Update on treatments for motor symptom of PD

The recent MDS EBMR on treatments for motor symptoms of PD updated the original comprehensive EBM reviews to end of 2010.

We have continued the process and present an update to Dec 2012

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'. Each intervention was 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, 31new 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 italics*.** Changes in conclusions are indicated in *italics.*

Interventions for motor symptoms that had not been previously reviewed in early EBM reviews were also included; levetiracetam, coenzyme Q10, methylphenidate, donepezil and repetitive transcranial magnetic stimulation (rTMS).

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	Insufficient evidence	Investigational	
	Pergolide	Unlikely efficacious	Unlikely useful	
Others	***Coenzyme Q10***	*Insufficient evidence*	*Unlikely useful*	

Co-enzyme Q10

Shults CW, Oakes D, Kieburtz K, et al. Effects of coenzyme Q10 in early Parkinson disease: evidence of slowing of the functional decline. Arch Neurol 2002;59(10):1541-50. In this study 80 patients with early (<5 years), untreated PD were randomised to one of three doses of coenzyme Q10 (300, 600, and 1200mg/d) or placebo and treated for 16 months or until symptomatic therapy was required, whichever occurred first. The primary outcome measure was a linear trend between dosages and the mean change in total UPDRS (apparently defined as parts I-III). This was reported to be positive although significance was set at a p value < .09. A secondary outcome measure, the difference in change in total UPDRS score between placebo and highest dose, was significant. Coenzyme Q10 was well tolerated. **QS 74%**

Müller T, Büttner T, Gholipour AF, Kuhn W. Coenzyme Q10 supplementation provides mild symptomatic benefit in patients with Parkinson's disease. Neurosci Lett. 2003;341(3):201-4. Coenzyme Q10 (360mg/d) and placebo was compared in 28 treated and stable PD patients over 4 weeks. There were baseline difference between the arms but the significance of these differences was not stated. The primary endpoint was not precisely stated. There was a 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. Tolerability was stated to be good but no details were reported **QS 62%.**

Storch A, Jost WH, Vieregge P, et al. Randomized, double-blind, placebo-controlled trial on symptomatic effects of coenzyme Q(10) in Parkinson disease.

Arch Neurol. 2007;64(7):938-44. This study randomly assigned 131 patients with stable PD to placebo or nanoparticular CoQ10 (100 mgs 3 times daily) for 3 months. Reduction in UPDRS parts II and III combined (the primary outcome) and the secondary outcome measures were not significantly different between the two treatment arms. Stratification for L-dopa treatment did not change the result. Adverse events were similar in the treatment groups. **QS 93%**

(A fourth study (NINDS NET-PD Investigators. A randomized clinical trial of coenzyme Q10 and GPI-1485 in early Parkinson disease. Neurology. 2007 Jan 2;68(1):20-8) was not included as this was a futility design study and efficacy of Co Q10 cannot therefore be evaluated from the results)

Conclusions for disease-modifying therapies

New Conclusions

There is *insufficient evidence* to make efficacy conclusions for **Coenzyme Q10**. There are no safety concerns. Due to the conflicting evidence (two negative studies (one high quality) and one low quality positive study) but more favoring a lack of benefit, the practice implications are that coenzyme Q10 is *unlikely useful* as a treatment to delay/prevent disease progression.

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 inhibitor	Standard formulation	Efficacious	Clinically useful	
	Controlled release	Efficacious	Clinically useful	
	Rapid-onset	Insufficient evidence	Investigational	
	Infusion	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	

Pramipexole IR

Kieburtz K; Parkinson Study Group PramiBID Investigators. Twice-daily, low-dose pramipexole in early Parkinson's disease: a randomized, placebo-controlled trial. Mov Disord. 2011;26(1):37-44. This study compared twice daily with three times daily pramipexole 0.5 bd, 0.75 bd, 0.5 tid in 311 early PD patients over 12 weeks. Change from baseline at week 12 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%). **QS 95%**

Pramipexole ER

Poewe W, et al; Pramipexole ER Studies Group. Extended-release pramipexole in early Parkinson disease: a 33-week randomized controlled trial. Neurology. 2011 23;77(8):759-66. The study randomised 523 early PD subjects and demonstrated non inferiority of pramipexole ER vs IR over 33 weeks. Rescue levodopa was allowed and required in 21.4% placebo, 4.3% pramipexole IR and 7% pramipexole ER. Primary end point was UPDRS II and III adjusted mean change (P 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. **QS 97%.** NB Part of this cohort has been previously reported as an interim analysis at 18 weeks with significant benefit of pramipexole ER vs placebo on UPDRS III (n= 250) (Hauser et al 2010)

Conclusions for symptomatic monotherapy

No changes in conclusions.

