Fox SH, Katzenschlager R, Lim S-Y, Barton B, De Bie RMA, Seppi K, Poewe W, Rascol O, Goetz CG, Sampaio C on behalf of the MDS EBM Committee.

Update on treatments for motor symptom of PD

The recent MDS EBMR[1] on treatments for motor symptoms of PD reviewed level 1 studies published from Jan 2004 to Dec 2010. This was followed by a web-update on studies published between Jan 2011- Dec 2012[2.] We have continued the process and present a second web update of studies published Jan 2013 - Dec 2013. Publications were included if in press or 'early view' status at the time of literature searches.

The methodology used was the same as in prior reports. Inclusion criteria included pharmacological, surgical and non-pharmacological therapies, available in at least one country, assessed using level 1, randomized controlled trials (RCTs); where motor symptoms were the primary endpoint measured with an established rating scale or well described outcome. A quality assessment for each article was calculated using predetermined criteria; each drug was assigned 'Efficacious, Likely Efficacious; Unlikely Efficacious; Non-Efficacious or Insufficient evidence' according to the level of evidence. Safety was assessed and assigned as 'acceptable risk with no specialized monitoring, or with specialized monitoring; unacceptable or insufficient evidence'. The overall implications for clinical practice were then assessed and classed as 'Clinically Useful, Possibly Useful, Investigational, Unlikely Useful or Not Useful'. Interventions were considered for the following indications: prevention/delay of clinical progression; symptomatic monotherapy, symptomatic adjunct therapy to levodopa, prevention/delay of motor complications (motor fluctuations and dyskinesia), treatment of motor complications (motor fluctuations and dyskinesia).

For the treatment of the motor symptoms, 29 new studies qualified for review and the updates, according to indication presented in Tables 1 - 5 attached. Interventions where new studies have been published are indicated in **bold.** Changes in conclusions are indicated in *italics.*

Table 1 Treatments that may delay/prevent disease progression

Drug Class	Drug	Efficacy conclusions	Implications for clinical practice	Safety
MAO-B inhibitor	Selegiline	Insufficient evidence	Investigational	Acceptable risk without specialized monitoring
	Rasagiline	Insufficient evidence	Investigational	
Dopamine Agonist	Ropinirole	Insufficient evidence	Investigational	
	Pramipexole	***Non efficacious***	***Unlikely Useful***	
	Pergolide	Unlikely efficacious	Unlikely useful	
Others	Coenzyme Q10	Insufficient evidence	Unlikely useful	
	Vitamin D	***Insufficient evidence***	***Investigational***	
	Exercise	***Insufficient evidence***	***Investigational***	

PRAMIPEXOLE

Pramipexole in patients with early Parkinson's disease (PROUD): a randomised delayed-start trial. Schapira AH, McDermott MP, Barone P, Comella CL, Albrecht S, Hsu HH, Massey DH, Mizuno Y, Poewe W, Rascol O, Marek K. Lancet Neurol 2013;12(8):747-755.

This RCT double blind study evaluated 535 patients with PD (age 30 – 79y) diagnosed within 2 years; 261 were randomised to pramipexole (1.5 mg/day) and 274 to placebo. At 9 months, or as early as 6 months if considered necessary, placebo recipients were

switched to pramipexole. The primary endpoint was the 15-month change from baseline in the total UPDRS score. At 15 months (n=411), 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). In a neuroimaging substudy (n=123), the adjusted mean change in striatal (123)I-FP-CIT binding was -15.1% (SE 2.1) for early and -14.6% (2.0) for delayed pramipexole (difference -0.5, 95% CI -5.4, 4.4, p=0.84). 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. By clinical and neuroimaging measures, pramipexole showed no evidence for different outcomes in denovo PD subjects when used immediately compared to delayed for 6-9 months. Quality Score (QS) = 90%

VITAMIN D

Randomized, double-blind, placebo-controlled trial of vitamin D supplementation in Parkinson disease. Suzuki M, Yoshioka M, Hashimoto M, Murakami M, Noya M, Takahashi D, Urashima M. Am J Clin Nutr 2013;97:1004–1013**.**

The objective of this double-blind RCT was to evaluate whether vitamin D3 supplementation inhibits the progression of PD with emphasis on the vitamin D receptor (VDR) genotype. 114 treated PD patients (mean age 72±7y; disease duration range 2 – 60 months; baseline H&Y median 2.0 [range 1-5] and on levodopa average dose 150 – 600 mg/day) were randomly assigned to receive vitamin D3 supplements (1200 IU/d) or placebo for 12 months. Outcomes were clinical changes from baseline and the percentage of patients that showed no worsening of the modified H&Y stage and UPDRS. All scores were assessed on therapy. 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]). Interaction analyses showed that the genotype *VDR fok1* modified the effect of vitamin D3 on H&Y (P-interaction=0.045), UPDRS (P-interaction=0.039). 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. QS 76%

EXERCISE

Effects of a formal exercise program on Parkinson's disease: A pilot study using a delayed start design. Park A, Zid D, Russell J, Malone A, Rendon A, Wehr A, Li X. Parkinsonism Relat Disord 2014;20(1):106-111 (early view 2013).

