Full version of NICE Guideline No. X

Parkinson’s Disease

Diagnosis and Management in Primary and Secondary Care.

Developed by
National Collaborating Centre for Chronic Conditions
Royal College of Physicians
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<th>Name</th>
<th>Job Title</th>
<th>Employing organisation</th>
<th>Representing</th>
</tr>
</thead>
<tbody>
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</tbody>
</table>
### Acknowledgments:
The National Collaborating Centre for Chronic Conditions would also like to thank Ester Klaeijsen, Rob Grant, Susan Varney, Ian Lockhart, Nyokabi Musila, Mike Hughes, Lina Bakhshi, Alison Richards, Jane Ingham, Sarah Williams, Steven Barnes, Patricia Van Hanswijck de Jonge, Melanie Pitt, Louise Martin, and Bernard Higgins for their work and advice on this project.
DRAFT FOR FIRST CONSULTATION

Preface
To be completed for publication by the Director of the National Collaborating Centre for Chronic Conditions.
1. Introduction

Background

1.1 Parkinson’s disease is named after the London general practitioner, James Parkinson, who vividly described many of the clinical features of the condition in his Essay on the Shaking Palsy (1817)\(^5\). In this work, Parkinson refers to the condition by its earlier name of paralysis agitans, a term that captures a peculiar characteristic of the disease, namely the combination of movement loss (for example bradykinesia) yet at the same time movement gain (for example, tremor at rest) which it causes.\(^6\) Paralysis agitans was named ‘maladie de Parkinson’ in 1888 by the French neurologist Jean-Martin Charcot. Charcot admired Parkinson’s clinical acumen and powers of description, but criticised him for omitting mention of rigidity, which Charcot believed to be a typical feature of the condition.\(^7\)

Modern Definition

1.2 Parkinson’s disease (PD) is a progressive neurodegenerative condition leading to the death of the dopamine containing cells of the substantia nigra. There is no consistently reliable test that can distinguish PD from other conditions with similar clinical presentations. The diagnosis is primarily a clinical one based on a history and examination.

1.3 People with PD classically present with the symptoms and signs associated with parkinsonism, namely bradykinesia, rigidity and rest tremor.

1.4 Less common conditions than PD also cause parkinsonism, including: multiple cerebral infarction, drugs and degenerative conditions such as progressive supra-nuclear palsy (PSP) and multiple system atrophy (MSA).

1.5 Although PD is predominantly a movement disorder, other impairments frequently develop, including psychiatric problems such as depression and dementia. Autonomic disturbances and pain (which rarely is a presenting feature of PD) may later ensue, and the condition progresses to cause significant disability and handicap with impaired quality of life for the affected individual, and indirectly for family and carers.

Health and resource implications

1.6 PD is a common, chronic, progressive neurological condition, estimated to affect 100-180 per 100,000 of the population (between 6-
11 people per 6000 of the general population in the UK)¹ and has an annual incidence of 4-20 per 100,000.⁸ There is a rising prevalence with age and no sex differences in the prevalence of PD.⁹

1.7 PD can lead to extensive disability which affects both the individual with the disease as well as indirectly family and carers. The economic impact of the disease includes:
- Direct cost to the NHS
- Indirect cost to society
- Personal impact of PD on individuals with the condition and their family and carers.

1.8 The direct costs of treatment to the NHS have been estimated at approximately £2,298 (£1998) per patient per year.¹⁰ Significant cost drivers include the onset of motor fluctuations and dyskinesias.¹¹ The condition is a frequent cause of falls and thus fractures and even death.¹²

1.9 The total annual cost of care including NHS, social services and private expenditure per patient in the UK has been estimated at approximately £5,993 (£1998).¹⁰ This results in direct costs of approximately £599,300,000 per year in the UK for 100,000 individuals with PD.¹⁰ Total costs of care increase with age and disease severity.¹⁰ Costs to the NHS were approximately 38% of the total costs.¹⁰

¹The size of the average general practice list in the UK.
2. Methodology

Aim

2.1 The aim of the National Collaborating Centre for Chronic Conditions (NCC-CC) is to provide a user-friendly, clinical evidence-based guideline for the National Health Service (NHS) in England and Wales that:
- Offers best clinical advice for Parkinson’s disease
- Is based on best published evidence and expert consensus
- Takes into account patient choice and informed decision making
- Defines the major components of NHS care provision for PD
- Indicates areas suitable for clinical audit
- Details areas of uncertainty or controversy requiring further research
- Provides a choice of guideline versions for differing audiences.

Scope

2.2 The guideline was developed in accordance with a scope, which detailed the remit of the guideline originating from the Department of Health and specified those aspects of Parkinson's disease to be included and excluded.

2.3 Prior to the commencement of the guideline development, the scope was subjected to stakeholder consultation in accordance with processes established by NICE. The full scope is shown in Appendix A.

2.4 The guideline covers:
- Diagnoses of Parkinson’s disease and parkinsonism
- Treatment of idiopathic Parkinson’s disease

2.5 The scope excludes:
- Juvenile onset Parkinson’s disease (in people younger than 20 years of age)
- Treatment of parkinsonism (a neurological disorder that manifests with bradykinesia, tremor or muscular rigidity) and other tremulous disorders (for example, essential tremor).

2.6 The guideline is relevant to primary, secondary and tertiary NHS care settings.

Audience

2.7 The guideline is primarily intended to provide guidance for NHS staff, but will also have relevance to the following people or organisations:
- All healthcare professionals
• People with the disease and carers of these people
• Patient support groups
• Commissioning organisations
• Service providers.

Involvement of people with Parkinson’s disease

2.8 The NCC-CC was keen to ensure the views and preferences of people with Parkinson’s disease and their carers informed all stages of the guideline. This was achieved by:
• Consulting the Patient Information Unit (PIU) housed within NICE during the pre-development (scoping) and final validation stages of the guideline
• By having a person with Parkinson’s disease and user organisation representative on the guideline development group

2.9 The patient and / or a representative of the user organisation were present at every meeting of the GDG. They were therefore involved at all stages of the guideline development process and were able to consult with their wider constituencies.

Guideline limitations

2.10 These include:
• Clinical guidelines usually do not cover issues of service delivery, organisation or provision (unless specified in the remit from the Department of Health)
• NICE is primarily concerned with Health Services and so recommendations are not provided for Social Services and the voluntary sector. However, the guideline may address important issues in how NHS clinicians interface with these other sectors.
• Generally the guideline does not cover rare, complex, complicated or unusual conditions

Other work relevant to the guideline

2.11 This guideline has been developed with the knowledge that other national work on PD and chronic neurological conditions has been completed or is in progress. This includes:
• The National Service Framework for Long-term Conditions published by the Department of Health in 2005
• The National Service Framework for Older People published by the Department of Health in 2001¹³
• NICE Guideline on Falls¹⁴
• NICE Guideline on Dementia¹⁵
• NICE Guideline on Depression¹⁶
• Guideline on multiple sclerosis commissioned by NICE and published by the Royal College of Physicians in 2004.
Methodology

2.12 The development of this evidence-based clinical guideline draws upon the methods described by the NICE Guideline Development Methods manual\textsuperscript{17} \url{http://www.nice.org.uk/page.aspx?o=201982} and the methodology pack specifically developed by the NCC-CC for each chronic condition guideline \url{http://www.rcplondon.ac.uk/college/ceeu/ncccc_index.htm}. The developers’ role and remit is summarised in Exhibit 2A.
### Exhibit 2A. Role and remit of the developers

#### National Collaborating Centre for Chronic Conditions (NCC-CC)

The NCC-CC was set up in 2001 and is housed within the Royal College of Physicians (RCP). The NCC-CC undertakes commissions received from the National Institute for Clinical Excellence (NICE).

A multi professional partners’ board inclusive of patient groups and NHS management governs the NCC-CC.

#### NCC-CC Technical Team

The technical team met and comprised the following members:
- GDG group leader
- GDG clinical advisor
- Information scientist
- Research fellow/Project Manager
- Health economist
- Administrative personnel.

#### Guideline Development Group (GDG)

The GDG met monthly for 13 months (2004 to 2005) and comprised a multi-disciplinary team of professionals, service users (a person with PD), carers, and user organisation representatives who were supported by the technical team.

The GDG membership details including patient representation and professional groups are detailed in the GDG Membership table at the front of this guideline.

#### Guideline Project Executive (PE)

The PE was involved in overseeing all phases of the guideline. It also reviewed the quality of the guideline and compliance with the DH remit and NICE scope.

The PE comprised of:
- NCC-CC Director
- NCC-CC Manager
- NCC-CC Senior Research Fellow
- NICE Commissioning Manager
- Technical Team.

#### Sign-off workshop

At the end of the guideline development process the GDG met to review and agree all the guideline recommendations.

Members of the GDG declared any interests in accordance with the NICE technical manual. A register is available from the NCC-CC for inspection upon request ncc-cc@rcplondon.ac.uk.
2.13 The basic steps in the process of producing a guideline are:
- Developing clinical evidence based questions
- Systematically searching for the evidence
- Critically appraising the evidence
- Incorporating health economics advice
- Distilling and synthesising the evidence and writing recommendations
- Grading the evidence statements and recommendations
- Agreeing the recommendations
- Structuring and writing the guideline
- Updating the guideline

Developing evidence based questions

2.14 The technical team drafted a series of clinical questions that covered the guideline scope. The GDG and Project Executive refined and approved these questions which are shown in Appendix B.