Pramipexole IR and pramipexole ER are Efficacious as monotherapy and Clinically Useful. No new safety concerns

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	
	Infusion	Insufficient evidence	Investigational	
COMT inhibitors	Entacapone	Efficacious (in patients with motor complications) Non-efficacious (in patients without fluctuations)	Clinically useful Not useful	
	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*	
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	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	*Insufficient evidence*	*investigational*	

Stimulation

Pramipexole ER

Schapira AH,et al ; Pramipexole ER Studies Group. Extended-release pramipexole in advanced Parkinson disease: a randomized controlled trial. Neurology 2011 23;77(8):767-74. This study compared once daily pramipexole extended release (ER) (av dose 2.7mg/d) vs three times daily pramipexole immediate release (IR) (2.8 mg/d) in 518 advanced PD over 18 weeks. There was a significant effect of treatment; Change in the UPDRS) part II+III score at 18 weeks decreased by an adjusted mean of -11.0 for pramipexole ER and- 12.8 for pramipexole IR vs- 6.1 for placebo (p<0.0001 and p< 0.0001) and off-time decreased (from baseline means of 5.8–6.0 hours/day) by an adjusted mean of -2.1 and -2.5 vs -1.4 hours/day (p = 0.0199 and p = 0.0001). 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. **QS 99%**

Mizuno Y, et al; Pramipexole ER Study Group. Efficacy and safety of extended- versus immediate-release pramipexole in Japanese patients with advanced and (L)-dopa-undertreated Parkinson disease: a double-blind, randomized trial. Clin Neuropharmacol. 2012 ;35(4):174-81.Pramipexole ER (average daily dose 3.36mg/d) and IR (3.54 mg/d) in advanced and L-dopa undertreated PD patients over 12 weeks. The population was not well defined and mixed; subjects had motor fluctuations, including wearing off and on/off (53.6%), however % subjects with dyskinesia at baseline was not stated. In addition there was a second group: stable "undertreated" patients. The mean L-dopa dose was 299.1mg/d in the ER group and 270.5 mg/day in the IR group. There was no predefined efficacy endpoint and the study was not powered for non-inferiority. Outcome measures: change in UPDRS II (average ON/OFF) + III (ON) was ER -13.6, IR -13.3 (both significant from baseline). **QS 85%**

Rotigotine

No new RCTs using rotigotine have been published but in keeping with prior EBM review, a comment on the long term follow-up of these studies is included**.** One-year open-label follow-up data (Trenkwalder C et al Basal Ganglia 2012;2:79-85) have been published following RECOVER, a randomised controlled study comparing the effect of rotigotine and placebo on early-morning motor function. Of the 287 patients originally randomised 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 adverse events were application site reactions (24%), somnolence (13%),

hallucinations (13%), nausea (12%) falls (12%), dizziness (11%) and dyskinesia (11%) . Twelve patients discontinued due to adverse events, mostly site reactions. The findings suggest sustained motor efficacy of rotigotine over 1 year.

Rasagiline

No new RCTs using rasagiline have been reported. However a comment is added about a sub-study but no quality rating was made. Stocchi and Rabey (Effect of rasagiline as adjunct therapy to levodopa on severity of OFF in Parkinson's disease. Eur J Neurol. 2011;18(12):1373-8.) reported on a sub-study of the previously published LARGO study that measured the efficacy of rasagiline 1mg, entacapone 200mg with each levodopa dose vs placebo in improving practically-defined OFF times in subjects with motor fluctuations. The inclusion criteria was the same as for the full LARGO study but in this sub-study hospitalized subjects undertook an overnight levodopa withdrawal for the partially defined OFF state assessments. The study demonstrated efficacy of rasagiline 1mg daily (n=32), compared to entacapone 200mg with each levodopa dose (n=36), over placebo (n=37) in improving practically-defined OFF score in subjects with motor fluctuations. 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).