The investigators in this RCT utilized a randomized delayed-start design to investigate a possible disease-modifying effect of exercise on disease progression. The primary outcome measure was change in UPDRS, with additional analysis of the get-up-and-go walking test, Tinetti Mobility test, and PDQ-39. Patients with relatively early-stage PD (within 3 years of diagnosis, H & Y< 3 and on dopaminergic treatment) were randomized to an early-start group (ESG; n=16) or a delayed-start group (DSG; n=15) 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. At week 48, there was no significant improvement in primary or secondary outcomes with early exercise, 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). The effects of medications on early vs delayed start outcomes were not included in the analysis. The study is limited by lack of measures of activity in the delayed-start group, small sample size, and single-blinding. QS 64%

Conclusions for disease-modifying therapies

The new study using the dopamine agonist pramipexole was a high quality study with negative outcomes; an efficacy conclusion of Non-Efficacious is thus assigned. In view of the unclear conclusions that can be drawn from change in total UPDRS score as a measure of disease progression, even in the setting of a delayed start design, a designation of Unlikely Useful has been given for practice implications. The study using Vitamin D, although good quality, was a single study with unclear conclusions due to

outcome measures (H&Y); thus a designation of Investigational has been given for clinical practice implications. The study evaluating early exercise was low quality and as such remains Investigational.

There were no new safety issues with any intervention

Table 2 Treatments for Symptomatic Monotherapy

Drug class	Drug	Efficacy conclusions	Implications for clinical practice	Safety
Dopamine agonists Non-ergot	Piribedil	Efficacious	Clinically useful	
	Pramipexole IR	Efficacious	Clinically useful	
	Pramipexole ER	Efficacious	Clinically useful	
	Ropinirole	Efficacious	Clinically useful	
	Ropinirole PR	Likely efficacious	Possibly useful	
	Rotigotine	**Efficacious**	**Clinically useful**	
	Apomorphine	Insufficient evidence	Investigational	
Ergot	Cabergoline	Efficacious	Clinically useful	Acceptable risk with specialized monitoring
	DHEC	Efficacious	Clinically useful	
	Pergolide	Efficacious	Clinically useful	
	Bromocriptine	Likely efficacious	Possibly useful	
	Lisuride	Likely efficacious	Possibly useful	
Levodopa/peripheral decarboxylase	Standard formulation	Efficacious	Clinically useful	

inhibitor	Controlled release	Efficacious	Clinically useful
	Rapid-onset	Insufficient evidence	Investigational
MAO-B inhibitors	Selegiline	Efficacious	Clinically useful
	Rasagiline	Efficacious	Clinically useful
Others	Anticholinergics	Likely efficacious	Clinically useful
	Amantadine	Likely efficacious	Possibly useful
	Zonisamide	Insufficient evidence	Investigational

ROTIGOTINE

Transdermal rotigotine in early stage Parkinson's disease: a randomized, double-blind, placebo-controlled trial. Mizuno Y, Nomoto M, Kondo T, Hasegawa K, Murata M, Takeuchi M, Ikeda J, Tomida T, Hattori N; Rotigotine Trial Group. Mov Disord 2013;28(10):1447-1450.

This double-blind RCT investigated use of transdermal rotigotine monotherapy in early-stage PD in Japan (mean H&Y 2, range 1-3); disease duration mean 2±1.9y. Patients received rotigotine (mean dose 12.8 mg, up to 16 mg/24 hours; n=82) or placebo (n=90) for 12 weeks. The mean improvement in UPDRS part II and 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). No serious drug-related adverse events were reported. QS 89%.

Conclusions for symptomatic monotherapy

The new study evaluating rotigotine confirms prior studies showing Efficacy as monotherapy in early PD, and the practice implication of Clinically Useful remains. No changes in safety conclusions.

Table 3 Treatments for symptomatic adjunct therapy to Levodopa

Drug Class	Drug	Efficacy conclusions	Implications for clinical practice	Safety
Dopamine agonists Non-ergot	Piribedil	Efficacious	Clinically useful	
	Pramipexole	Efficacious	Clinically useful	
	Pramipexole ER	Efficacious	Clinically useful	
	Ropinirole	Efficacious	Clinically useful	
	Ropinirole PR	Efficacious	Clinically useful	
	Rotigotine	Efficacious	Clinically useful	
	Apomorphine	Efficacious	Clinically useful	
Ergot	Bromocriptine	Efficacious	Clinically useful	Acceptable risk with specialized monitoring
	Cabergoline	Efficacious	Clinically useful	
	Pergolide	Efficacious	Clinically useful	
	DHEC	Insufficient evidence	Investigational	
	Lisuride	Likely efficacious	Possibly useful	
Levodopa/peripheral decarboxylase inhibitor	Rapid-onset	Insufficient evidence	Investigational	***Acceptable risk with specialized monitoring***
	Infusion	***Efficacious***	***Clinically useful***	
COMT inhibitors	Entacapone	Efficacious (in patients with motor complications)	Clinically useful	
		Non-efficacious (in	Not useful	

		patients without fluctuations)		
	Tolcapone	Efficacious	Clinically useful	Acceptable risk with specialized monitoring
MAO-B inhibitors	Selegiline	Insufficient evidence	investigational	
	Oral disintegrating selegiline	Insufficient evidence	investigational	
	Rasagiline	Efficacious	Clinically useful	
Others	Anticholinergics	Likely efficacious	Clinically useful	
	Amantadine	Likely efficacious	Possibly useful	
	Zonisamide	Efficacious	Clinically useful	
	Donepezil	Insufficient evidence	investigational	
	Methylphenidate	Insufficient evidence	investigational	
	Memantine	***Insufficient evidence***	***Investigational***	
Surgery	Bilateral STN DBS	Efficacious	Clinically useful	Acceptable risk with specialized monitoring
	Bilateral GPi DBS	Efficacious	Clinically useful	
	Unilateral	Efficacious	Clinically useful	

	pallidotomy			
	Unilateral thalamotomy	Likely efficacious	Possibly useful	
	Thalamic stimulation (uni or bilateral)	Likely efficacious	Possibly useful	
	Subthalamotomy	Insufficient evidence	investigational	
	Human fetal transplantation	Non-efficacious	investigational	Unacceptable risk
Non pharmacological	**Physical therapy**	**Likely efficacious**	**Clinically Useful**	
	Speech therapy	**Insufficient evidence**	**Possibly useful**	
	Occupational therapy	Insufficient evidence	Possibly useful	
	Acupuncture	Insufficient evidence	investigational	
	Repetitive Transcranial Magnetic Stimulation	Insufficient evidence	investigational	