Searching for the evidence

2.15 The information scientist developed a search strategy for each clinical question. In addition, the health economist searched for supplemental papers to inform models. Key words for the search were identified by the GDG. Papers that were published or accepted for publication in peer-reviewed journals were considered as evidence by the GDG. Conference paper abstracts and non-English language papers were excluded from all searches.

2.16 Each clinical question dictated the appropriate study design that was prioritised in the search strategy but the strategy was not limited solely to these study types. The research fellow or health economist identified titles and abstracts from the search results that appeared to be relevant to the question. Exclusion lists were generated for each question together with the rationale for the exclusion. The exclusion lists were presented to the GDG. Full papers were obtained where relevant. Literature search details are shown in Appendix B.

Appraising the evidence

2.17 The research fellow or health economist, as appropriate, critically appraised the full papers. In general no formal contact was made with authors however there were ad hoc occasions when this was required in order to clarify specific details. Critical appraisal checklists were compiled for each full paper. One research fellow undertook the critical appraisal and data extraction. The evidence was considered carefully by the GDG for accuracy and completeness.

2.18 All procedures are fully compliant with the:
Incorporating health economics advice

2.19 Due to the appointment of the health economist midway through the guideline development, the areas for health economic evidence were considered after the formation of the clinical questions. The health economist reviewed the clinical questions to consider the potential application of health economic evidence. Five key areas were separately identified by the clinical lead.

2.20 After agreement and selection of specific areas, the information scientist performed a literature search using economic filters on the related clinical questions. No study design criteria were imposed a priori i.e. the searches were not limited to RCTs or formal economic evaluations. See section 2.21 for details of the systematic search for evidence by the information scientist. Titles and abstracts identified in the economic searches were reviewed by the health economist and full papers were obtained as appropriate. The full papers were critically appraised by the health economist and the relevant data was presented to the GDG at subsequent GDG meetings. See section 2.22 for information on the critically appraising the evidence.

2.21 The health economist performed supplemental literature searches using key search terms in the York Centre for Review and Dissemination (CRD) database, NHS Economic Evaluation database NHS EED, Pubmed and Google search engine to obtain additional information for modeling. Areas were modeled due to the limited amount or relevance to the UK setting. Assumptions and designs of the models were explained and agreed by the GDG members during meetings and validated by an additional health economist.

Distilling and synthesising the evidence and writing recommendations

2.22 The evidence from each full paper was distilled into an evidence table and synthesised into evidence statements before being presented to the GDG. This evidence was then reviewed by the GDG and used as a basis upon which to formulate recommendations².

2.23 Evidence tables are available at: http://www.rcplondon.ac.uk/pubs/online_home.htm
### Exhibit X: Grading the evidence statements and recommendations

<table>
<thead>
<tr>
<th>Levels of evidence</th>
<th>Classification of recommendations</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Level</strong></td>
<td><strong>Type of evidence</strong></td>
</tr>
<tr>
<td>1++</td>
<td>High quality meta-analysis (MA), systematic reviews (SR) of RCTs, or RCTs with a very low risk of bias</td>
</tr>
<tr>
<td>1+</td>
<td>Well-conducted MA, SR or RCTs, or RCTs with a low risk of bias</td>
</tr>
<tr>
<td>1-</td>
<td>MA, SR of RCTs, or RCTs with a high risk of bias*</td>
</tr>
<tr>
<td>2++</td>
<td>High-quality SR of case-control or cohort studies High-quality case-control or cohort studies with a very low risk of confounding, bias or chance and a high probability that the relationship is causal</td>
</tr>
<tr>
<td>2+</td>
<td>Well-conducted case-control or cohort studies with a low risk of confounding, bias or chance and a moderate probability that the relationship is causal</td>
</tr>
<tr>
<td>2-</td>
<td>Case-control or cohort studies with a high risk of confounding bias, or chance and a significant risk that the relationship is not causal</td>
</tr>
<tr>
<td>3</td>
<td>Non-analytic studies (for example case reports, case series)</td>
</tr>
<tr>
<td>4</td>
<td>Expert opinion, formal consensus</td>
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</table>

Diagnostic study level of evidence and classification of recommendation was also included2.
Agreeing the recommendations

2.24 The sign-off workshop employed formal consensus techniques to:
- Ensure that the recommendations reflected the evidence-base
- Approve recommendations based on lesser evidence or extrapolations from other situations
- Reach consensus recommendations where the evidence was inadequate
- Debate areas of disagreement and finalise recommendations.

2.25 The sign-off workshop also reached agreement on the following:
- Five to ten key priorities for implementation
- Five key research recommendations
- Algorithms.

2.26 In prioritising key recommendations for implementation, the sign-off workshop also took into account the following criteria:
- High clinical impact
- High impact on reducing variation
- More efficient use of NHS resources
- Allowing the patient to reach critical points in the care pathway more quickly.

2.27 The audit criteria provide suggestions of areas for audit in line with the key recommendations for implementation².

Structuring and writing the guideline

2.28 The guideline is divided into sections for ease of reading. For each section the layout is similar and is described below:
- Clinical introduction
  - Sets a succinct background and describes the clinical context
- Methodological introduction
  - Describes any issues or limitations that were apparent when reading the evidence-base
- Evidence statements
  - Provides a synthesis of the evidence-base and usually describes what the evidence showed in relation to the outcomes of interest
- Health economics
  - Presents, where appropriate, an overview of the cost effectiveness evidence-base
- From evidence to recommendation
  - Sets out the GDG decision-making rationale and provides a clear and explicit audit trail from the evidence to the evolution of the recommendations.
- Recommendations
  - Provides stand alone, action orientated recommendations.
Evidence tables

2.29 The evidence tables are not published as part of the full guideline but are available on-line at [URL to be provided for publication]. These describe comprehensive details of the primary evidence that was considered during the writing of each section.

Writing the guideline

2.30 The first draft version of the guideline was drawn up by the technical team in accord with the decision of the GDG. The guideline was then submitted for two formal rounds of public and stakeholder consultation prior to publication. The registered stakeholders for this guideline are detailed in Appendix K. Editorial responsibility for the full guideline rests with the GDG.

2.31 The following versions of the guideline are available:

Full version: Details the recommendations. The supporting evidence base and the expert considerations of the GDG. Available at http://www.rcplondon.ac.uk/pubs/online_home.htm

NICE version: Documents the recommendations without any supporting evidence. Available at http://www.nice.org.uk/page.aspx?o=guidelines.completed

Quick reference guide: An abridge version. Available at XXX

Information for the public: A lay version of the guideline recommendations Available at XXX

Updating the guideline

2.32 Literature searches were repeated for all of the evidence based questions at the end of the GDG development process allowing any relevant papers published up until February 2005 to be considered. Future guideline updates will consider evidence published after this cut-off date.

2.33 Two years after publication of the guideline, NICE will commission a National Collaborating Centre to determine whether the evidence base has progressed significantly to alter the guideline recommendations and warrant an early update. If not, the guideline will be updated approximately four years after publication.

Disclaimer

2.34 Healthcare providers need to use clinical judgement, knowledge and expertise when deciding whether it is appropriate to apply guidelines. The recommendations cited here are a guide and may not be
appropriate for use in all situations. The decision to adopt any of the recommendations cited here must be made by the practitioner in light of individual patient circumstances, the wishes of the patient, clinical expertise and resources.

2.35 The British National Formulary (BNF) should be consulted alongside any drug recommendations cited in this guideline and note taken of the indications, contraindications, cautions and product characteristics.

2.36 The guideline will normally only make drug recommendations that fall within licensed indications. If a drug is recommended outside of its licensed indication this will be made clear in the guideline.

2.37 The NCC-CC disclaims any responsibility for damages arising out of the use or non-use of these guidelines and the literature used in support of these guidelines.

Funding

2.38 The National Collaborating Centre for Chronic Conditions was commissioned by the National Institute of Clinical Excellence to undertake the work on this guideline.
3. Key Messages

3.1 In this chapter three essential components of the guideline will be discussed:
- Recommendations for implementation
- Audit criteria
- Algorithm

3.2 Recommendations for implementation consist of recommendations selected by the GDG that highlight the main areas likely to have the most significant impact on patient care and patient outcomes in the NHS as a whole.\(^{17}\)

3.3 Audit criteria are explicit statements developed from the recommendations for implementation, used to define the structure of care, process or outcome that is to be measured.\(^{17}\)

3.4 The algorithm is a flow chart of the clinical decision pathway described in the clinical chapters.\(^{17}\)

3.5 Another important section of the guideline is Chapter 12 ‘Research Recommendations’. This chapter discusses the GDG selected, priority areas for future PD research. Specific research questions are stated, the proposed trial structure is described and an explanatory paragraph provided. General research recommendations are also included in this chapter.

Recommendations for implementation

Referral to expert for accurate diagnosis

3.6 Before treatment is initiated, people with suspected Parkinson's disease should be referred quickly\(^2\) to a specialist with expertise in the differential diagnosis of this condition.

Expert review of diagnosis

3.7 The diagnosis of Parkinson's disease should be kept under regular review\(^3\) and reconsidered if atypical features develop.

