protocol in a therapeutic swimming pool, vs. non-water-based physiotherapy protocol Intensive treatment (60-minute sessions, five days per week) for 8weeks	Changes in the degree of cervical and dorsal flexion and in the angle of lateral inclination of the trunk (evaluated by means of a posturographic system)	Only patients treated with the water-based protocol showed a significant improvement of trunk posture with a significant reduction of cervical flexion (water-based group: -65.2°; non-water-based group: +1.7°) and improved dorsal flexion and lateral inclination	**68**	The clinical relevance of the primary outcome measure reduces interpretation

Intervention class	Reference	Investigated population	Sample size	Intervention/comparator	Primary outcome	Main result	Quality score (%)	Comments
						Both groups improved significantly in the secondary clinical outcomes (UPDRS part III, PDQ-39, Timed Up and Go Test, Berg Balance Scale, Falls Efficacy Scale), without between-group differences		

Supplementary table e7: Movement Strategy Training: Exercise- and technology based studies

Intervention class	Reference	Investigated population	Sample size	Intervention/comparator	Primary outcome	Main result	Quality score (%)	Comments
Exercise-based	**Braun S. Journal of physiotherapy (2011)[73]**	PD; H&Y 1-4	47	Mental imagery (individualized, tailored to each patient, imagining attempts at movements) vs. relaxation (control group) for 6 weeks	Timed up and Go test, Visual Analogue Scale (participants and therapists), and 10 meter walk test.	There were no differences between the two study arms, both of whom showed motor improvement from baseline	**72**	
	Shen X. J Rehabil Med (2012)[74]	Mild-moderate PD without falls in the previous 12 months	29	60 minutes, 3 times a week per session) of repetitive step training (volitional and compensatory) with preparatory visual cues vs. controls (lower limb strength training) for 4 weeks	Stability measures and UPDRS III posture/gait subscores	The repetitive step-training group showed significant improvements in limit of stability (LOS) parameters (reaction time by 18% and movement velocity by 43%), UPDRS postural and gait subscores (items 27-30, by 30%) and stride length (by 8%). Gait speed increased significantly after training in both groups, by 5-6%. 95% CI values were not reported	**70**	No falls were recorded during study
	Capecci M. Arch Phys Med Rehabil (2014)[77]	PD with mild-to-moderate postural disorders	20	Postural rehabilitation (proprioceptive and tactile stimulation, with stretching and postural re-education combined with and without Kinesio taping of the back muscles as additional treatment) vs. controls (no intervention) for 4 weeks	Trunk Berg Balance Scale, Timed Up and Go, and degrees of trunk bending in the sagittal and coronal planes	All patients in postural rehabilitation group showed a significant improvement in trunk posture (in both the sagittal and coronal planes) compared with baseline, at the end of treatment and at one month after the end of treatment. Measures of gait and balance also improved. There was no additional gain from complementing postural rehabilitation with Kinesio taping	**55**	The clinical relevance of the primary outcome measure reduces interpretation
	Canning C. G. Neurology (2015)[70]	PD with one or more falls in the past year or at risk of falls based on physical assessment	231	Minimally Supervised Exercise vs. usual-care control groups. Exercises were practiced for 40 to 60 minutes, 3 times weekly for 6 months	Fall rates and proportion of fallers during the intervention period	There was no significant difference between groups in the rate of falls (incidence rate ratio [IRR] = 0.73, 95% CI 0.45-1.17) or in the proportion of fallers.	**77**	Preplanned subgroup analysis revealed a significant interaction for disease severity. In the lower disease severity subgroup (motor UPDRS score ≤26), there were fewer falls in the exercise group compared with controls (IRR = 0.31, 95% CI 0.15-0.62), while in the higher disease severity subgroup, there was a trend

Intervention class	Reference	Investigated population	Sample size	Intervention/comparator	Primary outcome	Main result	Quality score (%)	Comments
								toward more falls in the exercise group (IRR = 1.61, 95% CI 0.86-3.03)
	Wong-Yu I. S., et al. Parkinsonism Relat Disord (2015)[180]	Moderately advanced PD	84	A mixed indoor and outdoors balance training vs. upper limb exercises, both for 2hrs/week administered by trainer for 8 weeks	Balance Evaluation Systems Test (BESTest) (measure of balance, stability and biomechanical constraints) at 8 weeks (end of treatment) and 12 months follow-up	BESTest was significantly improved in the experimental group expressed as 10.7% improvement vs. 0.8% for control group ($P < 0.001$). This was maintained after 12 months follow-up (8.2% vs. 0.9%, $p = 0.001$)	**70**	There were >10% losses to follow-up and the clinical importance of the BESTest is unclear
	Wong-Yu I. S. Arch Phys Med Rehabil (2015)[72]	PD: no prior falls	70	Balance (BAL) group received 4 weeks of indoor and 4 weeks of outdoor balance training (2 hours / week). The control (CON) group received 8 weeks of upper limb training. Both were instructed to perform 3 hours of home exercise weekly	Mini-Balance Evaluation Systems Test (Mini-BESTest), Timed Tests (Timed Up and Go (TUG), and dual-task TUG tests); ratios of nonfallers to fallers and noninjurious to injurious fallers, total and injurious fall rates, times to first falls and injurious falls	At 8 weeks and then 6 months post training, the BAL group showed significant improvement compared to CON group in Mini-BESTest total scores, timed tests (all $p<0.05$). The number of injurious fallers was significantly lower in the BAL group at 6 months (2 vs. 7 patients, $p<0.05$)	**70**	Reduced quality score as unclear whether patients had motor fluctuations; whether their medical treatment remained unchanged and not stated whether a statistical correction for the large number of assessments was performed
	Agosti V. Neurol Sci (2016)[58]	PD without specific gait problems	20	A Global Postural Reeducation (GPR) method (stretching of antigravity muscles to improve contraction of antagonist muscles and improve gait) 3 times a week for individual 40 min sessions vs. controls (no intervention) for 4 weeks	Kinematic gait parameters measuring thigh, knee and ankle function and UPDRS-III scores	All primary outcomes significantly improved in the intervention group at all time points (4, 8 & 12 weeks) vs. controls	**60**	The lack of blinding and lack of intervention in the control group reduced the quality score
	Landers M. R. Clin Rehabil (2016)[76]	Community-based PD subjects	49	4 randomly allocated groups; balance training + "Internal focus" training; balance training vs. "external focus" training balance training vs. no training and no intervention	"Sensory Organisation Test" = computerized method of assessing balance, and Berg Balance Test	The study was discontinued mid-way following a negative futility analysis; thus, all 4 groups improved from baseline, regardless of intervention with no significant difference between groups	**54**	Power calculations reported that 22 subjects per group should be allocated, but the study was stopped at 12-13/group. Other limiting factors include lack of clinical information regarding PD patients such as fluctuations and dosing of Parkinson medications
	Morrone M. European journal of physical and rehabilitation medicine	PD with posture deformity	20	"Perceptive-rehabilitation" ("Su-Per"; a rigid wooden surface with latex cones that is designed to improve perception of alignment of the trunk	Objective measure of a range of spinal angles using an infrared camera	There was a significant improvement on kyphosis angle using the Su-Per after one month ($z= - 2.701$, $p =$	**65**	Important baseline clinical features related to PD are not reported including medications, and presence of