Donepezil

Chung KA, Lobb BM, Nutt JG, Horak FB. Effects of a central cholinesterase inhibitor on reducing falls in Parkinson disease. Neurology. 2010;75:1263-9. The cholinesterase inhibitor donepezil was evaluated in 23 advanced PD subjects with falls (> 2 /week); 6 of whom had received prior STN DBS surgery. A crossover design of donepezil (5mg/d for 3w then 10mg/d for 2w /placebo and 3 w wash out period. The primary outcome of falls per day as assessed using weekly home completed diaries significantly decreased to 0.13 ($\pm$ 0.03)/ d with donepezil vs 0.25($\pm$0.08) /d with placebo ($p < 0.05$). . The absolute risk reduction was 0.12 falls/d (CI -0.09 – 0.33). There was no change in near falls frequency. No secondary outcomes included the Berg Balance scale and UPDRS III were significant. The baseline mean number of falls per day is 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 **QS 62%**

Methylphenidate

Espay AJ, Dwivedi AK, Payne M, Gaines L, Vaughan JE, Maddux BN, Slevin JT, Gartner M, Sahay A, Revilla FJ, Duker AP, Shukla R. Methylphenidate for gait impairment in Parkinson disease: a randomized clinical trial. Neurology 2011;76(14):1256-62. This was a double-blind, placebo-controlled crossover study of PD patients with moderate gait impairment (mean disease duration 10.9 years). 17 out of 23 randomized patients completed the study (i.e., dropout rate of 26%). Patients were

assigned to methylphenidate [maximum 80 mg/day, mean 64 mg/day] or placebo for 12 weeks, and crossed over after a three-week washout. This was a negative study, with no benefit from methylphenidate seen with the primary outcomes (change in a gait composite score of stride length and velocity) or secondary outcomes (Freezing of Gait Questionnaire, freezing diary (e.g. at the end of the study freezing was reduced in both groups from baseline mean 5.4 (±4) h/d to 3.2 (±2.9)/d with methylphenidate and 3.3 (±3)h with placebo, UPDRS, and measures of depression, sleepiness, and quality of life). As a category, “hypersexual, manic, irritability, sweating” symptoms were more frequent in methylphenidate-treated patients vs. placebo (5 vs. 0) as well as, surprisingly, lack of energy (5 vs. 1). This study was limited by small sample size and a relatively high dropout rate. It was also unclear what the baseline values for outcome variables were for both groups in the first phase of the study and at cross-over **QS 64%**

Moreau C, Delval A, Defebvre L, et al. Methylphenidate for gait hypokinesia and freezing in patients with Parkinson's disease undergoing subthalamic stimulation: a multicentre, parallel, randomised, placebo-controlled trial. Lancet Neurol. 2012;11(7):589-96 In this French multicentre, double-blind placebo-controlled study, 69 patients with advanced PD (median disease duration 17 years, median duration of bilateral STN DBS 5-6 years) and moderate-to-severe gait difficulty and freezing despite optimized treatment with dopaminergic drugs and DBS were randomized to receive methylphenidate (1 mg/kg/day [mean 71 mg] in three divided doses) (n=35) or placebo (n=34) for 90 days. The dropout rate was <6%. The primary outcome, the number of steps taken during the stand-walk-sit (SWS) test OFF-medication, improved significantly in the methylphenidate group compared to placebo (median 31 vs. 33 steps; P = 0.017, adjusted effect size 0.61). However, there was no difference in ON state thus clinical importance is unclear. SWS completion time, number of freezing episodes, and OFF-medication UPDRS III were also significantly improved in methylphenidate-treated patients. Methylphenidate was well tolerated and there were no serious adverse events, but treated patients had increased heart rate (mean 3.6 beats per minute) and decreased weight (mean 2.2 kg) compared with the placebo group; upper gastrointestinal symptoms were also more frequent. Methylphenidate improved daytime somnolence and apathy. **QS 91%**