\(^2\) In suspected mild Parkinson's disease people should be seen within 6 weeks but new referrals in later disease with more complex problems require an appointment within 2 weeks

\(^3\) At 6 to 12 month intervals
Regular access to Parkinson's disease specialist nursing care

3.8 All people with Parkinson's disease should have regular access to specialist nursing care to provide monitoring and altering of medication, a point of contact for support including home visits, and a reliable source of information about clinical and social matters relevant to Parkinson's disease.

Regular access to rehabilitation interventions including physiotherapy, occupational therapy and speech and language therapy

3.9 At diagnosis and regular review meetings, consideration should be given to referring people with Parkinson's disease for physiotherapy, occupational therapy and speech and language therapy interventions.

Cholinesterase inhibitors for cognitive impairment and/or psychotic symptoms

3.10 The guideline development group consider that the cholinesterase inhibitors are clinically effective for the treatment of cognitive impairment and/or psychotic symptoms arising from dementia in people with PD. A recommendation on their use will be made in the second consultation draft of this guideline following an analysis of their cost effectiveness. This additional work is being undertaken at the request of the National Institute for Health and Clinical Excellence (see 9.71).
Audit criteria

The audit criteria shown below are linked to the recommendations for implementation (see section above). These are intended to be suggestions to aid and monitor the implementation of this guideline at the level of an NHS trust or similar scale healthcare provider.

<table>
<thead>
<tr>
<th>Recommendation</th>
<th>Audit criterion</th>
<th>Exceptions</th>
</tr>
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<tbody>
<tr>
<td><strong>Referral to expert for accurate diagnosis</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Before treatment is initiated, people with suspected Parkinson's disease should be referred quickly(^1) to a specialist with expertise in the differential diagnosis of this condition.</td>
<td>100% of people with suspected Parkinson's disease to be seen within 6 weeks of GP referral.</td>
<td>None</td>
</tr>
<tr>
<td>(^1)In suspected mild Parkinson's disease people should be seen within 6 weeks but new referrals in later disease with more complex problems require an appointment within 2 weeks.</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Expert review of diagnosis</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>The diagnosis of Parkinson's disease should be kept under regular review(^2) and reconsidered if atypical features develop.</td>
<td>100% of people with Parkinson's disease to be reviewed at 6 to 12 month intervals.</td>
<td>None</td>
</tr>
<tr>
<td>(^2)At 6 to 12 month intervals.</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Regular access to Parkinson's disease specialist nursing care</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>All people with Parkinson's disease should have regular access to specialist nursing care to provide monitoring and altering of medication, a point of contact for support including home visits, and a reliable source of information about clinical and social matters relevant to Parkinson's disease.</td>
<td>100% of people with Parkinson's disease to have access to Parkinson's disease specialist nursing.</td>
<td>None</td>
</tr>
</tbody>
</table>
Regular access to rehabilitation interventions including physiotherapy, occupational therapy and speech and language therapy

| At diagnosis and regular review meetings, consideration should be given to referring people with Parkinson's disease for physiotherapy, occupational therapy and speech and language therapy interventions. | Rehabilitation to be made available in 100% of people with Parkinson's disease at each visit. | None |

Cholinesterase inhibitors for dementia and/or psychosis

3.11 A recommendation on the use of cholinesterase inhibitors for dementia in PD will be made in the second consultation draft of this guideline following an analysis of their cost effectiveness. This additional work is being undertaken at the request of the National Institute for Health and Clinical Excellence (see 9.71).

Patient views

3.12 The GDG recommend that healthcare commissioning organisations survey the views of people with PD regarding patient-views. This approach would enable the organisations to investigate the totality of the services and identify particular areas in need development using a patient-centred approach.
**PD Algorithm**

**Interventions for people with PD**

- **Disease progression**
  - Diagnosis and early disease
    - Refer to a specialist who makes and reviews diagnosis:
      - Using UK PD brain bank criteria
      - Considers 123-FP-CIT SPECT
      - Specialist should review diagnosis at regular intervals
  - Throughout disease
    - Provide regular access to Parkinson’s disease nurse specialist care, particularly to:
      - Monitor and alter medication
      - Provide continuing support including home visits
    - Consider access to therapies, particularly to:
      - Maintain independence, including activities of daily living and ensure home safety
      - Help balance, flexibility, gait, movement initiation
      - Enhance aerobic activity
      - Assess and manage communication and swallowing
  - Late disease
    - It is not possible to identify a universal first choice drug therapy for people with early PD. The choice of drug first prescribed should take into account:
      - Clinical and lifestyle characteristics
      - Patient preference
    - Consider drugs for non-motor symptoms:
      - For moderate to severe depression SSRI therapy
      - For dementia cholinesterase inhibitors (To be confirmed. See 9.71)
      - For psychosis clozapine therapy if necessary
      - For daytime hypersomnia modafinil

- **Communication**
  - Collaborative care decisions reached by taking into account:
    - Patient preference and choice
    - Clinical characteristics, patient lifestyle and interventions available
  - Provide communication and information about:
    - PD services and entitlements
    - Falls, self-help, palliative care and end-of-life issues
4. Communication with People with Parkinson’s disease and their carers

**Introduction**

4.1 Good communication is at the heart of every interaction between people with PD, their carers and health professionals. Issues which need to be considered include:

- Style, manner and frequency of communication
- Content and means of transmission
- Ease of access to those receiving information and consistency of content
- Recognition that people with PD have particular clinical problems requiring carefully and sensitively tailored communication
- Encouragement of self management by people with PD
- Involvement of carers.

4.2 Communication for people with chronic diseases can be focused on two goals:

- Collaborative care in which clinicians are seen as experts in medical conditions, while people with a condition are seen as experts in their own lives and are encouraged to identify their problems and define goals.
- Self-management education that provides people with problem-solving and management skills for the self-care of a condition.

4.3 For people with PD the main objective should be collaborative care, although interventions such as the Expert Patient Programme\(^\text{18}\), which concentrated in the main on self-management, may have a part to play.

**Methodology**

4.4 Six studies\(^\text{19-24}\) have addressed communication about the diagnosis of PD. Since there were few RCTs in this area, qualitative studies and questionnaires were included. The literature search included the area of self-help in relation to communication and education of people with PD. However, no studies were found which specifically addressed this topic.

4.5 Qualitative studies were assigned evidence level 3 in accordance with NICE guidance\(^\text{17}\).
4.6 Many of the qualitative studies\textsuperscript{22,23} had very small sample sizes principally due to the in-depth qualitative data sought by the researchers.

4.7 It should be noted that:
- The PROPATH program\textsuperscript{19,20} was a pharmaceutically sponsored educational service only available in the United States.
- The survey from the Parkinson's Disease Society\textsuperscript{24} was based on a questionnaire of members in the United Kingdom.

4.8 The PROPATH program consisted of a disease assessment questionnaire, which was completed by persons with PD or their carer. The questionnaire was analysed and computer-generated reports returned to physicians and individualised recommendation letters returned to people with PD. The questionnaires were analysed by an advisory board of neurologists with broad experience in movement disorders. The reports and recommendation letters were primarily aimed at reducing medication side effects.

**Evidence statements**

4.9 Two RCTs\textsuperscript{19,20} were found, which assessed the effectiveness of the PROPATH education program, as a novel approach to communication with people with PD.

4.10 A six month follow-up PROPATH study\textsuperscript{19} (n=155) showed multiple benefits of the PROPATH intervention which are listed in Exhibit 4A. \textbf{Level 1+}

**Exhibit 4A: Effectiveness of PROPATH program versus standard care**

<table>
<thead>
<tr>
<th>Outcome measures (N=322)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rate of disease progression during the program</td>
<td>0.03</td>
</tr>
<tr>
<td>Number of people with PD exercising</td>
<td>0.006</td>
</tr>
<tr>
<td>Medical utilization (in terms of doctor visits)</td>
<td>0.06</td>
</tr>
<tr>
<td>Time ‘off’</td>
<td>&gt;0.01</td>
</tr>
<tr>
<td>Quality-of-life assessment: self-efficacy measure **</td>
<td></td>
</tr>
<tr>
<td>6 months score</td>
<td>&lt;0.05</td>
</tr>
<tr>
<td>Total scores</td>
<td>&lt;0.01</td>
</tr>
</tbody>
</table>

* Rate of disease progression was calculated by changes in summary score at particular times divided by elapsed time in years. The summary score was an average of on-score and off-score (from Unified Parkinson's disease Rating Scale (UPDRS)), side effects index, and patient global assessment.

**Self-efficacy was estimated by a battery of 15 questions, which were assessed on a 0 to100 horizontal analogue scale.

4.11 A separate 12 month follow-up PROPATH study (N=73)\textsuperscript{20} observed only one improved clinical outcome in the intervention group: 'patient perception of general health and psychological well-being', which declined in the standard care group (p=0.04). \textbf{Level 1+}
4.12 A multi-national Global Parkinson’s Disease Survey (GPDS)\textsuperscript{21} of people with PD (n=201) and their carers (n=176) assessed what factors affect health-related-quality-of-life (HRQL). This study found three factors which had an impact on quality of life and explained 60% of the variability in HRQL between people with PD:

- Depression as measured by Beck Depression Inventory (BDI) (p<0.001)
- ‘Satisfaction with explanation of condition at diagnosis’ (P<0.05)
- ‘Feelings of optimism’ which may be related to the style and manner of communication, especially at initial diagnosis (P<0.05).

