Appendix C: Review protocols

	Details -	Additional comments
Review question 1	What is the comparative effectiveness of pharmacological interventions to treat daytime hypersomnolence associated with PD?	
Objectives	To determine the comparative effectiveness of pharmacological interventions for daytime hyper somnolence associated with PD	
Type of review	Intervention review	
Language	English language only	
Study design	Systematic review RCT	
Status	Date limit imposed post previous guideline	
Population	People with a confirmed diagnosis of PD whom are suffering from daytime hyper somnolence	
Intervention	• Modafinil • Amantadine • Selegeline • Sodium oxybate • Pitolisant	NOTE: DAs can cause/exacerbate EDS. Reduction in DA may also be useful treatment, but this not specific pharmacological intervention to treat EDS. Sleep disturbance to be included as adverse event when examining pharmacological therapies.
Comparator	• Placebo	
Outcomes	• Adverse events • Resource use and cost • Sleep scale outcome measures ○ Epworth sleepiness scale • Health related quality of life • Carer burden	
Other criteria for inclusion / exclusion of studies	Exclusion: People without a confirmed diagnosis of PD Study design: • Case-control • Cohort study • Narrative review • Case-study • Qualitative review	Hypersomnolence also referred to as excessive daytime sleepiness (EDS). Use both search terms.
Review strategies	RCT evidence will only be used if: • no high quality up to date systematic reviews are identified or • new RCTs need to be added systematic review evidence	
Identified papers	See previous guideline	

	Details	Additional comments
Review question 2	What is the effectiveness of physiotherapy (physical activity) compared with usual care?	
Objectives	To ascertain the usefulness of physiotherapy in the management of the following symptoms of PD: Gait Functional mobility and balance Falls Motor function and mobility	Physiotherapy may not necessarily be delivered by physiotherapist. GDG recognised physical interventions may be delivered by others in the community, and information may be delivered by i.e. GP rather than physiotherapist
Type of review	Intervention review	
Language	English	
Study design	Systematic review or RCT	
Status	Date limited to post-existing guidance	
Population	People with a confirmed diagnosis of PD	
Intervention	Physiotherapy: exercise therapy; tai chi; alexander technique; cueing techniques; dance; wii interactive fitness and balance programs; physical activity; nordic walking	
Comparator	Usual care	Usual care can include no treatment, delayed onset of treatment, waiting list
Outcomes	1. Resource use and cost 2. Health related quality of life: PDQ39 3. Freezing 4. Falls; Berg balance score 5. Speed of gait: 2 or 6 min; 10m or 20m; timed up and go test; stride/step length 6. UPDRS 7. Depression 8. Posture 9. Carer outcomes	Relevant scales: • 2 or 6 min walk test • Freezing of gate questionnaire • Time to walk 10m or 20m • Stride length • Step length • Timed up and go test • Functional reach • Berg balance score • Number of falls • Falls efficacy scale • UPDRS ADL - motor function • PDQ39
Other criteria for inclusion / exclusion of studies	People without a confirmed diagnosis of PD Study design: • Case-control • Cohort study • Narrative review • Case-study • Qualitative review	
Review strategies	RCT evidence will only be used if: • no high quality up to date systematic reviews are identified or • new RCTs need to be added systematic review evidence	
What the GDG can recommend with this review	The GDG will be able to: • recommend the use of physiotherapy	

What the GDG will not be able to recommend with this review	The GDG will not be able to: • recommend the use of one physiotherapy over another	
Identified papers	Refer to previous guideline - PD REHAB study	

	Details	**Additional comments**
Review question 3	What is the effectiveness of nutritional support compared with usual care?	
Objectives	To ascertain the usefulness of nutritional support in the management of PD and effect on motor features and cognitive function	
Type of review	Intervention review	
Language	English language studies only	
Study design	RCT If RCT evidence insufficient move on to Cohort study evidence	
Population	People with a confirmed diagnosis of PD	Be aware of patients with swallowing problems which is a direct impact of Parkinson's and can effect diet May need to subgroup by stage of disease
Intervention	Nutritional support and diet supplements	Nutritional support may include: • advice (including leaflets) through to nutritionist input into the clinical management • management of postural hypotension; • management of constipation; • use of nutritional supplements/nutrition support/tube feeding; • dietetic involvement with compulsive behaviours/compulsive eating associated with PD meds.
Comparator	Usual care	Usual care can include no treatment.
Outcomes	1. Resource use and cost 2. Health related quality of life 3. UPDRS 4. Depression or anxiety 5. Social interaction 6. Cognitive function 7. Weight outcomes (including MUST scores, BMI or other indicators of malnutrition/weight gain) 8. protein distribution and absorption of dopamine medication; 9. Energy expenditure due to dyskinesia 10. Carer outcomes	Weight gain generally associated with compulsive eating or lack of mobility Weight loss generally associated with dyskinesia or malnutrition associated with dementia Nutritional supplements of interest would include products for gaining weight or tube feeding such as Ensure
Other criteria for inclusion / exclusion of studies	People without a confirmed diagnosis of PD Study design: • Case series • Narrative review	
Review strategies	RCT evidence will only be used if: • no high quality up to date systematic reviews are identified or	