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

Frazzitta G, Bertotti G, Riboldazzi G, et al Effectiveness of intensive inpatient rehabilitation treatment on disease progression in parkinsonian patients: a randomized controlled trial with 1-year follow-up *Neurorehabil Neural Repair* 2012 26: 144. 50 PD H&Y Stage III were randomised to 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. There were no drop outs. Primary outcome was UPDRS (total and II+III). The group undergoing IRT had no change in total and UPDRS II and III at 1 y compared to baseline (paired t-tests), whereas the control group significantly worsened in all UPDRS scores compared to baseline eg by 5.5 points for UPDRS III (paired t-tests). At the 12 month point, UPDRS III was 21 $\pm$ 6 in IRT group vs 28.7 $\pm$ 7 in control. 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). Limited interpretation is due to lack of statistical comparisons between IRT and control groups. **QS 65%**

Shulman LM, Katzel LI, Frederich M, Sorkin J et al Randomised Clinical Trial of 3 types of Physical Exercise for patients with Parkinson's disease JAMA Neurol 2013; 70(2):183-190. 80 PD subjects H&Y Stage I-III were enrolled into three 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. The primary outcomes were three motor tests: Gait speed (6 minute walk), cardiovascular fitness, and muscle strength. Multiple other secondary measures including UPDRS and PDQ were measured. Results showed that 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. **QS 76%**

Schenkman M, Hall DA, Barón AE, Schwartz RS, Mettler P, Kohrt WM. Exercise for People in Early- or Mid-Stage Parkinson Disease: A 16-Month Randomized Controlled Trial *Phys Ther 2012;92(11):1395-1410.* This study randomized PD H&Y Stage I-III patients to three 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) AE (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. Multiple measures of physical fitness were measured in addition to UPDRS and PDQ-39 scores. 96/121 patients completed the study and ITT analysis was performed. 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. Primary and secondary outcomes were similar between all groups

with the exception of superior walking economy in the AE 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. **QS 69%**

Movement strategy training with cuing or focused attention

Picelli Q, Melotti C, Origano F et al Does robotic gait training improve balance in Parkinson's disease? A randomized controlled trial. Parkinsonism and Related Disorders 18 (2012) 990-993. PD H&Y Stage III-IV subjects were randomized to 4 weeks of two different types of exercise interventions: A) Robot assisted gait training (a German manufactured device with harness/rope attachments assisting propulsion of gait); B) General physical therapy (control group, not posture/gait specific, i.e. joint mobilization, stretching, coordination exercises). Balance measures (Primary outcome of Berg Balance scale, Nutt's Rating; also multiple secondary measures) were performed at 4 weeks and also 4 weeks post treatment. Results favored robotic training in all primary and secondary outcomes at both study time points (BBS $p<0.001$ at 4 and 8 weeks; NUTT $p=0.001$ at 4 weeks and $p=0.002$ at 8 weeks) **QS 67%**

Braun S, Beurskens A, Kleynen M, Schols J, Wade D. Rehabilitation with mental practice has similar effects on mobility as rehabilitation with relaxation in people with Parkinson's disease: a multicentre randomised trial J Physiother. 2011;57(1):27-34. 47 PD Patients were randomized to two treatments as supplements to physical therapy (one hour/week): A) Mental imagery (individualized, tailored to each patient, imagining attempts at movements); B) Relaxation (control group) for 6 weeks of treatment. Three outcomes were measured: 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 **QS 72%**

Formalised patterned exercises

Li F, Harmer P, Fitzgerald K et al Tai Chi and Postural Stability in Patients with Parkinson's Disease N Engl J Med. 2012 February 9; 366(6): 511–519. 195 PD H&Y Stage I-IV subjects were randomized to three treatment groups: A) Tai Chi, 60 minute session twice weekly for 24 weeks; B) Progressive Resistance training; C) Stretching (control group). Interventions were carried out over a 6 month period. Primary outcomes (maximum excursion, directional control) were based on measurements from posturography with multiple secondary motor measurements. The primary outcome measurements were significantly better in the Tai Chi group that 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 **QS 88%**

Duncan RP, Earhart GM Randomized controlled trial of community-based dancing to modify disease progression in Parkinson disease. Neurorehabil Neural Repair. 2012 Feb;26(2):132-43. 62 PD H&Y Stage I-IV subjects were randomized to Tango (one hour, twice weekly) vs. Control (baseline activity) for 12 months. Primary outcome was change in MDS-UPDRS Part III, with multiple secondary measures of motor function. 35 subjects completed the protocol. 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. While the trial claims to provide evidence of "disease modification" it does not attempt to differentiate this from symptomatic effects **QS 69%**