LEVODOPA-INFUSION

see section 5a Treatments for Motor Fluctuations

MEMANTINE

Memantine for axial signs in Parkinson's disease: a randomised, double-blind, placebo-controlled pilot study. Moreau C, Delval A, Tiffreau V, Defebvre L, Dujardin

K, Duhamel A, Petyt G, Hossein-Foucher C, Blum D, Sablonnière B, Schraen S, Allorge D, Destée A, Bordet R, Devos D. J Neurol Neurosurg Psychiatry 2013;84(5):552-555**.**
The N-methyl-D-Aspartate (NMDA) antagonist, memantine was evaluated in a DBRCT in 25 advanced PD subjects with gait disorder defined as score of at least or greater than 2 on UPDRS part III item 29 subscore and abnormal forward stance. Sixteen subjects (8 per group) had prior STN DBS surgery. Subjects were randomized to memantine (n=13) or placebo (n=12) for 30 days titration up to 20 mg/d, then continued for 60 day. The primary outcome of change in stride length, 'ON' levodopa using gait analysis, was unchanged in both groups pre- and post-treatment ($F_{(1,21)}$=0.27; p = 0.61 adjusted effect size covariance analysis (-0.2). Secondary outcomes of truncal flexion and extension measured using dynamometers significantly improved with memantine (P<0.001) and UPDRS motor axial subscores improved by 1 point in memantine vs. placebo (P=0.014). Dyskinesia was significantly less with memantine (dyskinesia rating score mean reduction 2 vs 0 with placebo, P<0.001). There were no significant adverse events but data was sparse. The quality score is reduced due to the primary outcome measure of stride length making clinical relevance hard to assess and lack of intention-to-treat statistical analysis. QS 73%

PHYSICAL THERAPY

Several new studies have investigated different types of physical therapy. In keeping with the prior review, three groups have been delineated to categorize the methods of intervention.

Physiotherapy

A two-year randomized controlled trial of progressive resistance exercise for Parkinson's disease. Corcos DM, Robichaud JA, David FJ, Leurgans SE, Vaillancourt DE, Poon C, Rafferty MR, Kohrt WM, Comella CL. Mov Disord 2013;28(9):1230-1240.
This trial randomized matching (gender and OFF UPDRS III scores) pairs of PD subjects to progressive resistance exercise (PRE) (n=24) or modified fitness counts (mFC) (n=24) for 24 months. Subjects were recruited within a narrow age range (50 – 65y), with moderate disease (duration 6.5y average); the presence of motor fluctuations

was not stated. Each group was treated alike, apart from the actual exercises. Both groups had individual training twice a week for the first 6 months, with a certified personal trainer, and for the remaining 18 months subjects received one-on-one training once a week and performed the second session each week on their own. To maintain 24 per group; one subject in the PRE and 2 subjects in mFC groups who withdrew in the first 6 months were replaced; and as such were not randomized. There was no significant change in levodopa-equivalent doses between the groups at the end of the study. The primary end point of change in OFF UPDRS III at 24 months compared to baseline, was 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). Secondary outcomes of ON UPDRS III were not significant. Objective measurements of muscle strength and speed improved in the OFF drug with PRE vs. mFC. One subject developed wrist pain directly related to the mFC and 7 SAEs possible related involving back, hip and knee surgery were reported in both. The lack of benefit in ON reduces the clinical relevance of the interventions. QS 82%

Effect of Partial Weight-Supported Treadmill Gait Training on Balance in Patients With Parkinson Disease. Ganesan M, Sathyaprabha TN, Gupta A, Pal PK. PM R. 2014;6(1):22-33 (*2013 early view*)

This RCT evaluated the effect of 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) vs. no intervention on balance in 60 PD subjects. The 2 intervention groups received 30 min/day; over 4 days total 16 sessions in 4 weeks; the control group had no similar intervention. Outcome measures were UPDRS III, as well as objective dynamic posturography; Berg Balance scale (BBS) and Tinetti Performance-Orientated Mobility Assessment (POMA). Blinding of raters is not stated. 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 (95% CI were not stated). The relevance of the intervention in PD subjects with falls despite optimal medication is hard to assess as all participants were relatively young (mean age <60y) with short disease duration (5-6y), H&Y <2.5 and specific balance scores that indicated no major issues with balance in the participants. QS 63%

Influence of physiotherapy on severity of motor symptoms and quality of life in patients with Parkinson disease. Cholewa J, Boczarska-Jedynak M, Opala G. Neurol Neurochir Pol 2013;47(3):256-262.
This RCT evaluated PD subjects who received physiotherapy (n=40) and a control, no-exercise group (n=30). Physiotherapy was carried out for 60 minutes, twice a week for 12 weeks, and was aimed at improving movement range, balance, movement agility and walking. 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). 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. QS 55%

The effect of gym training on multiple outcomes in Parkinson's disease: a pilot randomised waiting-list controlled trial. Poliakoff E, Galpin AJ, McDonald K, Kellett M, Dick JP, Hayes S, Wearden AJ. NeuroRehabilitation 2013;32(1):125-134.
In this RCT 32 mild to moderate PD subjects not currently exercising formally were randomized to an immediate 20-week biweekly gym-training program or a 10-week program starting 10 weeks later. There was a greater disease duration in the active group (7.4y) compared to control (4.7y). Assessments at baseline, 10 weeks and 20 weeks included a number of outcome measures; reaction time, UPDRS III, PDQ-39 and illness perceptions. Timing of assessments in relation to ON/OFF drug status is not stated. A formal statistical comparison of the two treatment groups was not performed. 95% CI not stated. The UPDRS III score, PDQ-39, and illness perceptions did not change over time. QS 44%