Intervention class	Reference	Investigated population	Sample size	Intervention/comparator	Primary outcome	Main result	Quality score (%)	Comments
	(2016)[75]			via cognitive-perceptive tests) vs. conventional physiotherapy (a standard range of active joint mobilization and stretching) All subjects had 10 x 45 min sessions over 4 weeks	after 3 weeks; although the reported data stated one month	0.007) with no change in the control physiotherapy group; and no significant changes in lumbar lordosis or sagittal postural stability angle in either group		posture related to motor fluctuations. Patients developed redness over back from pressure of cones but this was not reported as an adverse event
	Schlick C., et al. Clin Rehabil (2016)[182]	PD H&Y 2-4;	23	12 training sessions within 5 weeks of visual cues combined with treadmill training vs. only treadmill training	Outcome measures were gait speed, stride length, and cadence. Functional tests included Timed Up and Go (TUG) Test, UPDRS and Freezing of gait-questionnaire at baseline; at 5 weeks (end of treatment) and then after 2 months follow up	At 5 weeks gait speed and stride length had increased in both groups. Patients receiving the combined training scored better in the TUG compared with pure treadmill training ($p \leq 0.05$). At 2 months (n=13), patients who underwent the combined training sustained better results in gait speed and stride length ($p \leq 0.05$) and sustained the improvement in the TUG ($p \leq 0.05$).	**54**	Limitations of the study include unclear clinical details related to fluctuation; lack of blinding, and a high rate of losses to follow-up (35% losses)
	Sparrow D. J Neurol Phys Ther (2016)[71]	Mild-moderate PD	23	3 months of active exercises (highly challenging, progressive, group balance exercise program), twice weekly for 90 minutes, vs. usual care [inactivity],	Falls rate, balance (Mini-BESTest), and fear of falling (Falls Efficacy Scale-International [FES-I])	There was an estimated 37% decline in falls rate per month (95% CI 24%-48%). Improvements were also observed in the Mini-BESTest (p=0.037) and FES-I (P=0.059)	**62**	There were two episodes of lower limb musculoskeletal pain that were considered to be related to the intervention The study was limited by a small sample size (only 16 patients completed the study)
Technology-based	**El-Tamawy M. S. Annals of Indian Academy of Neurology (2012)[87]**	Mild-moderate PD	30	"Routine", low-intensity and individually adapted physiotherapy program, (passive stretch, balance training, active exercises for muscle strength, and walking), 45 minutes 3 times weekly for 8 weeks; vs. "proprioceptive neuromuscular facilitation technique", (treadmill training and the use of vibratory devices inserted into the patients´ shoes and activated by the push-off phase of gait), over 6-25 minutes - this intervention was administered in addition to the physiotherapy program of the control group	Multiple outcomes:	Significant changes from baseline and between groups, favoring the combined treatment, were observed in all listed outcomes including cadence, stride length, walking speed and walking distance as well as hip and knee flexion and ankle dorsiflexion. 95% CI were not stated	**54**	Presence of motor complications not reported. Reduce quality score as active intervention occurred in addition to the physiotherapy program of the control group, which did not include treadmill training
	Picelli A. Parkinsonism	PD H&Y 3-4	34	Robot assisted gait training (device with harness/rope attachments	Berg Balance scale, Nutt's Rating at 4	Results favored robotic training: BBS p<0.001 at 4	**67**	

Intervention class	Reference	Investigated population	Sample size	Intervention/comparator	Primary outcome	Main result	Quality score (%)	Comments
	Relat Disord (2012)[82]			assisting propulsion of gait) vs. general physical therapy (control group, not posture/gait specific, i.e. joint mobilization, stretching, coordination exercises for 4 weeks	weeks (end of treatment) and 8 weeks	and 8 weeks; Nutt p=0.001 at 4 weeks and p=0.002 at 8 weeks		
	Pompeu J. E. Physiotherapy (2012)[84]	Early-stage PD	32	Nintendo Wii™-based motor cognitive training: 10 Wii Fit™ games selected for their potential effect on balance training vs. balance exercise therapy: stretching, strengthening and balance exercises without feedback or cognitive stimulation, (two 1hr sessions per week for 7 weeks)	UPDRS-II; Berg Balance Scale (BBS) and measures of Static balance using a Unipedal Stance Test	Both groups showed improvement in the UPDRS-II (mean differences of -0.7 [95% CI, -2.2 to 0.7] and -1.0 [95% CI, -1.9 to -0.1] points between before training and after training, in the experimental and control groups, respectively), but there was no significant difference between the experimental and control groups	**70**	Not clear if the study was sufficiently powered and there was no control group that received no intervention
	Bhatt T. Physical therapy (2013)[88]	Moderate PD, falls had occurred in 62% Healthy controls	21	Audiovisually cued training (verbal commands and cues on screen representing the patient´s center of mass; 3 times a week for 4 weeks) versus no training Compared with 12 matched healthy controls (who were younger than PD subjects; did not receive training and were assessed only once	Objective posture and balance measured with an electronic motion analysis system	After training, PD patients had improved backward stability improved through increased forward center-of-mass velocity at seat-off and forward balance loss was reduced due to a posterior shift in the center-of-mass position	**48**	Clinical features of the patients were not clear including motor complications. The study was unblinded and the clinical relevance of the outcome measures is uncertain
	Kegelmeyer D. A. Gait Posture (2013)[89]	PD patients > 50 years Falls in the previous 6 months had occurred in 52% able to walk 10 meters independently	27	5 different assistive devices (cane, standard walker, 2-wheel walker, 4-wheel walker, U Step walker with a laser as a visual cue) maneuvering around objects vs. none	Gait assessed using GAITRite System	Significant differences were found in a several comparisons. 95% CI were not stated. Seven falls occurred, 3 without walking assistance, 4 with the cane; stumbles were similarly more frequent with these modalities and also occurred with the standard and 2-wheel walkers. Freezing occurred with all devices, most frequently with the 2-wheel walker.	**45**	Conclusions are limited due to study design of a crossover study with six arms per patient and a small sample size. The statistical methods do not appear to have taken the large number of assessments into account
	van den Heuvel M. R. Parkinsonism Relat Disord (2014)[81]	PD H&Y 2-3	33	Commercially available interactive dynamic exercises with an "avatar" to provide feedback on balance training vs. conventional balance training for	Functional reach test of balance stability	No significant difference between the two groups	**81**	