\textbf{Level 3}

4.13 An interpretative phenomenological study\textsuperscript{22} in 16 people with PD identified the theme of ‘gaining formal knowledge’ and provided the following information on their perspectives:

- Once diagnosed, people with PD identified a need to know more about the condition
- Information provided at diagnosis was difficult to process by most participants
- By their own descriptions, they were in ‘shock’ and did not recall the dialogue between themselves and the diagnosing physicians
- There were a few exceptions to this and some clearly recalled being given a diagnosis but very little additional information
- The human significance was passed over and objectified by what is known about the disease and treatment. Self-care and day-to-day coping with the illness were ignored. \textbf{Level 3}

4.14 In a questionnaire study\textsuperscript{23} physiotherapists and occupational therapists were asked to compare the video recorded conversations of people with PD (n=4) and people with cardiac conditions (n=4) without the sound track. The aim was for the therapists to gauge their initial impressions of the people seen. The video recorded conversations were of interviews conducted by two doctors each of whom conversed with two individuals from each group using a semi-structured script covering non-medical aspects of the their personal histories. The study found there were significant differences in the ratings for all 15 variables. The therapists observed the people with PD to be:

- More anxious/worried/apprehensive; angry/irritable/hostile; suspicious/unforthcoming; morose/sad/down; bored/detached; tense/ill at ease (p<0.001)
- More introverted/shy; anxious/dissatisfied; sensitive/emotional; passive/dependent; less intelligent (p<0.001)
- Enjoying the conversation less well (p<0.001)
- Relating less well to the interviewer (p<0.001)
- Holding up their own end of the conversation less well (p<0.001).

\textbf{Level 3}
4.15 In addition to their observations, the therapists were asked how likeable the person with PD appeared to them. People with PD appeared less likeable (p<0.001). **Level 3**

4.16 It is worth noting that the people with PD in the above study had mild to moderate symptoms and were leading active lives. The impressions made by the therapists were formed from a short exposure to them on a video recording and therefore have the potential of being modified by further contact and greater knowledge of the individual. These results indicate that negative impressions may be induced in clinicians by a lack of verbal expressiveness from the person with PD, and this could influence the development of their relationship with their clinician.

4.17 Another study²⁵ (n=1200) assessed patient satisfaction with the educational information they had received (it did not assess the amount of information provided or who provided it). To summarise the findings:

- The average patient education score indicating that participants were neither particularly satisfied nor dissatisfied with the information they received
- There was no relation between this score and sex, age or Hoehn and Yahr stage
- When the analysis included all patients, a higher patient education score was associated with higher HRQL scores in all subscales of the SF-36 except for physical function and bodily pain
- Patients were most satisfied in regards to ‘role emotional’ and least satisfied in regards to ‘general health’
- After excluding patients with advanced disease (Hoehn and Yahr 4-5) the regression coefficient increased in several subscales (i.e. patients with less severe disease had better quality of life scores), see Exhibit 4B below for details.
- Scores in all subscales of SF-36 were generally lower in patients with more advanced disease, demonstrating that the disease stage is associated with a decline in HRQL involving all aspect of daily living
- Motor complications associated with therapy had a substantial affect on each subscale of SF-36. **Level 3**
Exhibit 4B: Relationship of patient education with SF-36 (regression coefficients of patient education score)

<table>
<thead>
<tr>
<th></th>
<th>All patients</th>
<th>Excluding Hoehn and Yahr (stage 4 &amp; 5)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Physical functioning</td>
<td>-0.76</td>
<td>-0.47</td>
</tr>
<tr>
<td>Role physical</td>
<td>3.74</td>
<td>5.23 *</td>
</tr>
<tr>
<td>Bodily pain</td>
<td>2.01</td>
<td>0.06</td>
</tr>
<tr>
<td>General health</td>
<td>2.10</td>
<td>1.99</td>
</tr>
<tr>
<td>Vitality</td>
<td>3.32</td>
<td>3.66 *</td>
</tr>
<tr>
<td>Social functioning</td>
<td>3.04</td>
<td>4.40 *</td>
</tr>
<tr>
<td>Role emotional</td>
<td>4.18*</td>
<td>4.91 *</td>
</tr>
<tr>
<td>Mental health</td>
<td>2.83</td>
<td>4.10 *</td>
</tr>
</tbody>
</table>

Adjusted for age, sex, number of co morbidities, and activities of daily living score, and complications of therapy. The patient education score was 1 for ‘not at all satisfied’ and 5 for ‘very satisfied’ with information given. Therefore the difference in subscale score of SF-36 between two extremes was fourfold the number in the table.

*P<0.05

4.18 The UK Parkinson’s Disease Society\(^{24}\) questioned 2,500 of their members from November 1997 to January 1998, regarding communication. Of these members, 1,693 (68%) replied and details of selected responses are given in Exhibit 4C. **Level 3**
Exhibit 4C: Parkinson’s Disease Society Survey (1999)

Whether the person had Parkinson’s explained to them on diagnosis (N=1127)

<table>
<thead>
<tr>
<th>Explanation Provided</th>
<th>(%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Very clearly explained</td>
<td>20</td>
</tr>
<tr>
<td>Fairly clearly explained</td>
<td>24</td>
</tr>
<tr>
<td>Neither clearly nor unclear explained</td>
<td>9</td>
</tr>
<tr>
<td>Not very clearly explained</td>
<td>17</td>
</tr>
<tr>
<td>Not at all clearly explained</td>
<td>9</td>
</tr>
<tr>
<td>No explanation given</td>
<td>15</td>
</tr>
</tbody>
</table>

Whether people were given an opportunity to ask questions on diagnosis

<table>
<thead>
<tr>
<th>Opportunity Provided</th>
<th>(%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Adequate opportunity</td>
<td>28</td>
</tr>
<tr>
<td>Fairly adequate opportunity</td>
<td>22</td>
</tr>
<tr>
<td>No opportunity at all</td>
<td>15</td>
</tr>
<tr>
<td>Did not want/feel able to ask questions at the time</td>
<td>22</td>
</tr>
</tbody>
</table>

How useful people find PD information resources (N=1693)

<table>
<thead>
<tr>
<th>Information Source</th>
<th>Very Useful</th>
<th>Not Very Useful</th>
<th>Not used/not available</th>
<th>Did not answer</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hospital doctor/ consultant</td>
<td>56</td>
<td>19</td>
<td>14</td>
<td>12</td>
</tr>
<tr>
<td>PDS-local branch</td>
<td>40</td>
<td>7</td>
<td>36</td>
<td>17</td>
</tr>
<tr>
<td>GP</td>
<td>39</td>
<td>37</td>
<td>13</td>
<td>11</td>
</tr>
<tr>
<td>PDS-national office</td>
<td>36</td>
<td>9</td>
<td>36</td>
<td>19</td>
</tr>
<tr>
<td>People who have Parkinson’s or care for someone with Parkinson’s</td>
<td>36</td>
<td>7</td>
<td>36</td>
<td>21</td>
</tr>
<tr>
<td>Newspapers or magazines</td>
<td>32</td>
<td>24</td>
<td>26</td>
<td>19</td>
</tr>
<tr>
<td>Pharmacist</td>
<td>25</td>
<td>11</td>
<td>45</td>
<td>19</td>
</tr>
<tr>
<td>PD nurse specialist</td>
<td>24</td>
<td>3</td>
<td>56</td>
<td>17</td>
</tr>
<tr>
<td>Physiotherapist</td>
<td>23</td>
<td>9</td>
<td>50</td>
<td>18</td>
</tr>
<tr>
<td>Occupational therapist</td>
<td>19</td>
<td>7</td>
<td>56</td>
<td>19</td>
</tr>
<tr>
<td>Television/radio</td>
<td>19</td>
<td>29</td>
<td>32</td>
<td>20</td>
</tr>
<tr>
<td>Social services department</td>
<td>18</td>
<td>12</td>
<td>51</td>
<td>18</td>
</tr>
<tr>
<td>Speech therapist</td>
<td>16</td>
<td>7</td>
<td>58</td>
<td>19</td>
</tr>
<tr>
<td>PDS-field staff (e.g. area officer)</td>
<td>15</td>
<td>6</td>
<td>57</td>
<td>21</td>
</tr>
</tbody>
</table>

Subjects on which people need information (N=945)

<table>
<thead>
<tr>
<th>Information Need</th>
<th>(%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>New treatments that may be available in future</td>
<td>90</td>
</tr>
<tr>
<td>What drugs are available and/or their side effects</td>
<td>84</td>
</tr>
<tr>
<td>Specific health problems related to Parkinson’s disease</td>
<td>81</td>
</tr>
<tr>
<td>How the disease is likely to affect me or the person I care for in the future</td>
<td>75</td>
</tr>
<tr>
<td>AIDS and equipment and how to get them</td>
<td>49</td>
</tr>
<tr>
<td>How Parkinson’s disease can affect personal relationships</td>
<td>44</td>
</tr>
<tr>
<td>How to get health or social services assistance</td>
<td>41</td>
</tr>
<tr>
<td>How to get welfare benefits and financial help</td>
<td>39</td>
</tr>
<tr>
<td>How to deal with difficulties in getting services for people with Parkinson’s from insurance companies, banks, etc</td>
<td>30</td>
</tr>
<tr>
<td>How to find a suitable holiday</td>
<td>29</td>
</tr>
<tr>
<td>How to find suitable respite care</td>
<td>26</td>
</tr>
</tbody>
</table>
From evidence to recommendation

4.19 People with PD have to live with the consequences of any clinical decision. Given the nature of the therapies currently available for the condition there are difficult trade-offs to be made over time between the beneficial therapeutic effects and the short and long term adverse consequences of a particular treatment. It is essential that these decisions are specific to an individual and agreed between the person with PD and the appropriate clinicians.