Community-based group exercise for persons with Parkinson disease: a randomized controlled trial. Combs SA, Diehl MD, Chrzastowski C, Didrick N, McCoin B, Mox N, Staples WH, Wayman J.NeuroRehabilitation 2013;32(1):117-124.
In a single-blind RCT a convenience sample of 31 PD patients were assigned to boxing training or to traditional exercise for 24–36 sessions, each lasting 90 minutes, over 12 weeks. 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). There was a dropout rate of 29%. 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). QS 51%

The effects of treadmill or overground walking training program on gait in Parkinson's disease. Bello O, Sanchez JA, Lopez-Alonso V, Márquez G, Morenilla L, Castro X, Giraldez M, Santos-García D, Fernandez-del-Olmo M. Gait Posture 2013;38(4):590-595.
In this RCT, 22 PD patients were randomised to individually adjusted treadmill training or overground walking for 5 weeks, 3 sessions per week, of increasing duration (up to 20 minutes). The study was not clearly blinded. Outcome measures were gait kinematics during walking at preferred and maximal speed; Timed Up and Go (TUG); static posturography using a stabilometric platform, and knee extensors strength, assessed on an isometric knee extensor machine. 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 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. 95% CI were not stated. Cadence and knee extension did not change. Re-evaluation after 1 month was carried out in the treadmill group only and showed maintained improvements in walking parameters. The study suggests an effect of treadmill training on walking in PD patients but conclusions are limited by the small sample size, lack of

clearl blinding; the fact that multiple comparisons were carried out without reporting of significance data, and the lack of a 1-month assessment in the control group. QS 53%

Home-based treadmill training for individuals with Parkinson's disease: a randomized controlled pilot trial. Canning CG, Allen NE, Dean CM, Goh L, Fung VS. Clin Rehabil 2012;26(9):817-826.
This RCT, single-blindedpilot study evaluated the efficacy of treadmill training on gait in PD, compared with a home-based protocol. Subjects with early PD (H & Y 1-2) were randomized to 6 weeks of semi-supervised treadmill training (n=10, 30-40 minutes, four times a week) followed by a further 6 weeks follow up; the control group was usual care (n=10, usual physical activities). The primary outcome of walking capacity (6-minute timed walk) was not significantly different between the two groups (36m vs 41.5m). Quality of life using PDQ-39 was improved in the treadmill group ($P< 0.05$). The study was not fully powered as 140 participants were required but only 20 were recruited due to funding issues. No active intervention in the control group may have biased outcomes in the active group. QS 67%

Assistive devices alter gait patterns in Parkinson disease: advantages of the four-wheeled walker. Kegelmeyer DA, Parthasarathy S, Kostyk SK, White SE, Kloos AD. Gait Posture 2013;38(1):20-24.
This multiple crossover RCT study investigated the effects of five different assistive devices vs. none, on gait and maneuvering around obstacles (figure-of-eight) in 27 PD patients over the age of 50, who used each device in randomized order, without specified intervals between assessment periods. Falls in the previous 6 months had occurred in 52% of the patients but none were dependent on devices and all were required to be able to walk 10 m independently. The devices were: cane, standard walker, 2-wheel walker, 4-wheel walker, U Step walker with a laser as a visual cue. Gait measures were assessed electronically, using a validated system. Significant differences were found in a considerable number of 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. The authors highlight that walking speed and safety appeared best with the 4-wheel walker, with the least variability in gait parameters. The conclusions from this study are considerably limited by the fact that this is essentially a cross-over 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. QS 45%

Effects of 24 Weeks of Treadmill Training on Gait Performance in Parkinson Disease. Nadeau A, Pourcher E, Corbeil P. Med Sci Sports Exerc 2014;46(4):645-655 *(early view 2013).*

The aim of this single-blind RCT was to evaluate the effects of 24 weeks Treadmill Training (TT). 93 PD patients, H&Y stage 1.5 or 2, were randomized to Speed TT, Mixed TT, and Control groups. The interventions consisted of 72 one-hour exercise sessions over 24 weeks. Main outcome measures were the MDS-UPDRS, PDQ-39, spatiotemporal parameters of gait and 6-minute walking distance. The measures were taken at baseline, 12 weeks and after 24 weeks. The data from 34 patients were available for analyses. 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. QS 59%

Exploring outcome measures for exercise intervention in people with Parkinson's disease. King LA, Salarian A, Mancini M, Priest KC, Nutt J, Serdar A, Wilhelm J, Schlimgen J, Smith M, Horak FB. Parkinsons Dis 2013;2013:572134.

In this single-blinded RCT, 39 PD patients were randomized to two exercise groups: Agility Boot Camp (ABC) vs. Treadmill training for 4 weeks. There were dual study outcomes: 1) the effects of the interventions for improving mobility, measuring multiple variables; 2) exploring which of five outcome measures was most sensitive to exercise intervention. The study was self-admittedly underpowered and exploratory to test for any different effects between exercise groups. 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). QS 65%

Movement strategy training with cuing or focused attention

Effects of augmented proprioceptive cues on the parameters of gait of individuals with Parkinson's disease. El-Tamawy MS, Darwish MH, Khallaf ME. Ann Indian Acad Neurol 2012;15(4):267-272.