	• new RCTs need to be added systematic review evidence	
Identified papers	See previous guideline	

	Details	Additional comments
Review question 4	What are the needs of people with Parkinson's disease for advance directives and palliative care plans throughout the course of their disease?	
Objectives	To determine the needs of people with Parkinson's disease for advance directives and palliative care plans throughout the course of their disease	
Type of review	Information and support	
Language	English language only	
Study design	Systematic review Qualitative	
Status	No date limit imposed	
Population	People with a confirmed diagnosis of PD	
Information needs	Information needs to help people process and plan for the various stages of their disease until end of life. Information needs to aid people with PD and their family and carers to put advance care directives into place	Palliative care team should be engaged when patient no longer seen in secondary care Encouraging case management is the goal.
Comparator	N/A	

Outcomes	• Patient information needs
	  ○ Legal power of attorney
	  ○ sharing of information with family and carer
	  ○ psychiatric support
	  ○ social support
	• Carer and family needs
	  ○ psychiatric
	  ○ social support
	  ○ information
	• Resource use and cost
	• End of life nutritional management
	• End of life medication management
	• Carer quality of life
		Establishing an advance care plan is key.
		Want to encourage clinician to mention palliative care issues i.e. power of attorney

Other criteria for inclusion / exclusion of studies	People without a confirmed diagnosis of PD Study design: • No study design will be excluded, except case report	
Review strategies	Qualitative studies may be used in a thematic analyses to inform specialist information needs	
Identified papers	None	

	Details	Additional comments
Review question 5	What is the effectiveness of speech and language therapy (SLT) compared with usual care?	
Objectives	To ascertain the usefulness of SLT in the management of the following complications of PD? Speech and communication Swallowing	Outcomes in Cochrane: loudness of voice, speech monotonicity, and articulation
Type of review	Intervention review	
Language	English language studies only	
Study design	Systematic review or RCT	
Status	Date limited to post existing guidance	
Population	People with a confirmed diagnosis of PD	
Intervention	SLT • vocal training – lee silvermal (LSVT) • rate of speech control • breathing control • auditory feedback alteration • singing • swallowing or dysphagia therapy	PD COMM uses Lee Silverman vs NHS SLT Apps for voice control
Comparator	Usual care	Usual care can include no treatment, delayed onset of treatment, waiting list
Outcomes	1. intelligibility of speech: vocal loudness, monotonicity; articulation 2. Resource use and cost. 3. Disease severity - UPDRS 4. Health related quality of life - PDQ39 5. Voice handicap 6. Dysarthria 7. Swallowing efficiency: mL per swallow. 8. Nutrition 9. Drooling Choking, aspiration, and penetration (of foodstuffs into laranx) 10. Carer outcomes	Outcomes in Cochrane: • Vocal loudness, speech monotonicity, and articulation PD COMM: • Voice handicap index • dysarthric speech • vocal loudness • PDQ-39 • EQ-5D
Other criteria for inclusion / exclusion of studies	People without a confirmed diagnosis of PD Study design: • Case-control • Cohort study • Narrative review • Case-study • Qualitative review Self-administered techniques IN swallowing protocol: If there are no RCT's we will examine cohort studies evidence	
Search strategies	TBC	Dysarthria Vocal loudness Speech Hypophonia Communication Articulation
Review strategies	RCT evidence will only be used if: • no high quality up to date systematic reviews	

	are identified or • new RCTs need to be added systematic review evidence	
Identified papers	See previous guideline - PDCOMM study	

	Details	Additional comments
Review question 6	What are the specific information needs of women of child-bearing age with Parkinson's disease	
Objectives	To ascertain the information needs specific to women of child-bearing age in relation to the diagnosis and management of Parkinson's disease	
Type of review	Information and support	
Language	English language studies only	
Study design	No restrictions except case-reports	
Status	No date limit on search	
Population	Women of childbearing age with a confirmed diagnosis of PD	
Intervention	Any information needs identified specific to women of childbearing age with PD	
Comparator	Usual care	
Outcomes	1. fertility complications of PD 2. contraception advice 3. genetic counselling 4. frequency of antenatal visits and support throughout pregnancy 5. Breast feeding 6. Drug treatment changes in pregnancy 7. depression/anxiety and Post Natal Depression 8. Safety profile of drug treatments suggested	• Medication • Balance problems • Slowness of movement • Nausea and vomiting • Constipation • Fatigue Pregnant mothers may require information about genetic risks to baby, signposting for further information – Care Plan Information about drug on baby while pregnant Link to nutrition (Nutrition in Pregnancy) Link to exercise Ongoing carer and family support, information fo them
Other criteria for inclusion / exclusion of studies	Women outside childbearing age People without a confirmed diagnosis of PD Study design: • Case-study	
Review strategies	Qualitative studies may be used in a thematic analyses to inform specialist information needs	
Identified papers	None	