Intervention class	Reference	Investigated population	Sample size	Intervention/comparator	Primary outcome	Main result	Quality score (%)	Comments
				2 days a week for 60 min for 5 weeks				
	Picelli A. Clin Rehabil (2015)[83]	PD H&Y 3	66	Robotic gait training vs. balance training 12, 45-minute treatment sessions, 3 days a week, for 4 consecutive weeks	Berg Balance Scale	No significant differences were found between the groups in primary and secondary UPDRS outcomes	**76**	Presence of motor fluctuations were not excluded but motor state was not controlled for during the exercises
	Ginis P. Parkinsonism Relat Disord (2016)[85]	PD H&Y 2-3	40	Wearable biofeedback intervention (using Smart Phone technology with an inertial measurement Unit ("CuPiD" system/"App")) vs. personalized feedback (weekly visit by researcher and diary) and all received weekly visits and were instructed to perform home-based gait training (30 min x 3d/week walking) for 6weeks	Gait speed under dual tasks and usual conditions	Both groups improved compared to baseline (e.g., dual task improved by 13% for CuPiD vs. 5.8% for control pre vs. post test) but with no-significant difference between the groups	**54**	Lack of clinical information on baseline characteristics of the participants, effects of PD medications on outcomes unknown and lack of blinding of the outcome measures reduces quality of the study
	Mirelman Anat The Lancet (2016)[78]	Subjects (aged 60 -90 years) with self-reported 2 or more falls in last 6 months. PD subgroup	302 (130 PD)	Virtual reality (V-TIME) plus treadmill, compared to treadmill alone ; 45 min 3 times a week for 6 weeks	Incident rate of falls over 6 months after the end of training	Incident rate of falls significantly decreased in the total group with V-TIME vs. treadmill alone. In the PD subgroup there was a similar significant reduction IRR 0.45 CI 0.24 - 0.86; p = 0.015) that persisted after adjusting for disease severity	**90**	The study was not statistically powered for the PD subgroup There was limited clinical information on PD groups at baseline (total levodopa equivalent; presence of fluctuations)
	Yang W. C. Journal of the Formosan Medical Association Taiwan yi zhi (2016)[80]	PD (55-85 years); H&Y 2-3	23	Home-based virtual reality balance training (custom-made virtual reality balance training system) vs. conventional home balance training (trained by a physical therapist) Twice weekly training sessions (50 minutes each) over 6 weeks	Berg Balance Scale	Both groups performed better in the Berg Balance at 6 weeks and 8 weeks vs. baseline, but with no significant between-group differences	**66**	
	Carpinella I. Arch Phys Med Rehabil (2017)[79]	PD H&Y 2-4	42	20 balance and gait sessions of either physiotherapy without biofeedback vs. tailored tasks using a Gamepad (The wearable sensors provided online visual and acoustic feedback by showing avatars replicating the patients´ movements) for 45 minutes 3 times a week for X weeks	Berg Balance Scale and 10-meter walk test	Significant differences in Berg Balance Scale scores suggested better balance performances of the experimental group posttraining (difference: 2.3 points, SD: 3.4; p=0.047) vs. physiotherapy without biofeedback and at 1 month follow-up (p=0.018)	**42**	Limitations include lack of clinical details on fluctuations; 5 early discontinuations without intention to treat analysis and a lack of correction for multiple comparisons
	Shen X. Neurorehabilitation and neural repair (2015)[86]	PD H&Y 2-3	51	Technology-assisted balance and gait training (dancing software, a pressure-sensitive carpet and 2 light-sensitive rods) vs. an active control	Number of fallers and fall rate at 3 moths (end of treatment and then 6	There were fewer fallers in the experimental group than in controls at 3, 6 and 15 months (p <0.05). The	**67**	Patients with motor fluctuations were excluded from participation. It is not stated whether medical

Intervention class	Reference	Investigated population	Sample size	Intervention/comparator	Primary outcome	Main result	Quality score (%)	Comments
				group doing strengthening exercises for 3 months	and 15 months follow-up	experimental group had a lower fall rate than the control group at 3 and 6 months (incidence rate ratio: 0.111-0.188, p <0.05)		treatment remained unchanged during the study

Supplementary table e8: formalized patterned exercises

Intervention class	Reference	Investigated population	Sample size	Intervention/comparator	Primary outcome	Main result	Quality score (%)	Comments
Formalized patterned exercises	**Li F. The New England journal of medicine (2012)[90]**	PD H&Y 1-4 (>1/3 with H&Y ≥3)	195	Tai chi (a balance-based exercise) vs. progressive resistance training vs. stretching (control group) 60-minute sessions 2x week for 24 weeks	Primary outcomes (maximum excursion, directional control) were based on measurements from computerized posturography at 24 weeks (end of treatment) and 68 weeks follow-up	The primary outcome measurements were significantly better in the tai chi group than in the other groups Secondary measurements favored both exercise intervention groups, with less falls and improved functional capacity in the tai chi group compared to controls The effects of tai chi were sustained 3 months after treatment	**88**	
	Duncan R. P. Neurorehabilitation and neural repair (2012)[95]	PD H&Y 1-4	62	Tango (one hour, twice weekly) vs. control (baseline activity) 12 months	MDS-UPDRS III	UPDRS (off medication) was improved in dancers vs. controls (reduced by 28.7%: 12.8 points, with multiple secondary measures in favor of improvement in the dance group	**69**	While the trial claims to provide evidence of "disease modification" it does not attempt to differentiate this from symptomatic effects
	Foster E. R. Arch Phys Med Rehabil (2013)[96]	PD H&Y 1 - 4	62	Argentine tango dance classes (twice-weekly) vs. no intervention for 12 months	MDS-UPDRS III	No significant change from baseline in the control group, whereas the tango group had a reduction of 28.7% (12.8 points).	**60**	
	Amano S. Parkinsonism Relat Disord (2013)[92]	PD H&Y 2-3	45	Two sites: Project 1: tai chi vs. qi-gong for 60 minutes 2 days/week. Project 2: tai chi (using same method as per project 1) vs. attending a living–well center with no active intervention for 3 days/week for 16 weeks	Multiple objective Gait measures and UPDRS III	No significant difference in any of the outcome measures	**53**	The final number of subjects in the statistical analysis is unclear; as are any changes that occurred in medications during the study
	Volpe D. BMC geriatrics (2013)[97]	Moderately advanced PD	24	Irish set dancing (90 minutes of weekly group dancing) vs. standard individualized physiotherapy for 6 months	UPDRS III	The Irish dance group showed significantly better improvement in UPDRS III at 6 months compared to baseline and the standard physiotherapy group (F1, 23); 6.35, ANOVA) p = 0.19)	**58**	
	Formalized patterned exercises	Mild-moderate PD	46	Dance vs PD exercise group vs. non-intervention. The dance and PD exercise groups performed one 60-min session per week for 12 weeks	Timed Up-and-Go Test (TUG) and Berg Balance Scale (BBS)	Interactions in favor of the dance group were found in TUG step number and, BBS, , and UPDRS (2 way ANOVA)	**50**	

Intervention class	Reference	Investigated population	Sample size	Intervention/comparator	Primary outcome	Main result	Quality score (%)	Comments
	Zhang T. Y. Am J Phys Med Rehabil (2015)[91]	PD H&Y 1-4	40	Tai chi (1 hour 2x week) vs. multimodal exercise training program for 12 weeks	Berg Balance Scale	The multimodal exercise group improved significantly on Berg Balance Scale: change 2.00 (2.18), CI 0.14-1.47), while the tai chi group did not. Secondary outcome of UPDRS III also showed no significance in Tai chi vs multimodel exercise group	**81**	
	Rios Romenets S. Complement Ther Med (2015)[99]	PD H&Y 1-3 (< 3 falls in past 1 year)	33	Argentine tango vs. self-directed exercise for 12 weeks	MDS-UPDRS III	Change in MDS-UPDRS from baseline was not significantly different between the two groups	**68**	At baseline, the number of fallers and a history of physical activity were significantly higher among the self-directed exercise group. A high dropout rate (n = 9) occurred in the tango group due to protocol violation. AES were not significantly different: commonest was falls (tango = 11%, control = 7%)
	Ni M. Arch Phys Med Rehabil (2016)[94]	PD (H&Y 1-3)	41	Specifically-designed yoga program (YOG) vs. power training (PWR)2x week for 12 weeks vs.non-exercise control group for 12 weeks	UPDSR III	There were significant treatment effects of both interventions vs non-exercise on UPDRS III; effects sizes of -1.07 (- 1.91 to .23) for PWR and -1.20 (2.07 to .33) for YOG, with no significant difference between the two interventions	**57**	Major limitation of the study was the lack of blinding of raters with regards to treatment assignment. **Ni M. Complement Ther Med (2016)[93]** Not rated as subanalysis of same study. There were no adverse effects or injuries