4.20 The evidence shows that the way in which the diagnosis of PD is communicated is important and often not well done. People with PD may need the information originally given at diagnosis to be repeated and will want more information as the condition progresses. This is one important role that could be carried out by a health professional such as the Parkinson's Disease Nurse Specialist (see Chapter 10). No evidence is available on what format this information should best be given in but a range of products are already available from the UK Parkinson's Disease Society.

4.21 Particular features that need to be taken into account when communicating with people with PD are:
- Occurrence of cognitive impairment and depression
- Negative impression that may be given by person with PD
- Need for emotional support
- Involvement of carers.

4.22 Effective communication requires well trained staff and an environment which enables sensitive discussions, as these discussions might lead to emotional distress. The UK Parkinson’s Disease Society recently published guidance about communication with people with PD and their carers. The recommendations arose from a group of 17 people with PD, with ages ranging from 47 to 67, and their carers. The document is shown in Appendix C.

4.23 It is important to communicate with carers, particularly when people with PD have cognitive impairment or depression. Carers need:
- General factual information about the condition
- Specific information, if permission is given, about the person with PD
- Information about services and entitlements to care assessment and support procedures
- Advice and support to maintain their health and well-being.

Recommendations

4.24 **R1** Communication with people with PD should empower them to participate in the judgements and choices about their own care. **Grade D**
4.25 **R2** Discussions should achieve a balance between the provision of honest realistic information about the condition and the promotion of a feeling of optimism. **Grade D**

4.26 **R3** As people with PD may develop impaired cognitive ability and depression, they require:
- Both oral and written communication throughout the course of the disease, which should be individually tailored and reinforced as necessary.
- Consistent communication from the professionals involved. **Grade D (GPP)**

4.27 **R4** Families and carers should be given information about the condition, their entitlements to care assessment and the support services available. **Grade D (GPP)**
5. Diagnosing Parkinson's disease

"...it knocked me for six...I became very low...I thought it can't be me...its just elderly people who got it ..."--patient

"...I found it hard to cope with life...I didn't tell anyone...I couldn't face the reality of it..."--patient

Introduction

5.1 This chapter addresses the following issues:
- Definition of PD
- Differential diagnosis of PD
- Methodological limitations of diagnostic studies
- Comparison of clinical versus post-mortem diagnosis
- Comparison of expert versus non-expert diagnosis
- Frequency of review of diagnosis
- Imaging diagnostic techniques:
  - Single photon emission computed tomography (SPECT)
  - Positron emission tomography (PET)
  - Magnetic resonance imaging (MRI)
  - Magnetic resonance volumetry
  - Magnetic resonance spectroscopy
- Other diagnostic techniques:
  - Acute levodopa and apomorphine challenge tests
  - Objective smell testing.

Definition and differential diagnosis

5.2 The manifestations of PD are protean but the classical diagnostic symptoms are:
- Slowness and poverty of movement
- Stiffness
- Shaking.

5.3 The physical signs of PD include:
- Slowness of movement (bradykinesia)
- Poverty of movement (hypokinesia), e.g. loss of facial expression and arm swing, difficulty with fine movements
- Rigidity
- Rest tremor.

5.4 At diagnosis, these signs are usually unilateral but become bilateral as the disease progresses. Later in the disease additional signs may be present including postural instability (e.g. tendency to fall backwards after a sharp pull from the examiner: the ‘Pull Test’), cognitive impairment and orthostatic hypotension.

5.5 There is no single way to define Parkinson's disease or what is often called idiopathic Parkinson's disease in order to differentiate it from
other causes of parkinsonism, such as multiple system atrophy (MSA) and progressive supranuclear palsy (PSP).

5.6 PD is traditionally defined pathologically by the finding of Lewy bodies and degeneration of catecholaminergic neurones at post mortem. Using a pathological definition of PD is problematic for a number of reasons:

- A pathological diagnosis is not practical in life.
- Lewy body inclusions in catecholaminergic neurones are seen in individuals without clinical evidence of PD; it is presumed that these are pre-clinical cases.
- Lewy bodies have not been found in otherwise typical individuals with PD with Parkin mutations, although such rare young-onset genetic cases of PD might be said not to have idiopathic Parkinson's disease.

5.7 In recent years attempts to define PD genetically have become possible with the discovery of monogenic forms of the disease. However, such families account for a very small proportion of cases.

5.8 Another potential way to diagnose PD is using the response to dopaminergic medication. However, this dopaminergic responsiveness can be seen in conditions other than PD such as MSA.

5.9 The decline in dopaminergic neurones identified by radionuclide PET or SPECT imaging has also been proposed as a method of defining PD. Unfortunately, this decline is seen in conditions other than PD such as MSA and PSP.

5.10 Given these difficulties, it is generally accepted that the diagnosis of PD should be based on clinical findings. The most widely accepted clinical criteria for the diagnosis of PD are those introduced by the United Kingdom Parkinson's Disease Society Brain Bank (Exhibit 5A).

5.11 It is important to make an accurate diagnosis in a person with suspected PD as this has an important bearing on prognosis. People with PD will have a longer life expectancy than those with MSA or PSP and will respond better to dopaminergic medication.

5.12 PD must also be differentiated from other conditions presenting with tremor (Exhibit 5B). This can be particularly difficult as PD can present with a postural and action tremor similar.

5.13 In addition, PD must be differentiated from other causes of a parkinsonian syndrome or parkinsonism (Exhibit 5C). The most common problems arise with multiple cerebral infarction and degenerative parkinsonian syndromes such as MSA and PSP. Differential diagnosis can also be difficult in elderly people since extrapyramidal symptoms and signs are common.27
### Exhibit 5A: United Kingdom Parkinson’s Disease Society Brain Bank Criteria for the Diagnosis of Parkinson’s Disease

#### Step 1 Diagnosis of a parkinsonian syndrome

- Bradykinesia and at least one of the following:
  - Muscular rigidity
  - Rest tremor (4-6 Hz)
  - Postural instability unrelated to primary visual, cerebellar, vestibular or proprioceptive dysfunction.

#### Step 2 Exclusion criteria for Parkinson's disease

- History of:
  - Repeated strokes with stepwise progression
  - Repeated head injury
  - Antipsychotic or dopamine-depleting drugs
  - Definite encephalitis and/or oculogyric crises on no drug treatment
  - More than one affected relative
  - Sustained remission
  - Negative response to large doses of levodopa (if malabsorption excluded)
  - Strictly unilateral features after three years
  - Other neurological features: supranuclear gaze palsy, cerebellar signs, early severe autonomic involvement, Babinski sign, early severe dementia with disturbances of language, memory or praxis
  - Exposure to known neurotoxin
  - Presence of cerebral tumour or communicating hydrocephalus on neuroimaging

#### Step 3 Supportive criteria for Parkinson's disease

- Three or more required for diagnosis of definite Parkinson's disease:
  - Unilateral onset
  - Rest tremor present
  - Progressive disorder
  - Persistent asymmetry affecting the side of onset most
  - Excellent response to levodopa
  - Severe levodopa – induced chorea
  - Levodopa response for over five years
  - Clinical course of over 10 years
Exhibit 5B: Common causes of tremor

<table>
<thead>
<tr>
<th>Rest tremor:</th>
</tr>
</thead>
<tbody>
<tr>
<td>Parkinson's disease</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Postural and action tremor:</th>
</tr>
</thead>
<tbody>
<tr>
<td>Essential tremor</td>
</tr>
<tr>
<td>Exaggerated physiological tremor</td>
</tr>
<tr>
<td>Hyperthyroidism</td>
</tr>
<tr>
<td>Drug-induced (e.g. β-agonists)</td>
</tr>
<tr>
<td>Dystonic tremor</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Intention tremor:</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cerebellar disorders</td>
</tr>
</tbody>
</table>

Exhibit 5C: Causes of a parkinsonian syndrome

<table>
<thead>
<tr>
<th>Parkinson's disease</th>
</tr>
</thead>
<tbody>
<tr>
<td>Alzheimer's disease</td>
</tr>
<tr>
<td>Multiple cerebral infarction</td>
</tr>
<tr>
<td>Drug-induced parkinsonism (e.g. phenothiazines)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Other degenerative parkinsonian syndromes:</th>
</tr>
</thead>
<tbody>
<tr>
<td>Progressive Supranuclear Palsy (PSP) (Steele-Richardson-Olszewski syndrome)</td>
</tr>
<tr>
<td>Multiple System Atrophy (MSA) (previously Shy-Drager syndrome, Olivopontocerebellar atrophy and Striatonigral degeneration)</td>
</tr>
</tbody>
</table>

Methodological limitations of the diagnostic studies

5.14 When interpreting the literature about PD diagnosis the following methodological issues should be considered:

- Lack of long-term prospective clinical and pathological follow-up as reference standard
- Lack of operational definitions such as defining specialists or clinical diagnostic criteria
- Unclear whether investigators were blinded to initial diagnosis
- Sample sizes necessarily limited by the number of cases available with neuropathological outcomes
- PD trial age groups are often young as studies were performed by neurologists who see a younger population of people with PD
- Most studies included people with established disease lasting some years
- Varying geographical locations
DRAFT FOR FIRST CONSULTATION

- Exclusion of some studies using magnetic resonance volumetry and magnetic resonance spectroscopy as they lacked appropriate population, intervention and outcome criteria
- Lack of statistical details of diagnostic accuracy such as sensitivity, specificity or positive predictive values

Clinical versus post-mortem diagnosis

5.15 Most experienced specialists have adopted the UK Parkinson’s Disease Society Brain Bank Clinical Criteria (Exhibit 5A) for the diagnosis of PD.