	Details	Additional comments
Review question 7	What is the effectiveness of occupational therapy (OT) compared with usual care on the complications of PD?	
Objectives	To ascertain the usefulness of OT in maintaining function of people with PD	
Type of review	Intervention review	
Language	English language studies only	
Study design	Systematic review or RCT	
Status	Date limited to post existing guidance	
Population	People with a confirmed diagnosis of PD	
Intervention	A person delivering occupational therapy interventions	
Comparator	Usual care	Usual care can include no treatment, delayed onset of treatment, waiting list
Outcomes	1. Resource use and cost 2. Health related quality of life: PDQ39 3. Functional tasks (eg. upper limb function) 4. Workplace adjustments 5. Activity of daily living 6. Recreation and leisure and participation 7. Driving 8. Cognition 9. Fatigue 10. Sleep 11. Anxiety/ mood	PD OT trial outcomes: • NEADL (ADL score) [stroke outcome] • Mobility index • UPDRS ADL • PDQ39 • EQ52 score • HADS anxiety • HADS depression • Continued employment • Workplace absence • Driving assessment • Parkinson's sleep scale
Other criteria for inclusion / exclusion of studies	Exclude people without a confirmed diagnosis of PD Consider the following study designs if **no** RCT evidence is found: • Case-control • Cohort study Exclude: • Narrative review • Case-study • Qualitative review	
Review strategies	RCT evidence will only be used if: • no high quality up to date systematic reviews are identified or • new RCTs need to be added systematic review evidence	
Identified papers	See previous guideline - PD REHAB study	

	Details	Additional comments
Review question 8	What factors should healthcare professionals consider as potential predictors for the development of impulse control behaviours as an adverse effect of dopaminergic treatment?	Hedonistic homeostatic dysregulstion (HHP)
Objectives	To determine potential predictors for the development of impulse control disorder	Specialists want to raise awareness of this common adverse effect and lower tolerance for diagnosing this
Type of review	Prognostic review	
Language	English language only	
Study design	We will only examine evidence from multivariate analysis from: Retrospective or prospective cohort studies Case-control	Weintraub, 2013 Neurology
Status	No date limit	
Population	Patients with a confirmed diagnosis of Parkinson's disease currently taking dopaminergic medication	
Predictors	Dopaminergic medication: • Prolonged release • Immediate release • Transdermal • Levodopa • Apomorphine	Sex Age Previous history and family history Disease duration Disease severity Dosage
Other criteria for inclusion / exclusion of studies	People without a confirmed diagnosis of PD Case-reports	
Identified papers	None	

	Details	Additional comments
Review question 9	How should dopaminergic treatment be managed in people who have developed impulse control disorder as an adverse effect?	
Objectives	To determine optimal management strategy for ICD as an adverse effect of dopaminergic treatment	
Type of review	Intervention review	
Language	English language studies only	
Study design	RCT evidence for adjunctive treatment – pharma or behaviour Cohort evidence for dopaminergic management	Okai et al., - CBT Amantadine study Naltrexone
Status	No date limit imposed	
Population	Those with a confirmed diagnosis of Parkinson's disease who are currently on dopaminergic therapy and have a diagnosis of impulse control disorder	
Intervention	• Titration of dopaminergic therapy at different levels of reduction • Change in type of dopaminergic therapy	
Comparator	• Usual care • Titration of dopaminergic therapy at different levels of reduction • Change in type of dopaminergic therapy • Adjunctive medication use • Psychological intervention	
Outcomes	Clinical/Patient improvement 1. adverse effects 2. Resource use and cost. 3. Disease severity - UPDRS 4. Health related quality of life - PDQ39 5. ICD measure: QUIP 6. Nutrition and overeating 7. carer quality of life	
Other criteria for inclusion / exclusion of studies	Persons who do not have a confirmed diagnosis of PD, Persons with PD whom are not currently on dopaminergic therapy Study design: • Narrative review • Case-study • Qualitative review	
Identified papers	None	

	Details	Additional comments
Review question 10	What are the information needs of people with Parkinson's disease and their families and carers about the potential for impulse control disorder (ICD) when considering or starting dopaminergic treatment?	
Objectives	To determine the information needs of people with PD and their families about the potential for ICD development when on dopaminergic treatment	Not taking levodopa is not an option for PD patients from a point in their treatment so this is important information for all people with PD
Type of review	Information and support	
Language	English language only	
Study design	No restrictions imposed, except case studies. Qualitative methodologies (survey, interview, questionnaire) are best suited to address this review question.	
Status	No date restrictions	
Population	People with a confirmed diagnosis of PD and their family and carers who are considering dopaminergic therapy	
Intervention	Any information needs identified specific to people with PD and their carer(s) who are considering dopaminergic therapy	The intervention will be people taking dopamine agonists alone, dopamine agonists with Levadopa and levadopa
Comparator	Usual care, or N/A for qualitative studies	
Outcomes	Salient Information needs might include: • Signs and symptoms of ICD; • Pre-existing risk factors in the person with Parkinson's; • Risks from different therapies e.g. dopamine agonists; • Who to contact if an ICD is suspected e.g. consultant, Parkinson's nurse; • Behavioural and therapeutic strategies available if an ICD occurs; • Adverse effects • Health related quality of life • Resource use and cost • Patient experience • Carer experience	Information for patients, their families and carers what it is how it can manifest and what can be done to stop/control ICD
Other criteria for inclusion / exclusion of studies	Case studies Populations of people who do not have a confirmed diagnosis of PD	It is not a time limit but is generally triggered by size of dose. Individuals differ and individuals differ depending on the brand of drugs being taken and the combination of the drugs being prescribed and the size of dose
Review strategies	Qualitative studies may be used in a thematic analyses to inform specialist information needs	
Identified papers	None	