Occupational Therapy

Sturkenboom IH, Graff MJ, Borm GF, Veenhuizen Y, Bloem BR, Munneke M, Nijhuis-van der Sanden MW. The impact of occupational therapy in Parkinson's disease: a randomized controlled feasibility study Clin Rehabil. 2012 Jul 18. 43 PD subjects with impaired ADLs were randomized to either no OT or underwent a flexible, non-uniform OT program with a maximum of 16 sessions (although the average number of completed sessions was 7.9). The primary outcomes (Canadian occupational performance measure, caregiver Zarit burden inventory) were not significantly different between both groups. **QS 67%**

Acupuncture

Cho SY, Shim SR, Rhee HY, Park HJ, Jung WS, Moon SK, Park JM, Ko CN, Cho KH, Park SU. Effectiveness of acupuncture and bee venom acupuncture in idiopathic Parkinson's disease. Parkinsonism Relat Disord. 2012 Sep;18(8):948-52. This study randomised 43 patients with stable PD to either acupuncture, bee venom acupuncture (both groups were treated twice weekly for 8 weeks, using 10 points), or control (no intervention). The analysis was not intention-to-treat and losses to follow-up were >10%. Assessors were blinded but patients were not. The primary outcome measure was the total UPDRS, defined as parts I-IV plus H & Y score. This was significantly improved in the analysed patients on acupuncture and bee venom acupuncture compared to placebo, with no significant differences between the active treatment arms. **QS 56%**

Repetitive Transcranial magnetic stimulation (rTMS)

Okabe S, Ugawa Y, Kanazawa I; Effectiveness of rTMS on Parkinson's Disease Study Group. 0.2-Hz repetitive transcranial magnetic stimulation has no add-on effects as compared to a realistic sham stimulation in Parkinson's disease. Mov Disord. 2003;18(4):382-8. This study evaluated the effects of low frequency (0.2Hz) rTMS in 85 PD subjects (mean H & Y stage 3). Subjects were randomised to 3 groups;

rTMS to right motor cortex; occipital cortex and sham once a week for 8 weeks. Evaluations were performed pre rTMS; at the end of treatment (8weeks) and then at 12 and 16 weeks. 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. The number of drop-outs was not reported and it was unclear how many subjects were included in the analysis. **QS 70%**

Hamada M, Ugawa Y, Tsuji S; Effectiveness of rTMS on Parkinson's Disease Study Group, Japan. High-frequency rTMS over the supplementary motor area for treatment of Parkinson's disease. Mov Disord. 2008;23(11):1524-31. This study evaluated the effect of high frequency (5Hz) rTMS in 99 PD subjects. There was a wide disease severity of included subjects with H & Y ranging from 2 to 4. Subjects were randomised to high frequency rTMS or sham stimulation over the supplementary motor cortex with weekly sessions for 8 weeks. The primary endpoint was UPDRS III and total UPDRS evaluated at weeks 2, 4, 6 and 8 during stimulation and at weeks 10 and 12 post treatment. Ratings were performed when subjects were midway between on and off, which was not clearly defined. There was a 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. There were no adverse events. **QS 73%.**

Yang YR, Tseng CY, Chiou SY, Liao KK, Cheng SJ, Lai KL, Wang RY. Combination of rTMS and Treadmill Training Modulates Corticomotor Inhibition and Improves Walking in Parkinson Disease: A Randomized Trial. Neurorehabil Neural Repair. 2012 Jul 10. [Epub ahead of print] This study evaluated high frequency (5Hz) rTMS and treadmill training together in 22 PD subjects, H & Y stage 2 -3, who were able to walk independently. Subjects were randomised to receive rTMS or sham to the motor cortex contralateral to the most affected side for 6 min followed by treadmill for 30 min, for 12 sessions over a 4w period. The outcome measures included speed of gait functions and included a timed 10m stand-walk test that was significantly improved by rTMS but treadmill speed was not significant y altered by rTMS. The dual intervention means it is hard to determine whether rTMS *per se* has an impact on PD gait and lack of other PD-related measures of gait function limits conclusions regarding clinical importance **QS 75%**.

