Appendix N: Research recommendations

N.1 First-line treatment of motor symptoms

Research recommendation 1	What is the effectiveness of initial levodopa monotherapy versus initial levodopa-dopamine agonist combination therapy?
Population	People with a diagnosis of Parkinson's disease confirmed by a specialist and who are about to commence pharmacotherapy.
Interventions	Levodopa monotherapy: • Co-beneldopa • Co-careldopa
Comparators	Levodopa preparations plus a non-ergot dopamine agonist: • Ropinirole • Pramipexole • Rotigotine
Outcomes	• Adverse events • Motor symptoms (UPDRS III) • Activities of daily living (UPDRS II) • Non-motor symptoms : hallucinations, impulse control disorders • Off time • Dyskinesia • Health-related quality of life • Carer quality of life an carer burden • Resource use and costs
Study designs	Randomised controlled trials

Criterion	Explanation
Importance to patients, service users or the population	Initial therapy with levodopa has been shown to provide better control of motor symptoms and improvement in activities of daily living than dopamine agonist monotherapy, but with a higher risk of long-term motor complications/dyskinesia. Initial combination therapy with levodopa and a dopamine agonist may make it possible to achieve good symptom control using lower doses of levodopa, therefore reducing the rate at which motor complications develop.
Relevance to NICE guidance	High priority: it is currently not possible to provide recommendations about first-line combination treatment for people with Parkinson's disease as no evidence exists, and these studies would enable this gap to be filled
Current evidence base	Whilst a number of randomised controlled trials have allowed the addition of levodopa to initial dopamine agonist therapy (or vice versa) over time, few trials have included a specific trial arm looking at combination treatment. Well conducted randomised controlled trials comparing initial levodopa monotherapy with initial levodopa-dopamine agonist combination therapy would fill in this gap in the evidence base.
Equality	No specific equality concerns are relevant to this research recommendation.
Feasibility	The PDMED study has already shown this type of research to be feasible in people with Parkinson's disease in the UK.

N.2 Orthostatic hypotension

Research recommendation 2	For people with Parkinson's disease, what is the most effective pharmacological treatment for orthostatic hypotension?
Population	People with a confirmed diagnosis of Parkinson's disease who are experiencing symptoms of orthostatic hypotension.
Interventions	• Midodrine • Fludrocortisone • Pyridostigmine • Ephedrine • Pseudoephedrine
Comparators	• Placebo • Each other
Outcomes	• Adverse events • Mortality • 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 • Resource use and costs
Study designs	Randomised controlled trials

Potential criterion	Explanation
Importance to patients, service users or the population	The GDG felt that orthostatic hypotension was important practical problem, common in people with Parkinson's disease and a contributor to falls and injuries.
Relevance to NICE guidance	Medium priority: the research is relevant to the recommendations in the guidance, but the research recommendations are not essential to future updates. It is currently possible to make some recommendations based on published evidence, but not all relevant comparators are included in the evidence base.
Current evidence base	The current best pharmacological treatment is not yet established and research in this area would be beneficial to determine this. The randomised controlled trials that have previously been undertaken have only provided low-quality evidence (due to both small sample sizes and weaknesses in the trial designs) and cover only a subset of the comparisons of interest, making future research in this area of value.
Equality	No specific equality concerns are relevant to this research recommendation.
Feasibility	There is a sufficiently large and well defined population available that randomised controlled trials in this area should be feasible.

N.3 Psychotic symptoms

Research recommendation 3	What is the effectiveness of rivastigmine compared with atypical anti-psychotic drugs for treating psychotic symptoms (particularly hallucinations and/or delusions) associated with Parkinson's disease?
Population	People with a confirmed diagnosis of Parkinson's disease who are suffering from psychosis.
Intervention	Rivastigmine
Relevant comparators	• Amisulpride • Aripiprazole • Clozapine • Donepezil • Galantamine • Haloperidol • Memantine • Olanzapine • Quetiapine • Risperidone • Rotigotine
Outcomes	• Delusions • Hallucinations • Adverse events (include worsening of motor symptoms) • Mortality • Disease severity - UPDRS • Health-related quality of life • Carer quality of life and carer burden • Resource use and costs
Study designs	Randomised controlled trials

Potential criterion	Explanation
Importance to patients, service users or the population	Rivastigmine is commonly used in practice for treating people with Parkinson's disease psychosis, because it has shown some effectiveness in improving behavioural symptoms in people with Parkinson's disease dementia. However, no evidence exists to support the efficacy of rivastigmine in the treatment of people with Parkinson's disease whose symptoms are predominantly psychotic. It would be beneficial to undertake primary research in this area in order to determine the most effective treatment options for managing Parkinson's disease psychosis.
Relevance to NICE guidance	Medium priority: the research is relevant to the recommendations in the guidance, but the research recommendations are not essential to future updates. It is currently possible to make some recommendations based on published evidence, but not all relevant comparators (in particular, rivastigmine) are included in the evidence base.
Current evidence base	Whilst trials have been conducted looking at the efficacy of atypical antipsychotics versus placebo or each other, at present, no evidence exists to support the efficacy of rivastigmine in the treatment of people with Parkinson's disease whose symptoms are predominantly psychotic.
Equality	No specific equality concerns are relevant to this research recommendation.
Feasibility	There is a sufficiently large and well defined population available that randomised controlled trials in this area should be feasible.