	Details	Additional comments
Review question 11	What is the comparative effectiveness of pharmacological interventions to treat nocturnal akinesia associated with PD?	
Objectives	To determine the comparative effectiveness of pharmacological interventions to treat nocturnal akinesia associated with PD	
Type of review	Intervention review	
Language	English language only	
Study design	Systematic review RCT	
Status	Date limit imposed post previous guideline	
Population	People with a confirmed diagnosis of PD whom are suffering from sleep disturbance: nocturnal akinesia or RBD	
Intervention	• Immediate-release levodopa • Controlled release levodopa • Prolonged release dopamine agonist (including transdermal patch) • Standard-release dopamine agonist • Apomorphine • Mirtazapine • Benzodiazepine: Clonazepam • Pregabalin • Melatonin • Rivastigmine • Gabapentin	NOTE: very little evidence exists in RCT for these different drugs in these disorders. Much of literature is in populations other than PD
Comparator	• Placebo • Active Comparative	
Outcomes	• Adverse events • Resource use and cost • PD sleep scale • NADCS (nocturnal akinesia, dystonia, cramps score • PD nonmotor scale • Health related quality of life • Carer related quality of life	
Other criteria for inclusion / exclusion of studies	Exclusion: People without a confirmed diagnosis of PD Study design: • Case-control • Cohort study • Narrative review • Case-study • Qualitative review	
Review strategies	RCT evidence will only be used if: • no high quality up to date systematic reviews are identified or • new RCTs need to be added systematic review evidence Intention to treat meta analyses	
Identified papers	See previous guideline	

	Details	Additional comments
Review question 12	What is the comparative effectiveness of pharmacological interventions for orthostatic hypotension associated with PD?	Other very effective non-pharma therapeutic options. Make sure to include these in clinical intro to chapter (from CG35)
Objectives	To determine the comparative effectiveness of pharmacological interventions for orthostatic hypotension associated with PD	
Type of review	Intervention review	
Language	English language only	
Study design	Systematic review of RCT's RCT If no RCT evidence is available, the following study types will be considered: • Case series • Prospective cohort studies	
Status	Date limit imposed post previous guideline	
Population	People with a confirmed diagnosis of PD whom are experiencing symptoms of orthostatic hypotension	

Intervention	• Salt-retaining steroids
	  ○ Fludrocortisone
	• Direct-acting sympathomimetic
	  ○ Domperidone
	  ○ Droxidopa
	  ○ Fipamezole
	  ○ Midodrine
	  ○ Ephedrine
	• Caffeine
	• NSAID's
		NB: Other advice given to PD patients with orthostatic hypotension: adjusting medicines that cause OT; Adding salt to meals, to wear support stockings, keep out of the sun, not to stand for long periods, take plenty of fluids before standing, eat small, frequent meals and gentle exercise

Comparator	• Placebo • Other comparator drugs	
Outcomes	• Adverse events • Mortality • Injury (fracture) • Resource use and cost • Non-motor features ○ Hypotension-related outcome scales • Blood pressure • Autonomic symptom scale • Falls • Heath related quality of life • Carer quality of life and carer burden	
Other criteria for inclusion / exclusion of studies	Exclusion People without a confirmed diagnosis of PD Study design: • Case-control • Cohort study • Narrative review • Case-study • Qualitative review	
Review strategies	RCT evidence will only be used if: • no high quality up to date systematic reviews	

	are identified or • new RCTs need to be added systematic review evidence Intention to treat meta analyses	
Identified papers	None	

	Details	Additional comments
Review question 13	What is the comparative effectiveness of pharmacological interventions for thermoregulatory dysfunction / hyperhidrosis associated with PD?	The key to the management is to optimise dopaminergic therapy and minimise the off state and dyskinesia which are the two states most often associated with hyperhidrosis. Make sure to include this in clinical introduction.
Objectives	To determine the effectiveness of pharmacological interventions for thermoregulation associated with PD	
Type of review	Intervention review	
Language	English language only	
Study design	Systematic review RCT	
Status	Date limit imposed post previous guideline	
Population	People with a confirmed diagnosis of PD whom are suffering from thermoregulation	
Intervention	• Levodopa • Dopamine agonists • Propantheline bromide Clonidine • Anticholinergic drugs	Some of these therapies may also exacerbate symptoms in some patients
Comparator	• Placebo • Other comparator drugs	
Outcomes	• Adverse events • Mortality • Resource use and cost • Disease severity- UPDRS • Health related QoL • Carer burden and quality of life • Thermoregulatory sweat test • Silastic sweat imprint • Quantitative sudomotor axon reflex test to test thermoregulatory pathways • Hyperhidrosis severity score	
Other criteria for inclusion / exclusion of studies	People without a confirmed diagnosis of PD Study design: • Case-control • Cohort study • Narrative review • Case-study • Qualitative review	
Review strategies	RCT evidence will only be used if: • no high quality up to date systematic reviews are identified or • new RCTs need to be added systematic review evidence Intention to treat meta analyses	
Identified papers	None	