5.16 How do these compare with the accuracy of pathological diagnosis?

Methodology

5.17 Three diagnostic studies were found that assessed the accuracy of clinical diagnosis in parkinsonism compared with autopsy.29-31 These studies compared clinical diagnosis, at various stages of disease progression, to a final diagnosis including details of autopsy findings. The clinical diagnosis was determined using the UK Parkinson’s Disease Society Brain Bank Criteria (Exhibit 5A) in two of three studies.30,31 A third study determined a diagnosis of PD when at least two of the three cardinal signs (bradykinesia, rigidity, and resting tremor) were present.29

Evidence statements

5.18 Two studies (n=5929 and n=10030) examined people with a terminal diagnosis of PD and found the frequency of people misdiagnosed with PD (i.e. they did not meet the pathological criteria at post-mortem) was 24% and 35% respectively.29,30 Level DSII

5.19 A more recent UK Parkinson’s Disease Society Brain Bank study31 examined the brains of 143 people with PD. These people had previously been seen by a neurologist, with five dedicated movement disorder specialists seeing 92% of the cases, and been given a clinical diagnosis of PD or alternative parkinsonian condition. The sensitivity of the clinical diagnosis was 91%, a specificity of 98% and a positive predictive value of 99% (72 out of 73 correctly diagnosed). Level DSII

Evidence to recommendation

5.20 The pathological studies emphasise the need for particular care in making a clinical diagnosis of PD. There is limited evidence to suggest that the UK Parkinson’s Disease Society Brain Bank Criteria have
adequate sensitivity and specificity in comparison with post-mortem findings.

**Recommendation**

5.21 **R5** PD should be diagnosed clinically and based on the United Kingdom Parkinson's Disease Society Brain Bank Criteria. **Grade B (DS)**

**Expert versus non-expert diagnosis**

5.22 The diagnosis of PD could be made in primary care by the person’s general practitioner or in secondary care by a neurologist, geriatrician or general physician. More recently, Parkinson's disease nurse specialists and other health professionals are developing diagnostic skills. Each may have different levels of expertise in evaluating people with possible PD.

5.23 What is the evidence that someone with special expertise is more accurate in diagnosing PD than someone with little experience?

**Methodology**

5.24 Four diagnostic studies,32-35 were found looking at the accuracy of PD diagnosis in a community-based population. The specialist diagnosis was based on the UK Parkinson's Disease Society Brain Bank Criteria in four of the studies.32,33,35 In a fourth study34 the expert diagnosis was based on the investigator's confidence in the diagnosis of PD, presence of atypical features, findings of imaging studies, response to levodopa and results of autopsy examinations. The criteria for the initial diagnoses were not specified in any of the trials. These studies were also performed on prevalent rather than incident PD populations.

**Evidence statements**

5.25 One study32 (n=126) assessed the diagnostic accuracy of neurologist and geriatrician clinical expert diagnosis versus existing clinical diagnosis of parkinsonism from medical records by a non-expert clinician. The study found that neurologists and geriatricians had a sensitivity of 93.5% (95% CI, 86.3% to 97.6%) and specificity of 64.5% (95% CI, 45.4% to 80.8%) compared with 'non-specialist' sensitivity of 73.5% (95% CI, 55.6% to 87.1%) and specificity of 79.1% (95% CI, 64.0% to 90.0%) for diagnostic accuracy. Whilst the positive predictive value of specialists was greater than for other doctors, negative predictive values were equivalent. **Level DS II**

5.26 Another study33 applied the UK Parkinson's Disease Brain Bank Criteria to 402 cases derived from a computerised list of people with PD receiving anti-parkinsonian medication from 74 general practices in North Wales. The initial diagnosis of PD was made by the general practitioner in 59% of cases. The people with PD were either seen at
home or in a specialist movement disorder clinic where a neurological examination was performed. A definite PD diagnosis was made in 53% of all cases, thus an error rate in the community-ascertained cases was 47%. Level DSII

5.27 DATATOP (Deprenyl and Tocopherol Antioxidative Therapy of Parkinsonism) was a large, multi-site clinical trial\textsuperscript{34} in the USA and Canada involving 800 people with PD who were cared for by 34 investigators with a major interest in movement disorders. A secondary analysis examined the number of people with PD with a change in diagnosis after a mean follow-up of six years. The study showed that only 8% had a revised diagnosis. Level DSII

5.28 UK-PDRG study\textsuperscript{35} which investigated the long-term effectiveness of bromocriptine, selegiline and levodopa therapy found a total of 49 /782 people with PD (6%) had their diagnosis changed during the course of the trial. Individuals were eligible for inclusion in the study if they fulfilled criteria for a clinical diagnosis of PD. The authors do not state whether the revised diagnosis was made by one of the specialists performing the study. The authors also do not state whether a specialist or non-specialist conducted the initial diagnostic examination. Level DSII

Evidence to recommendation

5.29 These studies provide only circumstantial evidence on the diagnostic ability of experts versus non-experts. However, they show that the diagnosis of PD is wrong in around 47% of community-ascertained cases, 25% of non-expert secondary care diagnosed cases, and 8% of cases diagnosed by an expert in movement disorders.

5.30 Since medication can mask the symptoms and signs of PD, the GDG felt that people with suspected PD should be referred before treatment is commenced. This can only be achieved if people are seen quickly by experts for an accurate diagnosis and commencement of treatment if necessary.

5.31 The GDG also had experience that delay in making an accurate diagnosis can lead to psychological stress for the patient and their carer. Similarly, the need to revise an incorrect diagnosis which has initially been made by a non-expert can be stressful for patients.

Recommendations

5.32 \textbf{R6} People with suspected PD should be referred quickly\textsuperscript{4} and untreated to a specialist with expertise in the differential diagnosis of this condition. \textbf{Grade B (DS)}

\textsuperscript{4} The Guideline Development Group considered that people with suspected mild PD should be seen within 6 weeks but new referrals in later disease with more complex problems require an appointment within 2 weeks.
Review of Diagnosis

5.33 Given the error rate in making a diagnosis of PD, even in expert hands, it is apparent that the diagnosis should be kept under regular review.

5.34 What is the most appropriate frequency of follow up after an initial diagnosis of PD?

Methodology

5.35 No trials were found which addressed the most appropriate frequency of follow-up of people with Parkinson’s disease.

Evidence Statements

5.36 No evidence was found on the most appropriate frequency of follow-up after the initial diagnosis of the disease.

Evidence to recommendation

5.37 In the absence of any evidence on the issue of frequency of follow up, the GDG concluded that this should be based on clinical priority. In people with early mild symptoms of PD who may not even be on treatment yet, follow up to check on the diagnosis and the need for treatment may be infrequent (every six to twelve months). Once treatment is commenced, follow up may need to be more frequent (every two to three months) to assess the response to medication, titrate dosage and to re-visit the diagnosis. In later disease, people with PD have more complex problems which require changes in medication. This may require review at frequent intervals (every two to three months).

Recommendation

5.38 R7 The diagnosis of PD should be kept under regular review and reconsidered if atypical clinical features develop. Grade D (DS)

SinglePhoton Emission Computed Tomography (SPECT)

5.39 In single photon emission computed tomography (SPECT), a gamma ray emitting radioactive isotope is tagged to a molecule of interest (a tracer), which is given to the person with PD by intravenous injection. The labelled cocaine derivatives $^{123}$I-$\beta$-CIT and $^{123}$I-FP-CIT (N-$\omega$-the Guideline Development Group considered that people diagnosed with PD should be seen at regular intervals of 6 to 12 months to review their diagnosis.
fluoropropyl-2β-carboxymethoxy-3β-(4-iodophenyl)tropane) have most commonly been used, although only the latter is licensed in the UK. These label the pre-synaptic dopamine re-uptake site and thus the pre-synaptic neurone which can be visualised in two-dimensional images. These demonstrate normal uptake in the caudate and putamen in controls, people with essential tremor, neuroleptic-induced parkinsonism, and psychogenic parkinsonism but reduced uptake in those with PD, PD with dementia, MSA and PSP.

5.40 How useful is SPECT in discriminating PD from alternative conditions?

**Methodology**

5.41 Sixteen studies addressed the diagnostic accuracy of SPECT scanning. The reference standard was clinical diagnosis in which eight out of the sixteen studies used the UK PDS Brain Bank Clinical Criteria, five studies used 'established' clinical criteria and three studies did not state the clinical criteria used to determine the diagnosis. Although many tracers are listed in the evidence statements, only 123I-FP-CIT is licensed for use in the UK. The 123I-β-CIT studies were included as it has a similar structure and acts on the same receptors as the FP-CIT tracer. The GDG agreed that this evidence is supportive of FP-CIT studies and provides a consistency of effect.