Supplementary Table e9 Other Non-Pharmacological therapies

Intervention Class	Reference	Investigated population	Sample size	Intervention/Comparator	Primary Outcome	Main result	Quality score %	Comments
Occupational therapy	**Sturkenboom I. H. Lancet Neurol (2014)[100]**	PD with impaired ADLs	191	No occupational therapy (OT) vs. flexible, non-uniform occupational therapy program with a maximum of 16 sessions over 10 weeks	Canadian occupational performance measure (COPM)—assessing self-perceived performance in ADLs, and multiple caregiver assessments at 3 and 6 months	OT groups had significant improvement of COPM scores at 3, but not 6 months (1.2; 95% CI 0.8-1.6; p<0.0001); only one of nine caregiver assessments was improved at 3 months	**79**	A short course of OT provided sustained subjective improvements but these were not validated by caregiver surveys
	Clarke C. E. JAMA Neurol (2016)[101]	PD H&Y 1-4	762	Physiotherapy and occupational therapy delivered by therapists in the community in a manner standard for usual practice and individually tailored to each patient using a patient-centered goal-setting approach (median of 4 therapy sessions (range 1-21), with mean time per session of 58 minutes) vs. no therapy for 8 weeks	The patient-reported Nottingham Extended Activities of Daily Living (NEADL) Scale score at 3 months	The trial found no difference between groups on primary outcomes (NEADL total difference 0.5 points (-0.7 to 1.7), 95% CI, p=0.41)	**78.5**	Recruitment favored patients for whom "the investigator was uncertain would require PT or OT," causing an inherent floor effect in patients who may not have needed therapy. The NEADL is not validated in PD and has been used for outcomes in stroke and aging. There were no significant AEs
Speech therapy and swallowing problems	**Manor Y. Parkinsonism Relat Disord (2013)[102]**	PD with swallowing disturbances	42	Video-assisted swallowing therapy (VAST) vs conventional therapy (control) 6 interventional sessions	Swallowing function - assessed by fiberoptic endoscopic evaluation of swallowing (FEES)	Significant improvement in swallowing functions following both interventions. Significantly greater reduction in food residues in the pharynx in the VAST group compared to the control group (95% CI not reported).	**66**	The lack of information on motor fluctuations and no specified primary outcome measure limits interpretation
Acupuncture	**Cho S. Y. Parkinsonism Relat Disord (2012)[107]**	Stable PD	43	Acupuncture vs. bee venom acupuncture vs. placebo twice weekly using 10 points for 8 weeks	Total UPDRS, ; H&Y score	Significant improvements in the analyzed patients in both acupuncture groups compared to placebo, with no significant differences between the active treatment arms	**56**	Losses to follow-up were >10%
	Hartmann A. PloS one (2016)[106]	PD H&Y 1-3	40	100 µg bee venom (via intradermal injections) vs. equivalent volumes of saline as placebo monthly for 11 months	UPDRS III	No significant change	**86**	Due to safety concerns, only small doses of bee venom were used,

								comparable to those used in an allergic desensitization protocol, Additionally, the study was likely underpowered Four patients were excluded during the trial due to positive skin tests but no systemic allergic reaction was recorded; otherwise no adverse events
Repetitive transcranial magnetic stimulation (rTMS)	**Okabe S. Mov Disord (2003)[105]**	PD mean H&Y 3	85	rTMS to right motor cortex vs. occipital cortex vs. sham once a week for 8 weeks	Total and motor UPDRS	Total and motor UPDRS improved in all groups at week 4 and 8 with some loss of effect at weeks 12 and 16; there was no significant effect of rTMS on the motor cortex	**70**	The number of dropouts was not reported and it was unclear how many subjects were included in the analysis. No adverse events
	Hamada M. Mov Disord (2008)[103]	PD H&Y 2-4	99	High-frequency rTMS vs. sham stimulation over the supplementary motor cortex with weekly sessions for 8 weeks	UPDRS III and total UPDRS evaluated at weeks 2, 4, 6 and 8 during stimulation and at weeks 10 and 12 post-treatment	Significant improvement in UPDRS III and total scores between weeks 4 and 12 with rTMS compared to sham stimulation (2 way ANOVA with post hoc $p < 0.005$). Subgroup analysis according to H&Y stage did not show any effect of disease severity on this outcome	**73**	Ratings were performed when subjects were midway between on and off, which was not clearly defined. No adverse events
	Yang Y. R. Neurorehabilitation and neural repair (2013)[104]	PD subjects, H&Y 2-3 who were able to walk independently	22	rTMS vs. sham to the motor cortex contralateral to the more affected side for 6 min followed by treadmill for 30 minutes, for 12 sessions for 4-weeks	Objective speed of gait	Speed of gait functions; timed 10-meter stand-walk test was significantly improved by rTMS but treadmill speed was not significantly altered by rTMS	**74**	The dual intervention (rTMS and treadmill) and the lack of other PD-related measures of gait function limits conclusions regarding clinical importance
Transcranial direct current stimulation (tDCS)	**Costa-Ribeiro A. J Rehabil Med (2016)[106]**	PD (including those with motor fluctuations; mean disease duration >6 years)	22	10 sessions of active anodal tDCS over the supplementary motor area vs. sham tDCS over a period of 4 weeks	Timed Up and Go test (TUG) at 4 weeks (end of treatment) and at one month follow-up	Both groups improved compared to baseline, There were no significant differences between the treatment groups. These gains were maintained only in the experimental group at 1-month follow-up.	**68.2**	Limitations include small sample size. It is unclear whether investigators were blinded and whether all patients completed the study. Side effects were partially recorded but not reported in results

Supplementary table e10 Treatments for motor fluctuations (F)

Intervention class	Reference	Investigated population	Sample size	Intervention/comparator	Primary outcome	Main result	Quality score (%)	Comments
Dopamine agonist: pramipexole ER	**Schapira A. H. Neurology (2011)[109]:**	Advanced PD; >2h OFF time/day	518	Once daily pramipexole extended release (ER) (average dose 2.7mg/d) vs. 3 times daily pramipexole immediate release (IR) (2.8 mg/d) over 18 weeks	Change in OFF time (hours/day)	Significant effect of treatment; OFF-time decreased (from baseline means of 5.8–6.0 hours/day) by an adjusted mean of -2.1 (for pramipexole ER) and -2.5 (for pramipexole IR) vs. placebo -1.4 hours/day (p = 0.0199 and $p < 0.0001$)	**99**	249 pramipexole patients completed a further extension to 33 weeks, UPDRS II+III and off-time findings showed -10.1% change from 18-week values. No significant AEs
	Mizuno Y. Clin Neuropharmacol (2012)[31]	Advanced and levodopa undertreated PD (53.6% had motor fluctuations)	130	Pramipexole ER (average daily dose 3.36mg/d) and pramipexole R (3.54 mg/d)	No predefined efficacy endpoint	The mean OFF time (all patients) was pramipexole ER -0.9 hours/day and pramipexole IR -1.3 hours/day (both significant compared to baseline)	**86**	
Dopamine agonists: ropinirole / rotigotine	**Mizuno Y. Parkinsonism Relat Disord (2014)[110]**	PD with motor fluctuations	420	Randomized 2:2:1 to receive rotigotine (up to 16 mg/day), ropinirole (up to 15 mg/day) or placebo during a 16-week treatment period	Change in UPDRS III during ON	Difference in the change in UPDRS III during ON was -6.4 ± 1.2 (95% CI: -8.7 to -4.1; p < 0.001) between rotigotine and placebo and -1.4 ± 1.0 (95% CI: -3.2 to 0.5) between rotigotine and ropinirole, fulfilling the criteria for non-inferiority of rotigotine to ropinirole	**90**	Application site reaction was seen in 57.7% of the rotigotine patients and 18.6% in the ropinirole group (p < 0.001). Impulse control disorders were reported in 6.6% of those in the ropinirole group and 3.5 % of rotigotine and 3.5% of placebo; this was not statistically significant
Dopamine agonist: ropinirole PR	**Zhang Z. Parkinsonism Relat Disord (2013)[111]**	PD with ≥3h of awake OFF time	345	Adjunct ropinirole PR (mean dose 11.4 mg/day, maximum 24 mg/day vs. placebo for 24 weeks	Change in awake OFF time	Significant reduction in awake OFF time with ropinirole PR (2.1 hours) compared with placebo (0.4h; p<0.001; 95% CI for adjusted treatment difference, -2.27 to -0.26).	**89**	The most frequent AE reported in the ropinirole PR group was dyskinesia (17.7% vs. 2.9% for placebo) **Zhang Z. Current medical research and opinion (2015)[112]:**Open label extension study: 282 out of 295 enrolled patients completed. Commonest reason for withdrawal was AEs (3.1%). The most frequent AEs were dyskinesia (6.1%), dizziness (4.1%), nausea (3.4%), hallucinations (3.4%), somnolence (2.7%) and decreased weight (2.4%).