	Details	Additional comments
Review question 14	What is the comparative effectiveness of levodopa preparations, monoamine oxidase B inhibitors, dopamine agonists and anticholinergics as first-line treatment of motor symptoms?	
Objectives	To determine the comparative effectiveness of levodopa preparations, monoamine oxidase B inhibitors, dopamine agonists and anticholinergics as first-line treatment of motor symptoms	
Type of review	Intervention review	
Language	English language only	
Study design	Systematic review RCT	
Status	Date limit imposed post publication of previous guideline	
Population	People with a diagnosis of PD confirmed by a specialist and commencing pharmacotherapy.	

intervention	• levodopa:
	  ○ co-beneldopa
	  ○ co-careldopa)
	• monoamine oxidase B inhibitors :
	  ○ selegiline
	  ○ rasagiline
	• dopamine agonists
	  ○ ropinirole
	  ○ pramipexole
	  ○ rotigotine
	• amantadine
	• combinations of above comparison
		Need to know how much different treatments vary. May need separate analysis on efficacy or safety profiles
		Subtle differences between DA's – failure on one does not imply failure on whole class
		Stalevo, beta blockers, anticholinergies not licenced as initial therapy
		Combinations OK as long as population is drug naive
		GDG happy to meta-analyse effectiveness of classes of drugs but wish to report safety outcomes separately as different drugs have different side effects.

Comparator	• placebo • each other (head to head comparison)	
Outcomes	1. Adverse events – trial discontinuation 2. Disease severity: motor symptoms - UPDRS 3. UPDRS – ADL 4. non motor symptoms : hallucinations, ICD 5. off time 6. dyskinesia 7. health related quality of life 8. carer quality of life	Apart from adverse events, outcomes will be analysed at class level
Other criteria for inclusion / exclusion of studies	People who do not have a confirmed diagnosis of PD People with PD who have already commenced pharmacological treatment for motor features of PD Study design: • Case-control • Cohort study • Narrative review • Case-study • Qualitative review	
Review strategies	RCT evidence will only be used if: • no high quality up to date systematic reviews are identified or • new RCTs need to be added systematic review evidence	
Identified papers	See previous guideline	

	Details	Additional comments
Review question 15	In people for whom deep brain stimulation (DBS) and levodopa–carbidopa intestinal gel (LCIG) are treatment options, what is the comparative effectiveness of DBS, LCIG, and best medical treatment?	
Objectives	To determine the comparative effectiveness of DBS, and LCIG	
Type of review	Intervention review	
Language	English language studies only	
Study design	Systematic review RCT	
Status	No date limit imposed	
Population	People with a confirmed diagnosis of PD who meet the eligibility criteria for consideration of surgery and LCIG. Best medical therapy no longer optimally controlling symptoms	
intervention	DBS surgery of: • STN + best medical therapy • GPI + best medical therapy • Thalamus + best medical therapy • Pedunculopontine nucleus + best medical therapy • Zona incerta LCIG	NB: different surgical targets will NOT be compared. We will pool all surgical targets to examine efficacy of 'surgery'
Comparator	• Best medical treatment	Need to make sure this is clearly defined, especially in terms of apomorphine.

Outcomes	• Adverse events – perioperative
	• Adverse events –long term complications
	• Symptom severity: UPDRS, dyskinesia
	• "on" and "off" time
	• Disease progression: Hoen & Yahr
	• Neuropsychiatric non-motor features:
	  ○ Cognitive impairment
	  ○ Sleep disorder
	  ○ Suicidal ideation
	• Health related quality of life- patient
	• Health related quality of life: carer
	• Medication load
	• Balance and falls
	• Information to inform decision making
	• Resource use and cost
	• Time to full time institutional care
		Adverse events can include: lead migration, weight gain, hardware complications, speech and swallowing difficulties;
		Peri and postoperative events may include withdrawals

Other criteria for inclusion / exclusion of studies	People without a confirmed diagnosis of PD or who are contraindicated for one or more of the interventions of interest. Study design: • Case-control • Cohort study • Narrative review • Case-study • Qualitative review	

Review strategies	RCT evidence will only be used if: • no high quality up to date systematic reviews are identified or • new RCTs need to be added systematic review evidence	
Identified papers	See previous guideline	