Conclusions for symptomatic adjunct therapy to Levodopa

New conclusions

Pramipexole ER is *Efficacious* and the Practice implication is that of *Clinically Useful* as adjunct therapy for motor symptoms

Donepezil – there is *insufficient evidence* for use in PD patients for gait problems, and the practice implication is *investigational.*

Methylphenidate - due to conflicting data (one positive but in subjects post STN-DBS and one negative study) there is *insufficient evidence* at this time and the practice implication is *investigational* for use in PD patients with gait problems

rTMS –There is one negative study using low frequency rTMS and 2 positive studies of high frequency rTMS. Due to the conflicting data there is *insufficient evidence* regarding use of rTMS in PD. The clinical implication is that this intervention is *investigational*

There are no changes in conclusions for **Pramipexole IR** which remains efficacious and clinically useful.

Physical therapy remains likely efficacious and clinically useful.

Occupational therapy and **Acupuncture** remain as insufficient evidence and investigational

No new safety concerns

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)No New Studies

No change in conclusions

Table 5a Treatments for motor fluctuations (F)

Drug Class	Drug	Efficacy conclusions	Implications for clinical practice	Safety
Dopamine agonists Non-ergot	Pramipexole	Efficacious I	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 inhibitor	Standard formulation	Efficacious	Clinically useful	
	Controlled release	Insufficient evidence	Investigational	
	Rapid onset	Insufficient evidence	Investigational	
	Infusion	Likely efficacious	Investigational	
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

Pramipexole ER

Schapira AH,et al ; Pramipexole ER Studies Group. Extended-release pramipexole in advanced Parkinson disease: a randomized controlled trial. Neurology. 2011 23;77(8):767-74. This study compared once daily pramipexole extended release (ER) (av dose 2.7mg/d) vs three times daily pramipexole immediate release (IR) (2.8 mg/d) in 518 advanced PD over 18 weeks. There was a 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). 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. **QS 99%**

Mizuno Y, et al; Pramipexole ER Study Group. Efficacy and safety of extended- versus immediate-release pramipexole in Japanese patients with advanced and (L)-dopa-undertreated Parkinson disease: a double-blind, randomized trial. Clin Neuropharmacol. 2012;35(4):174-81. This study compared pramipexole ER (average daily dose 3.36mg/d) and pramipexole R (3.54 mg/d) in 130 advanced and L-dopa

undertreated PD patients. The population was not well defined and mixed thus 53.6% of subjects had motor fluctuations, including wearing off and on/off ; . The percentage of subjects with dyskinesia at baseline was not stated. In addition there was a second group of stable "undertreated" patients. The mean L-dopa dose was 299.1mg/d in the ER group and270.5 mg/day in the IR group There was no predefined efficacy endpoint and the study was not powered for non-inferiority. Outcome measures included percentage OFF time (in all 112 patients, including those without fluctuations at baseline) was- 5.8 for pramipexole ER, - 7.8 for pramipexole IR -7.8. The mean OFF time (all patients) was pramipexole ER -0.9 h./d and pramipexole IR -1.3 h/d (both significant vs baseline) **QS 86%**

Entacapone

Rascol O, Barone P, Behari M, Emre M, Giladi N, Olanow CW, Ruzicka E, Bibbiani F, Squillacote D, Patten A, Tolosa E. Perampanel in Parkinson disease fluctuations: a double-blind randomized trial with placebo and entacapone. Clin Neuropharmacol. 2012;35(1):15-20. This was a study in 723 PD subjects with motor fluctuations to evaluate a novel agent, perampanel (4 mg/d), placebo, or the active comparator, entacapone (200 mg with each dose of L-dopa) in 723 L-dopa-treated patients with PD with "OFF" problems over 18 weeks. The study was terminated early due to no efficacy of perampanel in other studies. The study was included due to the large group of subjects receiving entacapone (n = 234, 66% completed) vs placebo (n = 247, 69% completed). The primary outcome measure was the change from baseline in mean total daily OFF time based on diaries that showed superiority of entacapone; entacapone - 1.29 (-1.63, -0.96) h/d vs placebo - 0.82 (-1.16, -0.48)h/d (P = 0.034). There was no significant difference in daily ON time without dyskinesia. **QS 87%**