In this RCT, 30 patients with mild to moderate PD (motor complications not reported) were randomized to either a "routine", low-intensity and individually adapted physiotherapy program, consisting of passive stretch, balance training, active exercises for muscle strength, and walking, for 45 minutes 3 times weekly for 8 weeks; or to a "proprioceptive neuromuscular facilitation technique", which involved treadmill training and the use of vibratory devices which were 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. Assessments were performed by electronic motion analysis; there was no blinding. No primary outcome was identified. 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 The conclusions from this study are greatly limited by the fact that the active intervention occurred in addition to the physiotherapy program of the control group, which did not include treadmill training. Therefore, any specific effects of the proprioceptive, vibratory stimulation the authors attempted to investigate cannot be disentangled from the effects of treadmill training as such in addition to general physiotherapy. An adequate control group was lacking. QS 54%

Effect of externally cued training on dynamic stability control during the sit-to-stand task in people with Parkinson disease. Bhatt T, Yang F, Mak MK, Hui-Chan CW, Pai YC. Phys Ther 2013;93(4):492-503.

To test the effects of externally cued training on the sit-to-stand task, 21 PD patients were randomised to audiovisually cued training (verbal commands and cues on screen representing the patient´s centre of mass; 3 times per week for 4 weeks) versus no training. Disease severity was moderate, motor complications were not reported, falls had occurred in 62%. No primary outcome or sample size calculation were reported. There was no blinding. Compared with 12 matched healthy controls (who were younger than PD subjects; did not receive training and were assessed only once), PD patients had a more anterior center-of-mass position at seat-off, increasing the risk of forward balance loss at movement termination, assessed by an electronic motion analysis system. After training, 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. The study reports very limited absolute figures, presenting results in graphs only. 95% CI were not stated The effect of the intervention in healthy controls was not assessed. The clinical relevance is uncertain**.** QS 48%

Repetitive step training with preparatory signals improves stability limits in patients with Parkinson's disease. Shen X, Mak MK. J Rehabil Med 2012;44(11):944-949.

This RCT examined the effects of 4 weeks (3/week, approximately 60 minutes per session) of repetitive step training (volitional and compensatory) with preparatory visual cues (n=15) vs. a control group, which undertook lower limb strength training (n=14), in patients with mild-to-moderate PD without falls in the previous 12 months. Assessors were blinded to group assignment. The repetitive step training group focused on increasing the speed and amplitude of steps and weight shifting to subjects' postural stability limits, and 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. No falls were recorded in both subject groups during training. QS 70%

Effect of Nintendo Wii™-based motor and cognitive training on activities of daily living in patients with Parkinson's disease: a randomised clinical trial. Pompeu JE, Mendes FA, Silva KG, Lobo AM, Oliveira Tde P, Zomignani AP, Piemonte ME. Physiotherapy 2012;98(3):196-204.

This single-blind RCT investigated the effect of Nintendo Wii™-based motor cognitive training versus balance exercise therapy in 32 patients with early-stage PD. The control group performed stretching, strengthening and balance exercises without feedback or cognitive stimulation, and the experimental group performed 10 Wii Fit™ games selected for their potential effect on balance training (two 1h sessions per week for seven weeks). Assessors were blind to group allocation. Both groups showed improvement in the UPDRS-II (the primary outcome) (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. Other outcomes included Berg Balance Scale (BBS) and measures of Static balance using a Unipedal Stance Test (non-motor outcomes included the MOCA) were similarly improved with both interventions with no group effect. The authors concluded that there were no additional advantages associated with the Wii-based motor and cognitive training, but it was not clear if the study was sufficiently powered to demonstrate the superiority of Nintendo training. There was no control group that received no intervention. QS 70%

Formalised patterned exercises

Community-based Argentine tango dance program is associated with increased activity participation among individuals with Parkinson's disease. Foster ER, Golden L, Duncan RP, Earhart GM. Arch Phys Med Rehabil 2013;94(2):240-249.

This RCT enrolled evaluted Tango dancing in 62 PD patients; 10 did not receive the allocated intervention, analysis was intention-to-treat. The patients were randomised to 12 months of twice-weekly Argentine tango dance classes, or to no intervention. Groups were similar at baseline and assessments were performed in a blinded manner. For the primary outcome, MDS-UPDRS III, there was no significant change from baseline in the control group, whereas the tango group had a reduction of 28.7% (12.8 points). There

were significant group by time interactions for the secondary outcomes MiniBESTest, Freezing of Gait Questionnaire, 6-Minute Walk Test, forward and dual task walking velocities, and 9-Hole-Peg-Test in favor of the dance group. Another secondary outcome measure was current, new, and retained participation in instrumental, leisure, and social activities, measured by the Activity Card Sort (with the dance activity removed). Total current participation in the tango group was higher at 3, 6, and 12 months compared with baseline (P=0.008), while the control group did not change (P=0.11). Only the tango group experienced a significant (p=0.006) increase in total activity retention (since onset of PD) from 77% to 90%, with similar patterns in all activity domains, and a significant number of new social activities (P=0.003). 95% CI were not stated QS 60.2%

The effect of Tai Chi exercise on gait initiation and gait performance in persons with Parkinson's disease. Amano S, Nocera JR, Vallabhajosula S, Juncos JL, Gregor RJ, Waddell DE, Wolf SL, Hass CJ. Parkinsonism Relat Disord 2013;19(11):955-960.
This study randomized 45 PD subjects to 2 interventions (Projects), according to 2 different geographical locations in the US. Project 1 evaluated Tai Chi vs. Qi-gong for 60 minutes for 2 days/week and project 2 evaluated Tai Chi (using same method as per project 1) vs. attending a living–well center with no active intervention for 3 days/week; all lasted 16 weeks. Gait and PD disability (UPDRS III) was assessed pre- and post-intervention. (95% CI values not stated). There was no significant difference in any of the outcome measures, including objective biomechanical changes in posture and gait and UPDRS III outcomes. The final number of subjects in the statistical analysis is unclear; as are any changes that occurred in medications during the study. QS 53%