Intervention class	Reference	Investigated population	Sample size	Intervention/comparator	Primary outcome	Main result	Quality score (%)	Comments
								Sixty-eight patients (23.1%) experienced treatment-related AEs
Dopamine agonist: rotigotine	**Trenkwalder C. Basal Ganglia (2012)[113]**	One-year open-label follow-up data have been published following RECOVER (Trenkwalder C., et al. Mov Disord (2011)[183]:), a RCT comparing the effect of rotigotine and placebo on early-morning motor function. Of the 287 patients originally randomized and 284 who completed RECOVER, 84 entered the follow-up study, and 66 completed it; the low enrollment was due to manufacturing issues. UPDRS III during ON was the primary outcome and was improved by 5.8 points relative to open-label baseline and by 10.9 points relative to baseline of the double-blind study. The most common AEs were application site reactions (24%), somnolence (13%), hallucinations (13%), nausea (12%) falls (12%), dizziness (11%) and dyskinesia (11%). Twelve patients discontinued due to AEs, mostly site reactions. The findings suggest sustained motor efficacy of rotigotine over 1 year. No QS as extension study							
Prolonged-release levodopa IPX066	**Hauser R. A. Lancet Neurol (2013)[114]**	PD with motor fluctuations; at least 2.5 hours per day of OFF-time underwent	471	3 weeks of open-label immediate-release carbidopa-levodopa (IR-CL) dose adjustment followed by 6 weeks of open-label IPX066 dose conversion; then IPX066 vs. IR-CL vs. matched placebos for 13 weeks	OFF-time as a percentage of waking hours adjusted for baseline value	Covariate-adjusted end-of-study off-time means were 23.8% (SD 14.9) for IPX066 and 29.8% (15.8) for IR-CL (mean difference -5.97, 95% CI -9.05 to -2.89)	**98**	During dose conversion with IPX066, 5% of patients withdrew due to AEs, 3% withdrew due to lack of efficacy. During maintenance period, most common AEs: insomnia (3% of IPX066 vs. 1% IR-CL, nausea (3% vs. 2%), and falls (3% vs. 2%). Three cases of ICD occurred in IPX066 vs. 1 IR-CL (none were on dopamine agonists)
	Stocchi F. Parkinsonism Relat Disord (2014)[115]	PD with motor fluctuations despite stable carbidopa-levodopa-entacapone preparations (CLE)	91	6-week conversion from CLE to IPX066, followed by two 2-week, double-blind crossover treatment periods in randomized order, one on IPX066 (and placebo CLE), the other on CLE (and placebo IPX066), separated by a 1-week open-label IPX066 treatment	Mean percent daily OFF time during waking hours (from patient diaries)	IPX066 significantly lowered percent OFF time (24.0% vs. 32.5%; p<0.0001) and higher "on" time without troublesome dyskinesia (11.4 vs. 10.0 hours/day; p < 0.0001) vs. CLE	**86**	20.2% and 13.6% of patients reported AEs on IPX066 and CLE, respectively. The most common were dyskinesia (4 patients), insomnia (3), and confusional state (3) for IPX066, and fall (2) for CLE. The actual controlled treatment periods were only 2 weeks duration and that all patients experienced the effects of the active drug during the conversion phase and between treatments, which may have had an effect on their blinding.
Levodopa infusion	**Olanow C. W. Lancet Neurol (2014)[116]**	Advanced PD with motor complications	71	Jejunal placement of a percutaneous gastrojejunostomy tube followed by randomization to treatment with LCIG plus oral placebo, or to oral levodopa-carbidopa plus placebo intestinal gel infusion (control) for 12 weeks.	Off time (h/day)	Mean off-time decreased more in the LCIG group (n=35) compared to the control group (n=31) (difference -1.91h [95% CI -3.05 to -0.76]). Mean on-time without troublesome	**87**	Two (3%) of 71 patients discontinued due to complications of surgery including peritonitis in 1 patient and 63 (89%) had device-related complications, including tube dislocations,

Intervention class	Reference	Investigated population	Sample size	Intervention/comparator	Primary outcome	Main result	Quality score (%)	Comments
						dyskinesia increased more in the LCIG group compared to the control group (difference 1.86h [95% CI 0.56 to 3.17]).		percutaneous gastrojejunostomy insertion complications, stoma insertion complications, pump malfunctions, and pneumoperitoneum. Four patients had symptoms consistent with the possibility of polyneuropathy (1 in the LCIG group and 3 in the control group)
COMT inhibitor: Entacapone	**Rascol O. Clin Neuropharmacol (2012)[117]**	PD with motor fluctuations and OFF problems	723	Perampanel (4 mg/d), placebo, or the active comparator, entacapone (200 mg with each dose of L-dopa) 18 weeks	Change from baseline in mean total daily OFF time based on diaries	Entacapone significantly improved off time; entacapone - 1.29 (-1.63, -0.96) hours/day vs. placebo - 0.82 (-1.16, -0.48) hours/day (p = 0.034) No significant difference in daily ON time without dyskinesia	**87**	The study was included due to the large number of PD subjects receiving entacapone (n = 234, 66% completed) vs. placebo (n = 247, 69% completed) However the study was terminated early due to no efficacy of perampanel in other studies.
	Tolosa E. J Neural Transm (Vienna) (2014)[118]	PD with mild fluctuations (i.e., wearing off and none or mild dyskinesias)	95	Subjects were randomized to the same baseline dose of levodopa with either levodopa/carbidopa/entacapone (LCE) (100/25/200 or 150/37.5/200 mg tablets) or levodopa/carbidopa (LC) (100/25 mg°	UPDRS II and III	UPDRS III improved by mean -3.6±4.7 in the LCE group vs. -1.2±5.3 in the LC group (p = 0.010)	**80**	No significant AEs
COMT inhibitor: opicapone	**Ferreira J. J. Lancet Neurol (2016)[119]**	PD with end-of-dose motor fluctuations	600	Opicapone (5 mg, 25 mg, or 50 mg once daily), placebo, or entacapone (200 mg with every levodopa intake) for 14–15 weeks	Change from baseline to end of study in daily OFF time (as assessed by patient diaries)	Opicapone 50 mg was superior to placebo (mean difference in change from baseline -60.8 min, 95% CI -97.2 to -24.4; p=0.0015) and non-inferior to entacapone (-26.2 min, -63.8 to 11.4; p=0.0051). Opicapone 5 mg (p=0.056) or 25 mg (p=0.080) were not significantly different from placebo	**98**	The most common AEs were dyskinesias and insomnia. No change in liver function were reported
	Lees A. J. JAMA Neurol (2017)[120]		427	Opicapone (25mg, 50mg), placebo 14-15 weeks.	Change from baseline to end of study in daily OFF time (as assessed by patient diaries)	The 25 mg group did not achieve significant reduction in OFF time, but 50 mg group was reported to be significantly effective (adjusted treatment effect was -54.3 [95% CI, -96.2 to	**98**	The most common AEs were dyskinesia, constipation, and dry mouth and there was no change in liver function or incidence of severe diarrhea