Surgery (Bilateral STN DBS and Gpi DBS)

Okun MS, Gallo BV, Mandybur G, et al. Subthalamic deep brain stimulation with a constant-current device in Parkinson's disease: an open-label randomised controlled trial. Lancet Neurol. 2012 Feb;11(2):140-9. In this study, Okun et al. evaluated the effects of STN DBS with a constant-current device (St. Jude Libram). Recruited patients had ≥ 6 hours daily OFF time or moderate-to-severe dyskinesia. Patients were randomly assigned to receive stimulation within 7 days of iplantation, or implantation without activation. Investigators and patients were not blinded to treatment allocation. The primary outcome variable was the 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). In the stimulation group, OFF-medication, ON-stimulation UPDRS Part III scores improved significantly by 39% from baseline (24·8 vs. 40·8) (p<0.0001 comparing the mean change from baseline in the stimulation vs. control groups). Adverse effects were similar

to other studies of DBS, including infections (4%) and intracranial hemorrhage (3%). 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, this study did not offer a comparison between the two types of devices. **QS 83%**

Odekerken, van Laar, Staal, et al Subthalamic nucleus versus globus pallidus bilateral deep brain stimulation for advanced Parkinson's disease (NSTAPS study): a randomised controlled trial [1] Lancet Neurol. 2013 Jan;12(1):37-44. (included as published on line 2012). In the Dutch NSTAPS study, the investigators compared bilateral GPi (n=65) vs. STN (n=63) DBS one year after surgery. Patients and assessors were masked to treatment. No significant difference was seen in either primary outcome: functional health as measured by the mean change in a generic disability scale (the Academic Medical Center Linear Disability Scale [ALDS; range of scale 0-100 points]), weighted by time spent in the off phase and on phase (3.0 in the GPi group vs. 7.7 in the STN group, P=0.28); and the number of patients with a negative composite score of cognitive, mood and behavioural effects (58% for GPi vs. 56% for STN, P=0.94). Secondary outcomes showed larger improvements for the STN group in the off-medication UPDRS III scores (20.3 vs. 11.4 points, P=0.03) and ALDS scores (20.3 vs. 11.8 points, P=0.04). There was no difference in the occurrence of adverse events between the two groups. The authors concluded that although there was no difference in the primary outcomes, the better improvement in off-phase motor symptoms and disability, and the need for less PD medications and lower battery consumption, favour the STN as the preferred target for DBS in PD. **QS 93%**

An extension of the Follett et al NEJM 2010 RCT of STN vs GPi DBS with open label extension with 36-month outcomes of GPi vs. STN DBS (n=89 and n=70) is reviewed below but with no QS rating. **Weaver FM, Follett KA, Stern M, et al. Randomized trial of deep brain stimulation for Parkinson disease: thirty-six-month outcomes. Neurology. 2012 Jul 3;79(1):55-65..** 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.

Conclusions for treatments for motor fluctuations (F)

New Conclusions

Pramipexole ER is *Efficacious* in treating motor fluctuations and is *clinically Useful.*

No change in conclusions for **Entacapone** which remains efficacious for motor fluctuations. **Bilateral STNDBS and GPi-DBS** are both efficacious for motor fluctuations.

There are no changes in safety concerns. For STN vs GPi DBS differing potential side-effect profile may alter choice for individual patients

Table 5b Treatments for dyskinesia

Drug Class	Drug	Efficacy conclusions	Implications for clinical practice	Safety
Dopamine agonists Non-ergot and ergot Ergot	All	Insufficient evidence	Investigational	As above
Levodopa/peripheral decarboxylase inhibitor	Infusion	Likely efficacious	Investigational	
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*	

Amantadine

Sawada H, Oeda T, Kuno S, Nomoto M, Yamamoto K, Yamamoto M, Hisanaga K, Kawamura T; Amantadine Study Group Amantadine for dyskinesias in