	Details	Additional comments
Review question 16	Is there a benefit in receiving deep brain stimulation (DBS) in earlier, stages of PD compared to usual care?	
Objectives	As above	
Type of review	Intervention review	
Language	English language only	
Study design	RCT Systematic review If RCT or systematic review unavailable, will consider: • Cohort study	
Status	No limits imposed	
Population	People with a confirmed diagnosis of Parkinson's who: • Within 5 years of developing motor complications Or • Hoehn & Yahr stage <3	EARLYSTIM key trial. Population was within 3 years of developing motor complications. Difference between motor symptom and complication. Complication
Intervention	• Early intervention surgery + usual care	Defining early versus late. Need to be clear on whether use A) time on levodopa B) time since diagnosis to define early vs. late C) Hoehn and Yahr stage of disease
Comparator	• usual care	Need very clear definition of late

Outcomes	• Adverse events – perioperative
	• Adverse events –long term complications
	• Symptom severity: UPDRS, dyskinesia
	• "on" and "off" time
	• Disease progression: Hoehn & Yahr
	• Neuopsychiatric non-motor features:
	  ○ Cognitive impairment
	  ○ Sleep disorder
	  ○ Suicidal ideation
	• Health related quality of life- patient
	• Health related quality of life: carer
	• medication load
	• balance and falls
	• Information to inform decision making
	• Resource use and cost
	• Time to full time institutional care
		Adverse events can include: lead migration, weight gain, hardware complications, speech and swallowing difficulties;
		Peri and postoperative events may include withdrawals

Other criteria for inclusion / exclusion of studies	People without a confirmed diagnosis of PD Study design: • Case-control • Cohort study • Narrative review • Case-study • Qualitative review	
Review strategies	RCT evidence will only be used if: • no high quality up to date systematic reviews are identified or • new RCTs need to be added systematic review evidence	
Identified papers	See previous guideline	

	Details	Additional comments
Review question 17	In people who are contraindicated for deep brain stimulation, what is the effectiveness of levodopa–carbidopa intestinal gel (LCIG) plus best medical therapy compared to best medical therapy alone?	
Objectives	To determine the clinical and cost effectiveness of LCIG	
Type of review	Intervention review	
Language	English language studies only	
Study design	RCT	
Status	No date limit imposed	
Population	People with a confirmed diagnosis of PD - *who have been deemed inappropriate candidates for surgical intervention, who are levodopa-responsive, in whom dopaminergic and adjuvant therapies no longer adequately control the motor symptoms of PD*	When are people offered LCIG? i.e. certain consideration criteria like when contraindicated for surgery?
intervention	LCIG	
Comparator	Best medical therapy, which may include apomorphine	
Outcomes	1. Adverse events – perioperative 2. Adverse events –long term complications 3. Symptom severity: UPDRS, dyskinesia 4. "on" and "off" time 5. Disease progression: Hoen & Yahr 6. Neuopsychiatric non-motor features: a. Cognitive impairment b. Sleep disorder c. Suicidal ideation 7. Health related quality of life- patient 8. Health related quality of life: carer 9. medication load 10. balance and falls 11. Information to inform decision making 12. Resource use and cost 13. Time to full time institutional care	• Adverse events can include: lead migration, weight gain, hardware complications, speech and swallowing difficulties; • Peri and postoperative events may include withdrawals
Other criteria for inclusion / exclusion of studies	People without a confirmed diagnosis of PD Study design: • Case-control • Cohort study • Narrative review • Case-study • Qualitative review	
Review strategies	RCT evidence to be used As this drug is not recommended for commissioning of routine use by NHS England and is new, may need to conduct a call for evidence	
Identified papers	See previous guideline	

	Details	Additional comments
Review question 18	In people who are contraindicated for levodopa–carbidopa intestinal gel (LCIG), what is the effectiveness of deep brain surgery plus best medical therapy, compared to best medical therapy alone?	
Objectives	To determine the effectiveness of DBS plus best medical therapy compared with best medical therapy alone?	
Type of review	Intervention review	
Language	English language studies only	
Study design	Systematic review RCT	
Status	No date limit imposed	
Population	People with a confirmed diagnosis of PD - *who have been deemed inappropriate candidates for LCIG and in whom dopaminergic and adjuvant therapies no longer adequately control the motor symptoms of PD*	
intervention	DBS surgery of: • STN + best medical therapy • GPI + best medical therapy • Thalamus + best medical therapy • Pedunculopontine nucleus + best medical therapy • Zona incerta	NB: different surgical targets will NOT be compared. We will pool all surgical targets to examine efficacy of 'surgery'
Comparator	Best medical therapy, which may include apomorphine	

Outcomes	1. Adverse events – perioperative
	2. Adverse events –long term complications
	3. Symptom severity: UPDRS
	4. Disease progression: Hoen & Yahr
	5. Neuopsychiatric non-motor features:
	  o Cognitive impairment
	  o Sleep disorder
	  o Suicidal ideation
	6. Health related quality of life- patient
	7. Health related quality of life: carer
	8. medication load
	9. balance and falls
	10. Information to inform decision making
	11. Resource use and cost
	12. Time to full time institutional care	