Intervention class	Reference	Investigated population	Sample size	Intervention/comparator	Primary outcome	Main result	Quality score (%)	Comments
						-12.4] minutes; p=0.008, and the off-time reduction was sustained at 1 year (open label) follow-up		
	Ferreira J. J. European journal of neurology (2015)[121]	This pharmacokinetic study evaluated 40 PD subjects with motor fluctuations Opicapone (OPC) vs. placebo once-daily, up to 28 days (maintenance phase), placebo (n = 10) or 5 (n = 10), 15 (n = 10) and 30 mg (n = 10) OPC. The study was not designed to detect any significant differences in motor performance, but the exploratory analysis performed shows improvement in various motor outcomes, including a dose-dependent change in absolute OFF time corresponding to a percentage decrease of 4.2% (p > 0.05), 29.6% (p > 0.05) and 32.7% (p < 0.05) with 5, 15 and 30 mg OPC, respectively. No significant AEs were noted.							
Selective monoamine oxidase B inhibitor: rasagiline	**Stocchi F., et al. European journal of neurology (2011)[184]**	PD with motor fluctuations Sub-study of the previously published LARGO study	105	Rasagiline 1mg, vs. entacapone 200mg with each levodopa dose vs. placebo: hospitalized subjects undertook an overnight levodopa withdrawal for the partially defined OFF state assessments	Morning OFF UPDRS III	UPDRS III in the practically defined OFF state improved by - 5.64 units with rasagiline (p = 0.013 vs. placebo), but not with entacapone (p = 0.14 vs. placebo).	**—**	As this is a subgroup of a previously graded study; no additional QS is given.
	Zhang L. The international journal of neuropsychopharmacology (2013)[122]	PD with fluctuations	244	Rasagiline 1 mg/day or placebo for 12 weeks	Improvement in diary-based mean ON-time and OFF-time as compared to baseline	In the rasagiline group, OFF-time decreased by 1.7 hours (95% CI 1.478 to 2.018) and ON-time improved by 1.6 hours (95% CI 1.3 to 1.9).	**77**	Rasagiline was well tolerated Issues with statistics, such as not using ITT analysis, reduced the quality score
Selective monoamine oxidase inhibitor and Channel blocker: zonisamide	**Murata M. Mov Disord (2015)[123]**	PD with wearing off	389	4 week placebo run-in zonisamide 25mg vs. 50mg daily vs. placebo, with other PD medications remaining constant over 12 weeks	Change from baseline in daily OFF time to week 12	OFF time was reduced by 0.719 hours (SD 0.179, p=0.005) in the zonisamide 50mg group compared to the placebo group, without increase of dyskinesia No changes in UPDRS scores	**90**	The placebo run-in resulted in the pre-randomization elimination of 33 subjects No significant AEs
Selective monoamine oxidase Inhibitor and channel blocker: safinamide	**Borgohain R. Mov Disord (2014)[124]**	PD with motor fluctuations	669	Safinamide 100 mg/day (n = 224), 50 mg/day (n = 223), or placebo (n = 222) for 24 weeks	Change in ON time with no or non-troublesome dyskinesia	Significant effect of treatment with safinamide vs placebo:, the change in ON time with no or non-troublesome dyskinesia was +1.36 ± 2.625 hours for safinamide 100 mg, +1.37 ± 2.745 hours for 50 mg, and +0.97 ± 2.375 hours for placebo	**96**	There were no significant adverse events. **Borgohain R. Mov Disord (2014)[126]:** was an extension study; subjects continued on their randomized treatments (placebo, 50, or 100 mg/d safinamide) for an additional 18 months. Dyskinesia Rating Scale total score during ON was evaluated and there was no significant difference in the three arms, although safinamide was associated with a numerical

Intervention class	Reference	Investigated population	Sample size	Intervention/comparator	Primary outcome	Main result	Quality score (%)	Comments
								decrease in contrast to an almost unchanged score on placebo. AEs and discontinuation rates were similar on safinamide and placebo
	Schapira A. H. JAMA Neurol (2017)[125]	PD patients with OFF time of ≥1.5 hours per day (excluding morning akinesia) on stable levodopa treatment mean age 61.9 years)	549	Adjunctive safinamide vs. placebo During screening, each patient's regimen was optimized to minimize motor fluctuations. If no tolerability issues arose by day 14, the starting dose, 50 mg, was increased to 100 mg for 24 weeks	Change from baseline to week 24 in daily ON time without troublesome dyskinesia, as assessed from diary data	Mean (SD) change in daily ON time without troublesome dyskinesia was +1.42 (2.80) hours for safinamide, from a baseline of 9.30 (2.41) hours, vs. +0.57 (2.47) hours for placebo, from 9.06 (2.50) hours (least-squares mean difference, 0.96 hour; 95% CI, 0.56-1.37 hours; p<0.001)	**99**	The most frequently reported AE was dyskinesia (in 40 patients [14.6%] on safinamide vs. 15 [5.5%] on placebo; as severe event in 5 [1.8%] vs. 1 [0.4%]). Limitations include the fact that the diaries were only completed for 18 hours a day and that only one dose was tested
A_{2A} receptor antagonist: istradefylline	**Hauser R. A. Neurology (2003)[127]**	PD with both motor fluctuations and dyskinesia	83	Istradefylline up to 20 mg/day (n = 26), or istradefylline up to 40 mg/day (n = 28) placebo (n = 29) for 12 weeks,	Multiple outcomes	Change in percentage of daily OFF time in istradefylline was -7.1 +/- 2.0% (no 95% CI reported for any measure) compared with an increase of 2.2 +/- 2.7% on placebo (p = 0.008). OFF time decreased by 1.2 +/- 0.3 hours in the istradefylline group and increased by 0.5 +/- 0.5 hour in the placebo group (p = 0.004). ON time with dyskinesia increased in the istradefylline group (+0.6 hour) and decreased in the placebo group (-1.5 hours; p for difference=0.001); dyskinesia severity was unchanged. No differences were observed in change in UPDRS	**85**	24% of placebo subjects and 20% of istradefylline-assigned subjects withdrew early. Both doses were generally well tolerated, and nausea was the most common AE
	Hauser R. A. Mov Disord (2008)[128]	PD with motor fluctuations	231	Istradefylline 20 mg once daily (n=116) versus placebo (n=115) as an adjunct to levodopa over 12 weeks	Daily OFF time as measured by patient diaries	Daily OFF time was significantly reduced in the istradefylline group vs. the placebo group (-1.6 hours vs. 0.9 hours, p=0.03)	**90**	AEs include dyskinesia (mild or moderate in intensity), lightheadedness, tremor, constipation, and weight decrease were reported more often with istradefylline than