SPEECH THERAPY

Video-assisted swallowing therapy for patients with PD Manor Y, Mootanah R, Freud D, Gilasi N, Cohen JT. Park Rel Disord 2013;19:207-211.
The aim of this single-blind RCT was to test the effectiveness of visual information while treating swallowing disturbances in PD. 42 PD patients with swallowing disturbances were randomized to video-assisted swallowing therapy (VAST) or to conventional

therapy (control). Both groups were given 6 interventional sessions. Swallowing function was assessed by fiberoptic endoscopic evaluation of swallowing (FEES). There was a significant improvement in swallowing functions following both interventions. The FEES demonstrated a significantly greater reduction in food residues in the pharynx in the VAST group compared to the control group (95% CI not reported). Swallowing Quality of Life (SWAL-QOL) and Swallowing Quality of Care (SWACARE) improved more in the VAST group. The lack of information on motor fluctuations and no specified primary outcome measure limits interpretation. QS 66%

Conclusions for symptomatic adjunct therapy to Levodopa

Ropinirole PR and Rasagiline were both evaluated in PD subjects from China. Both studies confirmed Efficacy rating from prior studies but in different populations and the practice implications conclusion remains unchanged as Clinically Useful.

A further study confirmed that entacapone is Efficacious as adjunct therapy in PD subjects with mild fluctuations and remains Clinically Useful.

There was Insufficient Evidence for using memantine to improve gait in PD and the practice implication was thus Investigational.

The large number of exercise studies reported generally positive outcomes in all interventions; there is wide variability in quality of studies; as such the efficacy conclusion for exercise (as a group) is Likely Useful. The implications for clinical practice are however unchanged as Clinically Useful.

One new study using speech therapy did not change the overall conclusions of Insufficient evidence for efficacy but Possibly Useful in clinical practice.

Table 4. Treatments to prevent/delay of motor fluctuations (F) or dyskinesia (D)

	Drug	Efficacy conclusions	Implications for clinical practice	Safety
Dopamine agonists Non-ergot	Pramipexole	Efficacious (F,D)	Clinically useful (F,D)	
	Ropinirole	Efficacious (D) Insufficient evidence (F)	Clinically useful (D) Investigational (F)	
	Pramipexole ER	Insufficient evidence	Investigational	
	Ropinirole PR	Insufficient evidence	Investigational	
	Rotigotine	Insufficient evidence	Investigational	
	Piribedil	Insufficient evidence	Investigational	
	Apomorphine	Insufficient evidence	Investigational	
Ergot	Cabergoline	Efficacious (F,D)	Clinically useful (F,D)	Acceptable risk with specialized monitoring
	Bromocriptine	Likely efficacious (D) Insufficient evidence (F)	Possibly useful (D) Investigational (F)	
	Pergolide	Likely efficacious (D) Insufficient evidence (F)	Possibly useful (D) Investigational (F)	

	DHEC	Insufficient evidence	Investigational	
	Lisuride	Insufficient evidence	Investigational	
Levodopa/peripheral decarboxylase inhibitor	Infusion	Insufficient evidence	Investigational	
COMT inhibitors	Entacapone	Non-efficacious (F,D)	Not useful (F,D)	
	Tolcapone	Insufficient evidence	Investigational	Acceptable risk with specialized monitoring
MAO-B inhibitors	Selegiline	Non-efficacious (D) Insufficient evidence (F)	Not useful (D) Investigational (F)	
	Oral disintegrating selegiline	Insufficient evidence	Investigational	
	Rasagiline	Insufficient evidence	Investigational	

Conclusions for treatments to prevent/delay of motor fluctuations (F) or dyskinesia (D)

There were no new studies.

Table 5a Treatments for motor fluctuations (F)

Drug Class	Drug	Efficacy conclusions	Implications for clinical practice	Safety
Dopamine agonists Non-ergot	Pramipexole	Efficacious	Clinically useful	
	Ropinirole	Efficacious	Clinically useful	
	Ropinirole PR	**Efficacious**	**Clinically useful**	
	Rotigotine	Efficacious	Clinically useful	
	Apomorphine	Efficacious	Clinically useful	
	Piribedil	Insufficient evidence	Investigational	
	Pramipexole ER	Efficacious	Clinically useful	
Ergot	Pergolide	Efficacious	Clinically useful	Acceptable risk with specialized monitoring
	Bromocriptine	Likely Efficacious	Possibly useful	
	Cabergoline	Likely Efficacious	Possibly useful	
	DHEC	Insufficient evidence	Investigational	
	Lisuride	Insufficient evidence	Investigational	
Levodopa/peripheral decarboxylase	Standard formulation	Efficacious	Clinically useful	

inhibitor	Controlled release	Insufficient evidence	Investigational	
	Rapid onset	Insufficient evidence	Investigational	
	Infusion	***Efficacious***	***Clinically useful***	***Acceptable risk with specialized monitoring***
COMT inhibitors	**Entacapone**	**Efficacious**	**Clinically useful**	
	Tolcapone	Efficacious	Possibly useful	Acceptable risk with specialized monitoring
MAO-B inhibitors	Selegiline	Insufficient evidence	investigational	
	Oral disintegrating selegiline	Insufficient evidence	investigational	
	Rasagiline	**Efficacious**	**Clinically useful**	
Others	Amantadine	Insufficient evidence	investigational	
	Zonisamide	Insufficient evidence	investigational	
Surgery	**Bilateral STN DBS**	**Efficacious**	**Clinically useful**	Acceptable risk with specialized monitoring
	Bilateral GPi DBS	Efficacious	Clinically useful	
	Unilateral pallidotomy	Efficacious	Clinically useful	

	Unilateral thalamotomy	Insufficient evidence	investigational	
	Thalamic stimulation (uni or bilateral)	Insufficient evidence	investigational	
	Subthalamotomy	Insufficient evidence	investigational	
	Human fetal transplantation	Non-efficacious	investigational	Unacceptable risk

ROPINIROLE PR

The efficacy and safety of ropinirole prolonged release tablets as adjunctive therapy in Chinese subjects with advanced Parkinson's disease: a multicenter, double-blind, randomized, placebo-controlled study. Zhang Z, Wang J, Zhang X, Chen S, Wang Z, Zhang B, Liu C, Qu Q, Cheng Y, Li J, Cao H, Cai M, Zhu R. Parkinsonism Relat Disord 2013;19(11):1022-1026.