N.4 REM sleep behaviour disorder

Research recommendation 4	What is the best first line treatment for REM sleep behaviour disorder in people with Parkinson's disease?
Population	People with a confirmed diagnosis of Parkinson's disease who are suffering from sleep disturbance (REM sleep behaviour disorder) and are about to commence pharmacotherapy
Interventions	• Clonazepam • Melatonin
Comparators	• Placebo • Each other
Outcomes	• RBD: reported frequency of episodes • RBD: severity scale • Parkinson's disease sleep scale • Parkinson's disease non-motor scale • Adverse events • Health-related quality of life • Carer quality of life and carer burden • Resource use and costs
Study designs	Randomised controlled trials

Potential criterion	Explanation
Importance to patients, service users or the population	The GDG highlighted the importance of minimising sleep behaviour disorder, for both people with Parkinson's disease and their carers, particularly due to potential safety concerns. The primary outcomes for such trials should be the frequency and severity of RBD episodes, and the adverse effects from treatment.
Relevance to NICE guidance	Medium priority: the research is relevant to the recommendations in the guidance, but the research recommendations are not essential to future updates. It is currently possible to make some recommendations based on published evidence, but not all relevant comparators (in particular, clonazepam and melatonin) are included in the evidence base.
Current evidence base	Only one paper was found to address optimal management, and this contained a population of people who had already failed on first line treatment. With multiple possible treatment options (in particular clonazepam and melatonin) and no current evidence on what the most effective first-line treatment is, research (in the form of randomised controlled trials) in this area would be beneficial.
Equality	No specific equality concerns are relevant to this research recommendation.
Feasibility	There is a sufficiently large and well defined population available that randomised controlled trials in this area should be feasible.

N.5 Pharmacological management of Parkinson's disease dementia

Research recommendations 5 and 6 (both answerable in a single study)	What is the effectiveness of memantine for people with Parkinson's disease dementia? What is the effectiveness of combination treatment with a cholinesterase inhibitor and memantine for people with Parkinson's disease dementia if treatment with a cholinesterase inhibitor alone is not effective or no longer effective?
Population	People with a diagnosis of Parkinson's disease dementia (PDD)
Interventions	• Memantine monotherapy • Memantine plus cholinesterase inhibitor
Comparator	Cholinesterase inhibitor monotherapy
Outcomes	• Cognitive outcomes • UPDRS • Global impression of change • NPI • Adverse events • Health-related quality of life • Carer quality of life and carer burden • Time to institutionalised care • Resource use and costs
Study designs	Randomised controlled trials (a single study with three arms of memantine monotherapy, cholinesterase inhibitor monotherapy and combination treatment)

Potential criterion	Explanation
Importance to patients, service users or the population	The GDG felt that cholinesterase inhibitors, memantine, and combination therapy with both treatments are all reasonable clinical options, but noted that some people do not tolerate cholinesterase inhibitors well due to side effects.
Relevance to NICE guidance	Low priority: the research would fill relevant gaps in the evidence base, but it is possible to make recommendations for initial monotherapy based on the available evidence
Current evidence base	The evidence base for memantine was considerably weaker than for cholinesterase inhibitors, and therefore there would be value in either additional trials of memantine versus placebo (in people for whom cholinesterase inhibitors are not an option), or non-inferiority studies versus cholinesterase inhibitors. In clinical practice, memantine is often added to a cholinesterase inhibitor when it is no longer proving effective, but again there is no evidence base for this and randomised trials to establish if there is additional benefit would be valuable.
Equality	No specific equality concerns are relevant to this research recommendation.
Feasibility	There is a sufficiently large and well defined population available that randomised controlled trials in this area should be feasible.