Intervention class	Reference	Investigated population	Sample size	Intervention/comparator	Primary outcome	Main result	Quality score (%)	Comments
								placebo (≥2% difference)
	LeWitt P. A. Annals of neurology (2008)[129]	PD patients with motor fluctuations	196	Istradefylline (40mg/day) vs. placebo for 12 weeks	Change in the percentage of daily OFF time	Change in percentage of daily OFF time was -10.8% (95% CI -13.46 to -7.52) for istradefylline and -4.0% (95% CI -7.73 to -0.31; p = 0.007) for placebo	**89**	Most frequent AEs were dyskinesia (30.2% istradefylline vs. 15.2% placebo), dizziness, insomnia, nausea, and falls; 3 deaths occurred (2 on active treatment, 1 on placebo), which were not attributed to the treatment.
	Stacy M. Neurology (2008)[130]	PD with motor fluctuations	395	Istradefylline 20 mg vs. 60 mg/day vs. placebo for 12 weeks	Change in the percentage of daily OFF time	Changes from baseline to endpoint in the percentage OFF time in the active groups compared with placebo were -4.35% (95% CI -8.16 to -0.54; p =0.026) for istradefylline 20 mg/day and -4.49% (95% CI -8.35 to -0.62; p = 0.024) for 60 mg/day	**78**	At baseline, OFF time differed among the arms and was 6.31 hours in the placebo group and 5.72 and 5.81 in the active treatment groups
	Mizuno Y., et al. Mov Disord (2010)[185]	PD with motor fluctuations	363	Istradefylline 20 mg vs. 40 mg/day vs. placebo for 12 weeks	Daily OFF time as measured by patient diaries	Daily OFF time was significantly reduced in the istradefylline 20 mg/day (-1.31 hours, p=0.013) and istradefylline 40 mg/day (-1.58 hours, p<0.001) groups, compared with placebo group (-0.66 hours)	**88**	The most common AEs were dyskinesia, (mild- moderate) (placebo, 2.5%; istradefylline 20 mg/day, 8.5%; istradefylline 40 mg/day, 6.4%), and nasopharyngitis (4.2%, 5.9% and 8.8%, respectively **<u>Extension Study:</u> Kondo T. Clin Neuropharmacol (2015)[132]:** This was an unblinded 1-year follow-up of 308 patients who received 20 or 40 mg of istradefylline, (depending on efficacy and tolerability). Daily OFF time remained similar to the findings at the end of the original double-blind study. Dyskinesia was observed in 21.4% of the patients. Other AEs included nasopharyngitis (24.4%), contusion (10.4%), constipation (9.4%) and hallucinations (8.8%)
	Pourcher E. Parkinsonism	PD with motor fluctuations	584	Istradefylline 10 mg vs. 20 mg vs. 40mg/day vs. placebo for 12 weeks	Daily OFF time as measured by	Improvement in the daily OFF time did not differ	**83**	The most frequently reported AE in the istradefylline

Intervention class	Reference	Investigated population	Sample size	Intervention/comparator	Primary outcome	Main result	Quality score (%)	Comments
	Relat Disord (2012)[133]				patient diaries	between istradefylline and placebo (1.1 hours in the 10 and 20 mg/day groups, 1.5 hours in the 40 mg group, and 1.4 hours in the placebo group)		groups was dyskinesia (placebo: 19.2%, istradefylline 10 mg/day: 21.6%, istradefylline 20 mg/day: 16.8%, and istradefylline 40 mg/day: 26.3%), The negative result was attributed to the large placebo effect seen in this study
	Mizuno Y. Mov Disord (2013)[131]	PD with motor fluctuations	373	Istradefylline 20 mg vs. 40mg/day vs. placebo for 12 weeks	Daily OFF time as measured by patient diaries	Daily OFF time as measured by patient diaries was significantly reduced in the istradefylline 20 mg/day (-0.99 hours, p=0.003) and istradefylline 40 mg/day (-0.96 hours, p=0.003) groups, compared with the placebo group (-0.23 hours)	**83**	Majority of istradefylline-treated patients were already on dopamine agonist therapy and entacapone at baseline (84-86% and 53-55%, respectively) The most common AE was dyskinesia, which was mild or moderate in severity (placebo, 4.0%; istradefylline 20 mg/day, 13.0%; istradefylline 40 mg/day, 12.1%); istradefylline was otherwise well tolerated
	Li Z. J. Current medical research and opinion (2015)[134]	PD with motor fluctuations	132	Istradefylline 20 mg/day plus sham-rTMS vs. istradefylline 40 mg/day plus sham-rTMS vs. placebo plus 1 Hz rTMS vs. placebo plus 10 Hz rTMS	Changes in ON-medication UPDRS part III score	Changes in ON-medication UPDRS part III score were -6.05, -6.39, -5.91 and -6.46 for Groups I (istradefylline 20 mg/day plus sham-rTMS), II (istradefylline 40 mg/day plus sham-rTMS), III (placebo plus 1 Hz rTMS) and IV (placebo plus 10 Hz rTMS), respectively (p=0.869 for between-group difference)	**64**	The study is limited by the lack of a proper placebo control group (i.e., placebo tablet plus sham-rTMS); use of ON-medication UPDRS III score as the primary outcome measure in this cohort of patients with motor fluctuations; and lack of reporting of diary outcomes in the rTMS-treated groups AEs events were not reported
Surgery: bilateral subthalamic nucleus deep brain stimulation (STN DBS)	**Okun M. S. Lancet Neurol (2012)[135]**	PD with ≥ 6 hours daily OFF time or moderate-to-severe dyskinesia	136	Stimulation within 7 days of implantation, or implantation without activation	Change in ON time without bothersome dyskinesia (i.e., good quality ON time) at 3 months, as recorded in patients' diaries	Both groups reported increased good quality ON time, greater in the stimulation group (4·27 h vs. 1·77 h, difference 2·51 [95% CI 0·87–4·16]; p=0·003)	**83**	This study demonstrated that verbal fluency deficits (the most common cognitive side effect of STN DBS surgery) are induced mainly by surgical implantation, rather than by stimulation. As noted by the authors, although constant-current devices have theoretical advantages over voltage-driven devices,

Intervention class	Reference	Investigated population	Sample size	Intervention/comparator	Primary outcome	Main result	Quality score (%)	Comments
								this study did not offer a comparison between the two types of devices
Surgery: bilateral (STN DBS) /GPI DBS	**Weaver F. M. Neurology (2012)[139]**	**<u>Extension Study:</u> Follett K. A. The New England journal of medicine (2010)[138]:** RCT of STN vs. GPi DBS with 36-month open label extension outcomes of GPi vs. STN DBS (n=89 and n=70) (no QS rating). Motor function improved significantly and this was similar between targets and stable over 36 months (OFF-medication ON-stimulation UPDRS part III scores improving from 41.1 to 27.1 for GPi DBS and 42.5 to 29.7 for STN DBS). The results for GPi DBS contrasts with several small case series suggesting that the efficacy of GPi DBS wanes over 1-3 years. There were some neurocognitive differences, with STN patients showing greater decline in the Mattis Dementia Rating Scale over time (p=0.01); however, the authors noted that STN patients were also slightly worse than GPi patients on some neurocognitive tests at baseline. Depression scores were comparable to baseline, with no group differences present. The outcomes continue to show equal efficacy for both targets; although side effects may be more in the STN vs. GPi group.						
	Odekerken V. J. Lancet Neurol (2013)[136]	PD with motor fluctuations	127	Bilateral GPi vs. STN after 12 months	Functional health as measured by the mean change in a generic disability scale (the Academic Medical Center Linear Disability Scale [ALDS° weighted by time spent in the OFF phase and ON phase	No significant difference was seen in either primary outcome	**93**	**Extension study. Odekerken V. J. Neurology (2016)[137]:** three-year follow-up (90 patients; 70% of the original cohort), with findings and conclusions similar to that of the original report. ITT analysis showed that STN DBS provided more off-phase motor improvement than GPi DBS (motor UPDRS score 28 vs. 33, p=0.04), but with a similar risk for cognitive, mood, and behavioral complications (86% STN and 83% GPi There were no differences in AEs. Eight patients were re-operated from bilateral GPi DBS (despite optimal electrode positioning in five) to bilateral STN DBS. In one patient with bilateral STN DBS, the right electrode was changed to GPi DBS (no QS)
Surgery: STN DBS/ medical therapy	**Schuepbach W. M. The New England journal of medicine (2013)[140]**	PD (mean disease duration 7.5 years) with early motor complications	251	DBS plus medical therapy vs. medical therapy alone after 2 years	Between-group difference in mean change from baseline to 2 years on the PDQ-39 summary index	The PDQ-39 mean score of the DBS group improved 7.8 points and the medical-therapy group score worsened 0.2 points (between-group difference	**89**	Serious AES occurred in 54.8% of the patients in the DBS group and in 44.1% of those in the medical-therapy group. Serious AEs related to surgical implantation or the