Other criteria for inclusion / exclusion of studies	People without a confirmed diagnosis of PD Study design: • Case-control • Cohort study • Narrative review • Case-study • Qualitative review	
Review strategies	RCT evidence will only be used if: • no high quality up to date systematic reviews are identified or • new RCTs need to be added systematic review evidence	
Identified papers	See previous guideline	

	Details	Additional comments
Review question 19	What is the comparative effectiveness of pharmacological interventions as adjuvants to oral levodopa preparations?	
Objectives	To determine the comparative effectiveness of pharmacological interventions as adjuvants to oral levodopa	
Type of review	Intervention review	
Language	English language only	
Study design	Systematic review RCT	
Status	Date limit imposed post publication of previous guideline	
Population	People with PD on oral levodopa monotherapy preparations and who are experiencing inadequate symptomatic control, such as exhibiting signs of wearing off or increasing motor symptoms	

Intervention	Oral levodopa preparations plus:
	• modified release levodopa preparations
	• monoamine oxidase B inhibitors :
	  ○ Selegiline
	  ○ Rasagiline
	• dopamine agonists
	  ○ Ropinirole
	  ○ Pramipexole
	  ○ Rotigotine
	  ○ Pergolide
	  ○ Cabergoline
	  ○ Bromocriptine
	  ○ Apomorphine
	• amantadine
	• COMT inhibitors
	  ○ Entacapone
	  ○ Tolcapone
	• anticholinergics (anti-muscarinics)
	  ○ Benzhexol (Trihexyphenidrl)
		Side effect profile important to take into account for each drug
		
		Tolcapone tends to be more effective but have much more serious side effects than entacapone. Tolcapone does not have marketing authorisation for adjuvant use. Explicit in SPC not to use this and to use entacapone instead. However, as the committee may wish to consider recommendations for which drugs to use if a first line option fails, it was felt necessary to include tolcapone in the evidence base.
		
		Levodopa with entacapone can be treated as the same intervention as Stalevo (combined tablet)
		
		Anti-cholinergics should be included as not licenced but a "do not" recc may be useful
		
		Ergot derived dopamine agonists included, but unlikely to find evidence since last guideline
		
		GDG happy to meta-analyse effectiveness of classes of drugs but wish to report safety outcomes separately as different drugs have different side effects.

Comparator	Oral levodopa preparation monotherapy Each other (head to head trials)	
Outcomes	1. Adverse events 2. Disease severity: motor symptoms - UPDRS ;UPDRS – ADL 3. Non motor symptoms : hallucinations, delusions, ICD , psychosis 4. Off time 5. Dyskinesia 6. Health related quality of life 7. Carer quality of life 8. Mortality 9. Time to institutional care	
Other criteria for inclusion /	People who do not have a confirmed diagnosis of PD People who are drug naive	

exclusion of studies	Study design: • Case-control • Cohort study • Narrative review • Case-study • Qualitative review	
Review strategies	RCT evidence will only be used if: • no high quality up to date systematic reviews are identified or • new RCTs need to be added systematic review evidence	
Identified papers	See previous guideline	

	Details	Additional comments
Review question 20	What is the comparative effectiveness of donepezil, galantamine, memantine and rivastigmine for cognitive enhancement in dementia associated with Parkinson's disease?	Review to inform both PD and dementia guidelines (for the latter's RQ concerning dementia with Lewy bodies) Dementia (the progressive loss of global cognitive function) is common in PD; 48% to 80% of people may develop dementia at some point in the course of the condition.
Objectives	To determine the comparative effectiveness and cost-effectiveness of donepezil, galantamine, memantine and rivastigmine for cognitive enhancement in dementia associated with Parkinson's disease.	
Type of review	Intervention review	
Language	English language only	
Study design	• Systematic review of randomised controlled trials (RCTs) • RCTs If insufficient evidence is available progress to: • Systematic reviews of non-randomised controlled trials • Non-randomised controlled trials • Observational studies • Economic analyses	
Status	Published papers only (full text) Published after August 2005	
Population	People with a diagnosis of Parkinson's disease dementia (PDD) or dementia with Lewy bodies (DLB)	
Intervention	• Donepezil • Galantamine • Memantine • Rivastigmine • Memantine plus cholinesterase inhibitor	Only rivastigmine is licensed for mild to moderate dementia in Parkinson's disease.
Comparator	• Each other • Combination of memantine plus cholinesterase inhibitor • Placebo	

Outcomes	• Cognitive outcomes, including:
	  ○ Mini Mental State Examination (MMSE)
	  ○ Alzheimer's Disease Assessment Scale – cognitive subscale (ADAS-cog)
	  ○ Montreal Cognitive Assessment (MoCA)
	• Global outcomes, including:
	  ○ Unified Parkinson's Disease Rating Scale (UPDRS)
	  ○ Global impression of change
	• ADL, e.g.
	  ○ Unified Parkinson's Disease Rating Scale – activities of daily living scale (UPDRS-ADL)
	  ○ Measures used in DLB research (inc. AD-derived ones)
	• Non-cognitive outcomes, e.g.
	  ○ NPI
	• Adverse events, such as hallucinations
	• Study withdrawal	