Parkinson's disease: a randomized controlled trial. PLoS One 2010;5(12):e15298 This was a RCT with a crossover design that evaluated amantadine 300mg/d (for 27 days) vs placebo for dyskinesia in a Japanese population. The drug was titrated at weekly intervals from 100mg, to 300mg/d so the maximal dose was only taken for 1 week. There was a down-titration and washout before the second treatment phase. The end point was videos recording performed by the subject's family at home and a blinded rating of the Rush Dyskinesia Scale. Unusual statistics were performed using a change in RDRS expressed as < 0 as a 'responder' or > or = 0 as a 'non-responder'. The population analysed was not ITT. Adjusted odds ratio for an improvement in RDSR with amantadine vs placebo was 10.4% (2.0 to 47) P = 0.002. The 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. **QS 83%.**

Levetiracetam

Stathis et al Levetiracetam for the management of levodopa-induced dyskinesia in Parkinson's disease. Mov Disord. 2011 Feb 1;26(2):264-70 The study was initially a RCT crossover trial using vs placebo with 76 subjects but the data after the crossover was excluded due to carry-over effects. Treatment was 1 week escalation, then 2 weeks maintenance for 500mg and then 1000mg/d with a 2w wash-out period. Power of the study was lost as only 38 subjects were enrolled. The primary end point of patient-competed diaries of 'On time with dyskinesia' was reduced by 75 min (CI 3.31, 12.4 P = 0.002) for levetiracetam 1g/d; statistical comparisons were not clearly defined. Secondary endpoints of UPDRS part 32 was significant; Goetz dyskinesia scale after a levodopa challenge was not significant. Common adverse events included dizziness and somnolence but only one subject withdrew. **QS 73.2%**

Wolz M, et al Levetiracetam for levodopa-induced dyskinesia in Parkinson's disease: a randomized, double-blind, placebo-controlled trial. J Neural Transm. 2010 Nov;117(11):1279-86 This study evaluated levetiracetam (mean final dose possibly 1800 mg) vs placebo in 34 PD subjects with bothersome dyskinesia . Treatment was escalated over 7w with a 4 w maintenance period. There was no significant change in the primary endpoints; the modified Abnormal Involuntary Movement Scale (AIMS) mean % change from baseline was -1.5 (-26%) for levetiracetam (p = 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). Likewise, secondary outcomes were not significantly improved and included patient diary assessments of ON time with and without dyskinesia and OFF times; there was also an objective measure using a levodopa challenge using CAPSIT-PD protocol were not significantly improved vs placebo. No significant adverse events, and no worsening of PD using UPDRS III. There was a large range of dyskinesia scores using AIMS at baseline which may have impacted validity of outcome measures **QS 81.5%**

Physical Therapy

Frazzitta *G,* Bertotti G, Morelli M et al , Rehabilitation improves dyskinesias in Parkinsonian patients: a pilot study comparing two different rehabilitative treatments NeuroRehabilitation 30 (2012) 295–301 This was an inpatient intensive rehabilitation study that randomized patients to either intensive inpatient therapy (IRT) with 3 hours/day, 5 days/week of treadmill, stability, and stretching exercises, and were sent out with instructions to continue these exercises. The less supervised control group was assigned to general home exercises. 50 Hoehn and Yahr stage III PD subjects that could walk without assistance were enrolled. Primary outcomes were UPDRS (total and parts II + III), secondary outcomes were total levodopa dose and effect of a second IRT stay at the end of 12 months. The group undergoing IRT had better improvement in motor outcomes 12 months after IRT (UPDRS II 33% and UPDRS III 29% reduction) than the control group (22% and 22% reduction, respectively), and the benefit of the second IRT treatment was similar to the first treatment. The IRT group was on less Levodopa equivalents at 12 months (- 210 mg vs -30 mg). **QS 59.5%**

Bilateral STN and GPi DBS

See above with Motor Fluctuations section

Conclusions for treatments for dyskinesia

New Conclusions

Levetiracetam was positive in one low quality study and negative in one good quality study; thus due to the conflicting evidence the efficacy conclusion is ***i****nsufficient evidence;* and the practice implication is *investigational*

Physical therapy as inpatient was positive in one low quality study; the efficacy conclusion is ***i****nsufficient evidence;* and the practice implication is *investigational*

Other conclusions remain the same:-

Amantadine remains efficacious for treating dyskinesia.

STn DBS and GPi DBS are both efficacious for dyskinesia.

No change in safety conclusions

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