**Health economic methodology**

5.42 Only one study met quality criteria that addressed the economic evaluation of SPECT. Study was based on the 123I-FP-CIT tracer licensed for use in the UK. SPECT effectiveness data, specificity and sensitivity of clinical examination and prevalence of PD were based predominantly on UK data. However, costs were based on German 2002 data.

5.43 An estimate of the cost per true positive case diagnosed and cost per true negative case diagnosed in the UK context was calculated to compare the costs and effectiveness of using SPECT to differentiate suspected parkinsonism (i.e. PD, MSA or PSP) from essential tremor in a specialised centre at initial examination (Appendix D).

**Evidence statements**

5.44 For the differentiation of people with parkinsonism (i.e. PD, MSA or PSP) from people with essential tremor or controls using SPECT, all studies produced a high sensitivity (range 87% to 98.3%) and specificity (range 80% to 100%). A summary of the evidence produced in these five studies is provided in Exhibit 5D. Level DS Ib

5.45 Three studies (n=80, n=17, n=183) attempting to differentiate PD from other parkinsonian conditions (e.g. MSA, PSP) had insufficiently high levels of sensitivity (range 77% to 97%) and specificity (range 75% to 83%). One study (n=33) included a two-
year follow-up and found a negative predictive value of 92%.\textsuperscript{38} \textbf{Level DS Ib}

5.46 One study\textsuperscript{51} found by comparing the \textsuperscript{123}I-\textbeta-CIT SPECT imaging diagnosis for people with parkinsonian syndrome with a clinical diagnosis (based on six-months follow-up) there was only disagreement between three out of thirty-five cases (8.6%) with visual diagnosis and two out of thirty-five cases (5.7%) with quantitative imaging diagnosis. \textbf{Level DS Ib}

\textbf{Exhibit 5D: Diagnostic accuracy of SPECT imaging (differentiation of tremulous disorders)}

<table>
<thead>
<tr>
<th>Test</th>
<th>Number of participants</th>
<th>Sensitivity (%)</th>
<th>Specificity (%)</th>
<th>Grade</th>
</tr>
</thead>
<tbody>
<tr>
<td>\textsuperscript{123}I-FP-CIT SPECT:</td>
<td>158 PD</td>
<td>27 ET</td>
<td>97</td>
<td>100 \textsuperscript{Ib}</td>
</tr>
<tr>
<td>(institutional read)\textsuperscript{37}</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>\textsuperscript{123}I-FP-CIT SPECT:</td>
<td>Same as above</td>
<td></td>
<td>95</td>
<td>93 \textsuperscript{Ib}</td>
</tr>
<tr>
<td>(consensus read)\textsuperscript{37}</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>\textsuperscript{123}I-FP-CIT SPECT\textsuperscript{38}</td>
<td>38 PD</td>
<td>38 Non-PD</td>
<td>87</td>
<td>- \textsuperscript{Ib}</td>
</tr>
<tr>
<td>\textsuperscript{123}I-\textbeta-CIT SPECT \textsuperscript{41}</td>
<td>60 PD &amp; PSP</td>
<td>36 ET &amp; controls</td>
<td>98</td>
<td>83 \textsuperscript{Ib}</td>
</tr>
<tr>
<td>\textsuperscript{123}I-\textbeta-CIT SPECT:</td>
<td>29 PD</td>
<td>62 controls &amp; ET</td>
<td>98.3</td>
<td>- \textsuperscript{Ib}</td>
</tr>
<tr>
<td>Striatum/cerebellum and putamen/cerebellum binding ratio factors\textsuperscript{44}</td>
<td>29 PD</td>
<td>32 ET</td>
<td>96.7</td>
<td></td>
</tr>
<tr>
<td>\textsuperscript{123}I-\textbeta-CIT SPECT:</td>
<td>35 suspect PD</td>
<td></td>
<td>96</td>
<td>80 \textsuperscript{Ib}</td>
</tr>
<tr>
<td>Visual imaging analysis\textsuperscript{51}</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>\textsuperscript{123}I-\textbeta-CIT SPECT:</td>
<td>Same as above</td>
<td></td>
<td>90</td>
<td>100 \textsuperscript{Ib}</td>
</tr>
<tr>
<td>Quantitative imaging analysis\textsuperscript{51}</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>\textsuperscript{123}I-IBZM SPET:</td>
<td>49 PS</td>
<td>52 Non-PS</td>
<td>87</td>
<td>90 \textsuperscript{II}</td>
</tr>
<tr>
<td>Automated method of analysis\textsuperscript{47}</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>\textsuperscript{123}I-IBZM SPET:</td>
<td>Same as above</td>
<td></td>
<td>85</td>
<td>90 \textsuperscript{II}</td>
</tr>
<tr>
<td>Manual method of analysis\textsuperscript{47}</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Institutional read: visual assessment of \textsuperscript{123}I-FP-CIT striatal uptake by investigator blinded to clinical diagnosis
Consensus read: hard-copy images - agreement from three or more of the five panel members
PS: parkinsonian syndrome
ET: Essential Tremor

\textbf{Exhibit 5E: Diagnostic accuracy of SPECT imaging: differentiation of Parkinson’s disease and controls}
### Test 1

<table>
<thead>
<tr>
<th>Test</th>
<th>Number of participants</th>
<th>Sensitivity (%)</th>
<th>Specificity (%)</th>
<th>Grade</th>
</tr>
</thead>
<tbody>
<tr>
<td>123I-β-CIT SPECT: Striatum/cerebellum binding ratio alone</td>
<td>29, 32</td>
<td>94.9</td>
<td>-</td>
<td>Ib</td>
</tr>
<tr>
<td>123I-FP-CIT SPECT: Binding index in putamen contralateral to initially clinically affected side</td>
<td>76, 20</td>
<td>95</td>
<td>86</td>
<td>II</td>
</tr>
<tr>
<td>TRODAT-1 SPECT: Binding index in putamen contralateral to initially clinically affected side</td>
<td>Same as above</td>
<td>92</td>
<td>70</td>
<td>II</td>
</tr>
<tr>
<td>TRODAT-1 SPECT: Logistic discriminant parametric mapping</td>
<td>42, 23</td>
<td>100</td>
<td>95</td>
<td>II</td>
</tr>
<tr>
<td>TRODAT-1 SPECT: Visual inspection</td>
<td>188, 45</td>
<td>98</td>
<td>86</td>
<td>Ib</td>
</tr>
<tr>
<td>TRODAT-1 SPECT: Quantitative analysis</td>
<td>Same as above</td>
<td>98</td>
<td>88</td>
<td>Ib</td>
</tr>
<tr>
<td>TRODAT-1 SPECT: Contralateral putamen/occipital and contralateral putamen/caudate</td>
<td>78, 40</td>
<td>100</td>
<td>100</td>
<td>II</td>
</tr>
<tr>
<td>TRODAT-1 SPECT: Quantitative imaging analysis Mean uptake in ipsilateral and contralateral posterior putamen</td>
<td>29, 38</td>
<td>0.79</td>
<td>0.92</td>
<td>II</td>
</tr>
</tbody>
</table>

**TRODAT-1**: selective dopamine transporter (DAT) technetium-99m labelled TRODAT-1

**Logistic discriminant parametric mapping (LDPM)**: technique to distinguish sets of data with maximum accuracy

### Health economic evidence statements

5.47 The economic findings indicated:

- SPECT has greater sensitivity but costs more than clinical examination
- SPECT should not be used in all people with PD in place of initial clinical exam
- SPECT could be used to avoid the costs of treating people who do not suffer from PD

5.48 For approximately an additional €733 in Euro 2002 (approximately £511) for the equivalent of a patient-month with adequate treatment, SPECT could be used to confirm a PD diagnosis in people with a positive clinical examination before the initiation of treatment. Adequate treatment month equivalents (ATME) were used to reflect both duration of adequate treatment and severity of incorrect treatments. The authors indicated a 0.55 ATME gain per patient is equivalent to approximately 17 additional days of treatment to a PD patient or withholding approximately 2 days of treatment and side effects to a patient that does not have PD.
5.49 The specificity of clinical examination and frequency of PD in the clinic population of PD had the greatest relative impact on the incremental cost effectiveness ratio (ICER) of SPECT following positive clinical examination compared to clinical examination alone. In the sensitivity analysis, when the specificity of clinical examination is reduced to 0.80 (from 0.984) the ICER drops to €63 (approximately £44)\textsuperscript{52}. This suggests that as more non-PD cases are incorrectly classified as PD cases in clinical examination, the greater the cost-effectiveness of SPECT. When the frequency of PD in the clinic population is increased to 74\% (from 53\%) the ICER increases to €2,411 (approximately £1,697)\textsuperscript{52}. This suggests that the cost-effectiveness of SPECT decreases when the frequency of PD in the clinic population increases. In these populations, there may be fewer false-negative results and therefore fewer people incorrectly being treated for PD. This would mean there is less cost-savings from withholding incorrect treatment and therefore an increase in the relative cost-effectiveness of SPECT.

5.50 Using base-line estimates, it costs approximately £30,429 per additional true positive case diagnosed by SPECT in comparison to initial clinical examination. Alternatively, using true negatives as the outcome, it costs £9,467 per additional true negative case diagnosed. SPECT produces the benefit of avoiding the costs of treating individuals who do not suffer from PD, allowing earlier diagnosis and preventing treatment delays in those with PD and avoiding reduced quality of life of the individual over the uncertain diagnostic period. This outcome is not in terms of cost per QALY and the cost-effectiveness is subject to interpretation [APPENDIX E].