	• Health-related quality of life • Carer-reported outcomes • Resource use and cost • Time to institutionalised care	

Other criteria for inclusion / exclusion of studies	Exclusions:
	• People with a diagnosis of non Lewy body dementia, for example:
	  ○ Alzheimer's disease
	  ○ Frontotemporal dementia
	  ○ Vascular dementia
	• People with mild cognitive impairment associated with Parkinson's disease	

Review strategies	**Appraisal of evidence quality:** For studies, NICE methodology checklists will be used to appraise the quality of individual studies, where appropriate. All key outcomes from evidence will be presented in GRADE profiles, where possible. **Synthesis of data:** Data on all included studies will be extracted into evidence tables. Data will be pooled to give an overall summary effect. Network meta-analyses will be conducted to determine the comparative clinical effectiveness of these pharmacological interventions, if appropriate data are available. **Presentation of data:** Where possible, results will be stratified according to diagnosis (e.g. 'pure' PDD, DLB, and mixed populations)	
Identified papers	Aarsland D, Laake K, Larsen JP et al. Donepezil for cognitive impairment in Parkinson's disease: A randomised controlled study. Journal of Neurology, Neurosurgery & Psychiatry 2002; 72(6): 708–12 Emre M, Aarsland D, Albanese A et al. Rivastigmine for dementia associated with Parkinson's disease. New England Journal of Medicine 2004; 351(24): 2509–18 Leroi I, Brandt J, Reich S et al. Randomized placebo-controlled trial of donepezil in cognitive impairment in Parkinson's disease. International Journal of Geriatric Psychiatry 2004; 19(1): 1–8 Ravina B, Putt M, Siderowf A et al. Donepezil for dementia in Parkinson's disease: a randomised, double blind, placebo controlled, crossover study. Journal of Neurology, Neurosurgery & Psychiatry 2005; 76(7): 934–39	

	Details	Additional comments
Review question 21	What is the comparative effectiveness of pharmacological interventions for psychotic symptoms associated with PD?	Psychotic symptoms include: hallucinations, delusions, thought disorder
Objectives	To determine the comparative effectiveness of second generation antipsychotics for psychotic symptoms associated with PD	
Type of review	Intervention review	
Language	English language only	
Study design	Systematic review RCT	
Status	Date limit imposed post previous guideline	
Population	People with a confirmed diagnosis of PD whom are suffering from psychosis	
Interventions	• Amisulpride • Aripiprazole • Clozapine • Donepezil • Galantamine • Haloperidol • Memantine • Olanzapine • Quetiapine • Risperidone • Rivastigmine	Safinamide not included as wasn't licensed when guideline was scoped
Comparator	• Placebo • Each other	
Outcomes	• Adverse events (include worsening of motor symptoms) • Mortality • Resource use and cost • Psychosis measure: • Disease severity - UPDRS • Health related QoL - PDQ39 • Cognitive function (MMSE, MoCA, neuropsychological assessment) • Hallucinations	
Other criteria for inclusion / exclusion of studies	People without a confirmed diagnosis of PD Study design: • Case-control • Cohort study • Narrative review • Case-study • Qualitative review	Exclude patients with a diagnosis of DLB Include patients with a diagnosis of PDD
Review strategies	RCT evidence will only be used if: • no high quality up to date systematic reviews are identified or • new RCTs need to be added systematic review evidence Intention to treat meta analyses	
Identified	See previous guideline	

papers	

	Details	Additional comments
Review question 22	What is the comparative effectiveness of pharmacological interventions to treat REM sleep behaviour disorder (RBD) associated with PD?	
Objectives	To determine the comparative effectiveness of pharmacological interventions to treat RBD associated with PD	Check Cochrane database
Type of review	Intervention review	
Language	English language only	
Study design	Systematic review RCT	
Status	Date limit imposed post previous guideline	
Population	People with a confirmed diagnosis of PD who are suffering from sleep disturbance: nocturnal akinesia or RBD	
Intervention	• Immediate-release levodopa • Controlled release levodopa • Prolonged release dopamine agonist (including transdermal patch) • Standard-release dopamine agonist • Apomorphine • Mirtazapine • Benzodiazepine: Clonazepam • Pregabalin • Melatonin • Rivastigmine • Gabapentin	NOTE: very little evidence exists in RCT for these different drugs in these disorders. Much of literature is in populations other than PD RBD can be a precursor to PD
Comparator	• Placebo • Active Comparative	
Outcomes	• Adverse events • Resource use and cost • RBD: reported frequency of episodes • RBD severity scale • PD sleep scale • PD nonmotor scale • Health related quality of life • Carer health related quality of life	Gold standard for RBD is showing on polysomnogram frequency of episodes with a loss of atonia
Other criteria for inclusion / exclusion of studies	Exclusion: People without a confirmed diagnosis of PD Study design: • Case-control • Cohort study • Narrative review • Case-study • Qualitative review	
Review strategies	RCT evidence will only be used if: • no high quality up to date systematic reviews are identified or • new RCTs need to be added systematic review evidence Intention to treat meta analyses	
Identified	See previous guideline	

papers	