This multicenter double-blind RCT evaluated the efficacy and safety of ropinirole prolonged release (PR) as an adjunct in levodopa-treated Chinese patients with ≥3h of awake OFF time. Subjects were randomized to ropinirole PR (mean dose 11.4 mg/day, maximum 24 mg/day; N=175) or placebo (N=170). At 24 weeks, subjects receiving ropinirole PR experienced a significant reduction in awake OFF time (the primary outcome measure; 2.1h) compared with placebo (0.4h; P<0.001; 95% CI for adjusted treatment difference, -2.27 to -0.26). The responder rate (those with ≥20% reduction in awake OFF time) was significantly higher in the ropinirole PR (22.8%) than placebo group (2.5%). The most frequent adverse event experienced in the ropinirole PR group was dyskinesia (17.7% vs. 2.9% for placebo). QS 89%.

LEVODOPA INFUSION

Continuous intrajejunal infusion of levodopa-carbidopa intestinal gel for patients with advanced Parkinson's disease: a randomised, controlled, double-blind, double-dummy study. Olanow CW, Kieburtz K, Odin P, Espay AJ, Standaert DG, Fernandez HH, Vanagunas A, Othman AA, Widnell KL, Robieson WZ, Pritchett Y, Chatamra K, Benesh J, Lenz RA, Antonini A; LCIG Horizon Study Group. Lancet Neurology 2014;13(2):141-149 *(2013 early view)*.

This double blind, double-dummy, double-titration RCT assessed efficacy and safety of levodopa-carbidopa intestinal gel (LCIG) over 12-weeks. Advanced PD subjects with motor complications (n= 71) had jejunal placement of a percutaneous gastrojejunostomy tube and were then randomly allocated to treatment with LCIG plus oral placebo, or to oral levodopa-carbidopa plus placebo intestinal gel infusion (control). 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 dyskinesia increased more in the LCIG group compared to the control group (difference 1.86h [95% CI 0.56 to 3.17]). Two (3%) of 71 patients discontinued from the study because of complications of surgery and 63 (89%) had device-related complications, including tube dislocations, percutaneous gastrojejunostomy insertion complications, stoma insertion complications, pump malfunctions, and pneumoperitoneum. Four patients had symptoms consistent with the possibility of polyneuropathy (one in the LCIG group and three in the control group). QS 87%

ENTACAPONE

Efficacy of levodopa/carbidopa/entacapone versus levodopa/carbidopa in patients with early Parkinson's disease experiencing mild wearing-off: a randomised, double-blind trial. Tolosa E, Hernández B, Linazasoro G, López-Lozano JJ, Mir P, Marey J, Kulisevsky J. J Neural Transm 2014;121(4):357-366 *(2013 early view).*

This randomized, double-blind, parallel group phase IV study recruited 95 PD patients with mild fluctuations (i.e., wearing off and none or mild dyskinesias). 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). Baseline clinical features were noted to be well balanced but not stated; levodopa dose was kept the same between the two groups. The primary outcome measure was UPDRS II and secondary outcomes were UPDRS Part III and CGI scores with LCE. LCE showed better efficacy with a UPDRS II group adjusted mean difference LCE vs. LC of 1.5 points (-2.1 points (95% CI -3.03 to -1.12) in the LCE group and -0.6 points in the LC group (95% CI -1.51 to 0.33)); the 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). There were no significant adverse events. QS = 80%

RASAGILINE

Efficacy and safety of rasagiline as an adjunct to levodopa treatment in Chinese patients with Parkinson's disease: a randomized, double-blind, parallel-controlled, multi-centre trial. Zhang L, Zhang Z, Chen Y, Qin X, Zhou H, Zhang C, Sun H, Tang R, Zheng J, Yi L, Deng L, Li J. Int J Neuropsychopharmacol 2013;16(7):1529-1537.

This randomized, placebo-controlled, multicenter, double-blinded study investigated the safety and efficacy of rasagiline in 244 Chinese PD subjects with fluctuations. Rasagiline 1 mg/day or placebo was administered for 12 weeks as an adjunct to levodopa. Improvement in diary-based mean on-time and off-time as compared to baseline was the primary measure. 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)There was improvement in UPDRS in the rasagiline groupIssues with statistics, such as not using intention-to- treat analysis, reduced the quality score. Rasagiline was well tolerated. The findings of this trial are not novel but validate use in a different population of patients exposed to different antiparkinsonian drugs such as anticholinergics. QS = 77%

BILATERAL SUBTHALAMIC NUCLEUS DEEP BRAIN STIMULATION

Neurostimulation for Parkinson's Disease with Early Motor Complications

Schuepbach, J. Rau, K. Knudsen, J. Volkmann, P. Krack, L. Timmermann,T.D. Hälbig,

H. Hesekamp, S**,** Navarro SM, Meier N, Falk D, Mehdorn M, Paschen S, Maarouf M, Barbe MT, Fink GR, Kupsch A, Gruber D, Schneider GH, Seigneuret E, Kistner A, Chaynes P, Ory-Magne F, Brefel Courbon C, Vesper J, Schnitzler A, Wojtecki L, Houeto JL, Bataille B, Maltête D, Damier P, Raoul S, Sixel-Doering F, Hellwig D, Gharabaghi A, Krüger R, Pinsker MO, Amtage F, Régis JM, Witjas T, Thobois S, Mertens P, Kloss M, Hartmann A, Oertel WH, Post B, Speelman H, Agid Y, Schade-Brittinger C, Deuschl G; EARLYSTIM Study Group. N Engl J Med 2013;368:610-622.