Intervention class	Reference	Investigated population	Sample size	Intervention/comparator	Primary outcome	Main result	Quality score (%)	Comments
						8.0 points; p=0.002; 95% CI 4.2 to 11.9)		DBS device occurred in 17.7% of patients
Surgery: STN DBS /GPI DBS	**St George R. J. Mov Disord (2014)[141]**	Advanced PD OFF H&Y 3-4	28	STN DBS vs. GPi DBS after 6 months	Posture and Gait subscores of UPDRS and 'BaG' scales for balance; baseline and after overnight withdrawal/on and off	Both clinical balance and gait testing in the off state after surgery were marginally better in the GPi than the STN group	**54**	Lower quality score due to methodological issues, and unclear of falls rate in subjects

Supplementary table e11 Treatments for dyskinesia

Intervention class	Reference	Investigated population	Sample size	Intervention/comparator	Primary outcome	Main result	Quality score (%)	Comments
Dopamine agonists: pramipexole	**Utsumi H. Internal medicine (Tokyo, Japan) (2013)[142]**	PD (mean disease duration 12.3 years) and peak-dose dyskinesia on levodopa and an ergot dopamine agonist	34	Add-on pramipexole (mean dose 1.2 mg/day) or the ergot dopamine agonist was switched to pramipexole (mean dose 2.1 mg/day) for 24 weeks	Core Assessment Program for Surgical Interventional Therapies (CAPSIT).	CAPSIT was significantly reduced from baseline only in the switch group but not in the add-on group. (However, none of the outcome values are reported as absolute figures but are only shown in graphs)	**50**	AEs occurred in 8.8%. Between-group comparisons were not reported. The lack of precise reporting of the outcome parameters limit the conclusions from this study.
NMDA receptor antagonist: amantadine	**Sawada H. PloS one (2010)[143]**	PD with dyskinesia	36	Amantadine 300mg/d (for 27 days) vs. placebo titrated at weekly intervals from 100mg, to 300 mg/day so the maximal dose was only taken for 1 week. There was a down-titration and washout before the second treatment phase.	Video-recording performed by the subject's family at home and a blinded rating of the Rush Dyskinesia Scale	Adjusted odds ratio for an improvement in RDSR with amantadine vs. placebo was 10.4% (2.0 to 47) p = 0.002. UPDRS IVa improved by - 1.83 (SD 1.56) vs. -0.03 (1.51) p < 0.05. There was no significant effect on motor fluctuations or UPDRS III.	**83**	Unusual statistics were performed using a change in RDRS expressed as < 0 as a "responder" or > or = 0 as a "non-responder"
	Goetz C. G. Mov Disord (2013)[144]	PD with dyskinesia	61	Amantadine (up to 300 mg/day) vs. placebo for 8 weeks	Objective to compare sensitivity to treatment effects, at 4 and 8 weeks, in 8 different dyskinesia rating scales	4/8 scales (Unified Dyskinesia Rating Scale (UDysR); Lang-Fahn, Parkinson Disease Dyskinesia scale (PDys-26) and CGI-C) demonstrated a significant improvement in dyskinesia after 8 weeks treatment with amantadine vs. placebo Using the UDysR, the mean change from baseline at 8 weeks for amantadine was -9.36 (SD 9.31) points vs. -3.60 (SD 7.77) points with placebo (p<0.001); with the Lang-Fahn scale the change was 2.44 (SD 3.32) with amantadine vs. 0.63 (SD 2.44) with placebo (p<0.001) and for the PDys-26, 4.47 (SD 10.51) points vs. 0.93 (SD11.74) for placebo (p<0.05)	**89.5**	No significant AEs
	Ory-Magne F. Neurology (2014)[145]	PD with dyskinesia	57	Amantadine (≥200 mg/d for ≥6 months) vs. placebo Parallel-group, wash-out study	Change from baseline in UPDRS dyskinesia subscore item 32 [duration] and item 33 [severity]	UPDRS items 32 + 33 deteriorated more in patients switched to placebo (+1.7 ± 2.0 units) as compared with those maintained on amantadine (+0.2 ± 1.5 units; p=0.003)	**94**	
Levetiracetam	**Wolz M. J Neural Transm (Vienna)**	PD with dyskinesia	34	Levetiracetam (mean final dose possibly 1800 mg) vs. placebo Treatment was escalated over 7 weeks with a 4-week	Change in modified Abnormal Involuntary	No significant change: AIMS mean % change from baseline was -1.5 (-26%) for levetiracetam (p =	**81.5**	No significant AEs, and no worsening of PD using UPDRS III

Intervention class	Reference	Investigated population	Sample size	Intervention/comparator	Primary outcome	Main result	Quality score (%)	Comments
	(2010)[147]			maintenance period.	Movement Scale (AIMS), UPDRS IV	0.332) and +0.9 (+13%) for placebo (p = 0.588) UPDRS IV significantly improved from baseline with levetiracetam (-1.0 (-20%); p = 0.012, but not in the placebo group (-0.4 (-8%); p = 0.306)		There was a large range of dyskinesia scores using AIMS at baseline which may have impacted validity of outcome measures
	Stathis P. Mov Disord (2011)[146]	PD with dyskinesia	76 but only only 38 subjects were enrolled	Levetiracetam vs. placebo 1-week escalation, then 2 weeks maintenance for 500 mg and then 1000mg/day with a 2-week wash-out period	Patient-competed diaries of "ON time with dyskinesia"	"ON time with dyskinesia" was reduced by 75 minutes (CI 3.31, 12.4, p = 0.002) for levetiracetam 1g/day; statistical comparisons were not clearly defined	**73.2**	Common AEs included dizziness and somnolence but only one subject withdrew.
Physical therapy	**Frazzitta G., et al. NeuroRehabilitation (2012)**[186]	PD H&Y 3 able to walk without assistance	50	Intensive inpatient therapy (IRT) with 3 hours/day, 5 days/week of treadmill, stability, and stretching exercises, and given instructions to continue these exercises vs. control group assigned to general home exercises	UPDRS IV and AIMS	The group undergoing IRT had better improvement in UPDRS II 33%, UPDRS III 29% and UPDRS IV 74% reduction than the control group (22%, 22% and 10% reduction, respectively). Abnormal Involuntary Movement Scale (AIMS) also improved by 71% vs. 8%. The IRT group was on less levodopa equivalents (- 210 mg vs. -30 mg).	**59.5**	

References: See manuscript for references.

Abbreviations

(ADL) Activities of daily living

(AE[s]) Adverse event(s)

(BMT) Best medical therapy

(COMT) Catechol-*O*-methyltransferase

(DA) Dopamine agonist

(DBS) Deep brain stimulation

(ER) Extended release

(GST) Global statistical test

(H&Y) Hoehn & Yahr

(IR-CL) Immediate-release carbidopa-levodopa

(ICD) Impulse control disorder

(IR) Immediate release

(IRT) Intensive rehab therapy

(ITT) Intention-to-treat

(LCIG) Levodopa-carbidopa intestinal gel

(MAOBI) Monoamine oxidase type B inhibitors

(OT) Occupational therapy

(OL) open-label

(PD) Parkinson's disease

(PDQ-39) Parkinson's Disease Questionnaire

(QS) Quality score

RCT Randomized controlled trial

(rTMS) Repetitive transcranial magnetic stimulation

(STN DBS) Subthalamic nucleus deep brain stimulation

(SPECT) Single-photon emission computed tomography

(UPDRS) Unified Parkinson's Disease Rating Scale