N.6 Physiotherapy and physical activity

Research recommendation 7	Does physiotherapy started early in the course of Parkinson's disease, as opposed to after motor symptom onset, confer benefits in terms of delaying symptom onset and/or reducing severity?
Population	People with a confirmed diagnosis of Parkinson's disease within the past 1 year
Intervention	Early physiotherapy intervention in people with early PD (prior to motor symptom onset), which may include: • Exercise therapy • Tai chi • Alexander technique • Cueing techniques • Dance • Wii interactive fitness and balance programs • Nordic walking
Comparators	Physiotherapy interventions offered at the current standard times in the UK in people with Parkinson's disease who have already developed motor symptoms
Outcomes	• Posture • Gait • Falls • Berg balance scale • UPDRS scores • Depression • Health-related quality of life • Carer quality of life and carer burden • Resource use and cost
Study designs	Randomised controlled trials

Potential criterion	Explanation
Importance to patients, service users or the population	The GDG felt that physiotherapy was beneficial for those in the earlier course of the disease as it may delay or lessen problems associated with symptoms, as well as for those who have developed symptoms and problems. If physiotherapy was shown to have a beneficial effect in either delaying the onset or decreasing the severity of symptoms, this would have a substantial beneficial impact on the quality of life of people with Parkinson's disease and their family and carers.
Relevance to NICE guidance	High priority: there is currently no robust evidence on which to base recommendations for when during the disease course physiotherapy should first be offered to people with Parkinson's disease.
Current evidence base	At present, no substantial evidence exists to support the efficacy of physiotherapy as an early intervention to prevent the onset or reduce severity of motor symptoms, as most of the trials have been conducted in people who have already developed motor symptoms. Relevant trials would not compare physiotherapy with no physiotherapy, but rather early physiotherapy (at the time of diagnosis) with physiotherapy offered at the current standard times in the UK.
Equality	No specific equality concerns are relevant to this research recommendation.
Feasibility	There is a sufficiently large and well defined population available that randomised controlled trials in this area should be feasible.

N.7 Nutrition

Research recommendation 8	How effective is long term creatine supplementation on clinical outcomes in Parkinson's Disease?
Population	People with a confirmed diagnosis of Parkinson's disease
Intervention	Creatine supplementation
Comparators	Placebo
Outcomes	• UPDRS scores • Hoehn and Yahr scores • Dyskinesia • Depression or anxiety • Social interaction • Cognitive function • Health-related quality of life • Resource use and costs
Study designs	Randomised controlled trials

Potential criterion	Explanation
Importance to patients, service users or the population	The evidence surrounding creatine supplementation for those with Parkinson's disease was limited. However it may be beneficial in other neurological conditions such as Motor neurone disease, and therefore research in this area is justified.
Relevance to NICE guidance	Low priority: the research would fill relevant gaps in the evidence base, but it is possible to make recommendations for treatment based on the available evidence
Current evidence base	Current evidence base for creatine supplementation and Parkinson's disease is limited. It is proposed that a blinded randomised controlled trial is undertaken to explore this question. The proposed study would monitor UPDRS, Hoehn and Yahr, and health related quality of life scores, whilst also considering other important outcomes such as cost of therapy, levels of dyskinesia, depression or anxiety, social interaction and cognitive function.
Equality	No specific equality concerns are relevant to this research recommendation.
Feasibility	There is a sufficiently large and well defined population available that randomised controlled trials in this area should be feasible.

N.8 Deep brain stimulation compared with best medical treatment for earlier Parkinson's disease

Research recommendation 9	What is the effectiveness and cost effectiveness of early DBS compared with intensified medical management (with DBS delayed until conventional indications develop)?
Population	People with a confirmed diagnosis of Parkinson's disease
Intervention	Early DBS (earlier than standard times it is currently used) + usual care
Comparators	Late DBS (standard times it is currently used) + usual care
Outcomes	• Symptom severity: UPDRS, dyskinesia • "on" and "off" time • Disease progression: Hoehn & Yahr scores • Neuropsychiatric non-motor features (cognitive impairment, sleep disorder) • Medication load • Health-related quality of life • Carer quality of life and carer burden • Time to full time institutional care • Resource use and costs
Study designs	Randomised controlled trials

Potential criterion	Explanation
Importance to patients, service users or the population	There is a growing trend towards DBS surgery being undertaken at earlier stages of Parkinson's disease (before all other medical options have been exhausted). This has the potential to provide symptomatic benefit earlier in the disease course, but also possible downsides, including the development of DBS-related complications and a tapering of the treatment benefit at an earlier stage.
Relevance to NICE guidance	Low priority: the research would fill relevant gaps in the evidence base, but it is possible to make recommendations for treatment based on the available evidence
Current evidence base	Currently, the question of early versus late DBS can only be addressed indirectly, through trials that compare early DBS versus no DBS, and trials that compare late DBS versus no DBS. The evidence base could be improved with a specific RCT comparison of early DBS versus DBS at the standard times it is currently used. Such a trial would have the additional advantage of being easier to recruit to (since everyone will be offered DBS) than a trial of DBS versus nothing, which is likely to be impractical to perform now DBS has become such a commonly available procedure.
Equality	Since it is unlikely to be considered ethical to run a trial of DBS versus no DBS (since DBS is now standard practice in the UK), future trials will need to look at comparing the timing of DBS, with all individuals recruited ultimately receiving the treatment.
Feasibility	There is a sufficiently large and well defined population available that randomised controlled trials in this area should be feasible.