This single-blind RCT investigated whether STN DBS is beneficial at an earlier stage of PD. 251 patients with PD (mean disease duration 7.5y) and early motor complications were randomized to DBS plus medical therapy or to medical therapy alone. The primary outcome was the between-group difference in mean change from baseline to 2 years on the Parkinson's Disease Questionnaire (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 8.0 points; P=0.002; 95% CI 4.2 to 11.9). DBS was superior to medical therapy with respect to motor disability (P<0.001), activities of daily living (P<0.001), levodopa-induced motor complications (P<0.001), and time with good mobility and no dyskinesia (P=0.01). Serious adverse events occurred in 54.8% of the patients in the DBS group and in 44.1% of those in the medical-therapy group. Serious adverse events related to surgical implantation or the DBS device occurred in 17.7% of patients. QS 89%

Conclusions for treatments for motor fluctuations (F)

Levodopa-carbidopa gel infusion is Efficacious for treating motor fluctuations without worsening ON time with dyskinesia and is Clinically Useful. The potential side-effects of the procedure result in a safety conclusion of 'acceptable with specialized monitoring'. Bilateral STN-DBS remains an efficacious therapy for motor fluctuation and dyskinesia and is clinically useful. The conclusion holds for PD subjects from average disease duration of 7.5y. The practice implication remains unchanged as Clinically Useful and safety conclusions of an acceptable risk with specialized monitoring remains.

Table 5b Treatments for dyskinesia

Drug Class	Drug	Efficacy conclusions	Implications for clinical practice	Safety
Dopamine agonists Non-ergot and ergot Ergot	See Table 5a **Pramipexole**	**Insufficient evidence**	**Investigational**	See Table 5a
Levodopa/peripheral decarboxylase inhibitor	Infusion	Efficacious	Clinically Useful	
Others	**Amantadine**	**Efficacious**	**Clinically useful**	
	Clozapine	Efficacious	Clinically useful	Acceptable risk with specialized monitoring
	Zonisamide	Insufficient evidence	Investigational	
	Levetiracetam	Insufficient evidence	Investigational	
Surgery	**Bilateral STN DBS**	**Efficacious**	**Clinically useful**	Acceptable risk with specialized monitoring
	Bilateral GPi DBS	Efficacious	Clinically useful	
	Unilateral pallidotomy	Efficacious	Clinically useful	
	Unilateral thalamotomy	Insufficient evidence	Investigational	

	Thalamic stimulation (uni or bilateral)	Insufficient evidence	Investigational	
	Subthalamotomy	Insufficient evidence	Investigational	
	Human fetal transplantation	Non-efficacious	investigational	Unacceptable risk
Non Pharmacological	Physical therapy	Insufficient evidence	Investigational	

PRAMIPEXOLE

Evaluation of the efficacy of pramipexole for treating levodopa-induced dyskinesia in patients with Parkinson's disease. Utsumi H, Okuma Y, Kano O, Suzuki Y, Iijima M, Tomimitsu H, Hashida H, Kubo S, Suzuki M, Nanri K, Matsumura M, Murakami H, Hattori N; Tokyo Parkinson's Disease Study Group. Intern Med 2013;52(3):325-332.

In this multicenter RCT, 34 patients with PD (mean disease duration 12.3y) and peak-dose dyskinesia on levodopa and an ergot dopamine agonist were randomized to either add-on pramipexole (mean dose 1.2 mg/day) or the ergot dopamine agonist was switched to pramipexole (mean dose 2.1 mg/day). Levodopa remained largely unchanged in both groups. Dyskinesia was evaluated using Core Assessment Program for Surgical Interventional Therapies (CAPSIT). The UPDRS, modified ON period H&Y, PDQ-39 and clinical global impression-improvement scores were also used for evaluation. At 24 weeks, 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. The UPDRS part IV subscores for dyskinesia did not change. UPDRS part III improved only in the switch group. Advese events occurred in 8.8%. Between-group comparisons were not reported. The small sample size, the open-label design and the lack of precise reporting of the outcome parameters limit the conclusions from this study. QS 50%

AMANTADINE

Which dyskinesia scale best detects treatment response? Goetz CG, Stebbins GT, Chung KA, Hauser RA, Miyasaki JM, Nicholas AP, Poewe W, Seppi K, Rascol O, Stacy MA, Nutt JG, Tanner CM, Urkowitz A, Jaglin JA, Ge S. Mov Disord 2013;28(3):341-346. This was a RCT using amantadine (up to 300 mg/day) vs. placebo to primarily compare sensitivity to treatment effects, at 4 and 8 weeks, in 8 different dyskinesia rating scales in 61 PD subjects with dyskinesia. As data was also evaluated using an ITT for efficacy, this study was included. Four out of the eight 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 ($p<0.05$). Adverse events were as previously reports with amantadine. QS 89.5%

BILATERAL SUBTHALAMIC NUCLEUS DEEP BRAIN STIMULATION

See above with Motor Fluctuations section

Conclusions for treatments for dyskinesia

Pramipexole was evaluated as treatment for dyskinesia; there was no change in conclusions from previously, thus there remains Insufficient Evidence for use of pramipexole to treat dyskinesia and the classification of Investigational for clinical practice.

The new study using amantadine confirmed prior studies that this drug is Efficacious in treating dyskinesia and is Clinically Useful.

No new safety issues

References

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2 Fox SH, Katzenschlager R, Lim S-Y, Barton B, Seppi K, Coelho M, Poewe W, Rascol O, Goetz CG, Sampaio C. http://www.movementdisorders.org/MDS/Resources/Publications-Reviews/EBM-Reviews1.htm 2013