**Evidence to recommendation**

5.51 Considerable evidence supports the use of \(^{123}\text{I}\)-FP-CIT SPECT in people with postural and/or action tremor of the upper limbs in the differentiation of essential tremor from a dopaminergic deficiency state. \(^{123}\text{I}\)-FP-CIT SPECT cannot, with high accuracy, differentiate PD from other dopaminergic deficiency states such as MSA and PSP. Future work may demonstrate the value of this technique in differentiating parkinsonism due to neuroleptic medication and psychogenic parkinsonism from a dopaminergic deficiency state.

5.52 Several clinical trials using SPECT or PET to follow the progression of PD found that 4\%\textsuperscript{53}, 11\%\textsuperscript{54} and 14\%\textsuperscript{55} with a clinical diagnosis of PD had normal imaging at the start of the trial. Further long-term clinical follow-up of these people is required.

5.53 Due to the subjectivity of the effectiveness measurement, the GDG decided the economic study\textsuperscript{52} does not support nor refute the clinical recommendations. Further development of comparable effectiveness outcomes in diagnostic economic evaluations is required.
Recommendations

5.54 **R8** $^{123}$I-FP-CIT SPECT should be available to specialists with expertise in the differential diagnosis of tremor. **Grade D (DS)**

5.55 **R9** $^{123}$I-FP-CIT SPECT should be considered in people with tremor where essential tremor cannot be differentiated from parkinsonism. **Grade A (DS)**

Positron Emission Tomography (PET)

5.56 In positron emission tomography, a positron emitting radioactive isotope is tagged to a tracer molecule, which is administered by intravenous injection. The most frequently used positron-emitting isotope used in PET in this field is $^{18}$fluorine, which is attached to dopa or deoxyglucose. $^{18}$F-fluorodopa is taken up by the pre-synaptic dopaminergic neurones of the caudate and putamen (corpus striatum). $^{18}$F-fluorodeoxyglucose (FDG) is taken up by all metabolically active cells and phosphorylated to a metabolite, which is trapped in the tissue for the time course of the study.

5.57 How valuable is PET in the differential diagnosis of parkinsonism?

Methodology

5.58 Six diagnostic studies$^{56-61}$ were found which addressed the effectiveness of PET scanning compared with clinical diagnosis in the differential diagnosis of a parkinsonian syndrome. No studies were found which compared the effectiveness of PET in the differentiation of PD from essential tremor.

Evidence statements

5.59 In one study$^{61}$ the diagnostic accuracy of $^{18}$F-DMFP PET imaging for the differential diagnosis of atypical (n=16) versus idiopathic (n=16) parkinsonian syndromes showed a threshold value of 2.495 (caudate uptake ratio). The sensitivity, specificity and accuracy were 74%, 100% and 86% respectively. Using this threshold, the positive and negative predictive values for the diagnosis of atypical parkinsonian syndromes were 100% and 76%. **Level DS Ib**

5.60 In one study$^{60}$ the multi-diagnosis group discriminate analysis from $^{18}$F-FDG PET scan images found sensitivity of 75% and a specificity of 100% in PD group (n=8), sensitivity 100% and specificity of 87% MSA group (n=9), and sensitivity of 86% and a specificity of 94% in PSP group (n=7). **Level DS II**

5.61 One study$^{62}$, using $^{18}$F-FDG uptake, reported 74% of all participants (early PD (n=15), atypical PD (n=9), and controls (n=15)) were correctly classified when regional cerebral glucose metabolism (rCMRGlc) was analysed. This diagnostic accuracy increased to 95% using topographical profile rating, which is a method for calculating participant
scores for abnormal regional metabolic co-variance pattern in individual people with PD. **Level DS II**

5.62 One study (n=90)\(^6\), using \(^{18}\)F-fluorodopa uptake found people with clinically diagnosed PD were correctly classified by PET in 64% of the cases and those with atypical parkinsonism (MSA and PSP) in 69% of the cases.

5.63 In another study\(^6\) the probability of the correct diagnosis by \(^{18}\)F-fluorodopa PET was \(\geq 99\%\) for the majority of people with PD (40/41) and controls (26/28). **Level DS II**

**Evidence to recommendation**

5.64 PET has better spatial resolution than SPECT, so it might be anticipated that PET should be of value in differential diagnosis. However, the evidence for PET’s role in differentiating PD from other parkinsonian conditions using FDG requires further confirmation. No work was found on PET’s ability to differentiate PD from essential tremor. This lack of evidence stems from the high cost and poor availability of PET. Further research is required in this area.

**Recommendation**

5.65 **R10** PET should not be used in the differential diagnosis of parkinsonian syndromes except in the context of clinical trials. **Grade B (DS)**

**Magnetic Resonance Imaging (MRI)**

5.66 Structural MRI provides two- and three-dimensional images of intracranial structures using high magnetic field strengths to excite the hydrogen atoms in water molecules. In PD this technique has been used to examine various structures known to be involved in the pathology of the condition in the hope that it may prove of value in differential diagnosis.

5.67 How useful is structural MRI in the differential diagnosis of parkinsonian conditions and essential tremor?

**Methodology**

5.68 Eight diagnostic studies\(^57,59,64-69\) were found which addressed the effectiveness of MRI compared to long-term clinical follow-up in diagnosing people with a parkinsonian syndrome. Various MRI scanning sequences were used.

**Evidence statements**

5.69 Seven of these studies\(^57,64-69\) provided diagnostic accuracy data for MRI using various techniques. The results are summarised in Exhibit 5E.
Exhibit 5E: Diagnostic accuracy of MRI imaging

Regional apparent diffusion coefficient (rADC)

<table>
<thead>
<tr>
<th>Technique</th>
<th>Participants (N=)</th>
<th>Sensitivity (%)</th>
<th>Specificity (%)</th>
<th>Grade</th>
</tr>
</thead>
<tbody>
<tr>
<td>Abnormal putaminal T2 hypointensity</td>
<td>MSA-P (24) vs. PD (27)</td>
<td>87.5</td>
<td>88.9</td>
<td>DS Ib</td>
</tr>
<tr>
<td>Proton density putaminal hyperintensity</td>
<td>Same as above</td>
<td>83.3</td>
<td>100</td>
<td></td>
</tr>
<tr>
<td>T1 MRI: midbrain superior profile</td>
<td>PD (27) vs. PSP (25)</td>
<td>68</td>
<td>88.8</td>
<td>DS Ib</td>
</tr>
<tr>
<td>T1 MRI: midbrain atrophy</td>
<td>Same as above</td>
<td>68</td>
<td>77.7</td>
<td></td>
</tr>
<tr>
<td>T2 MRI: tegmental hyperintensity</td>
<td>Same as above</td>
<td>28</td>
<td>100</td>
<td></td>
</tr>
<tr>
<td>Putaminal T2 hypointensity &amp; T2 hyperintensity combined</td>
<td>MSA (28) vs. PD (32)</td>
<td>32</td>
<td>100</td>
<td>DS II</td>
</tr>
<tr>
<td>Putaminal T2 hypointensity &amp; T2 hyperintensity combined</td>
<td>MSA (28) vs. PSP (30)</td>
<td>32</td>
<td>93</td>
<td></td>
</tr>
<tr>
<td>Putaminal T2 hypointensity &amp; T2 hyperintensity combined</td>
<td>MSA (28) vs. CBD (26)</td>
<td>32</td>
<td>85</td>
<td></td>
</tr>
<tr>
<td>Overall MRI abnormalities</td>
<td>PD (32) vs. MSA (28)</td>
<td>71</td>
<td>91</td>
<td></td>
</tr>
<tr>
<td>Overall MRI abnormalities</td>
<td>PD (32) vs. PSP (30)</td>
<td>70</td>
<td>91</td>
<td></td>
</tr>
<tr>
<td>Overall MRI abnormalities</td>
<td>PD (32) vs. CBD (26)</td>
<td>92</td>
<td>91</td>
<td></td>
</tr>
<tr>
<td>T1 MRI: voxel based morphometry of cerebral peduncles and midbrain</td>
<td>PSP (12) vs. PD (12) and controls (12)</td>
<td>83</td>
<td>79</td>
<td>DS II</td>
</tr>
<tr>
<td>Diffusion weighted MRI Putaminal rADC</td>
<td>MSA-P (10) vs. PD (11)</td>
<td>100</td>
<td>100</td>
<td>DS II</td>
</tr>
<tr>
<td>Diffusion weighted MRI Putaminal hyperintense rim</td>
<td>Same as above</td>
<td>80</td>
<td>91</td>
<td></td>
</tr>
<tr>
<td>Diffusion weighted MRI Putaminal atrophy</td>
<td>Same as above</td>
<td>60</td>
<td>100</td>
<td></td>
</tr>
<tr>
<td>Diffusion weighted MRI Putaminal rADC</td>
<td>PSP (10), PD (13) and MSA-P (12) vs. clinical diagnosis</td>
<td>96</td>
<td>100</td>
<td>DS II</td>
</tr>
</tbody>
</table>

Progressive Supranuclear Palsy (PSP)
Multiple System Atrophy (MSA)- parkinsonian type (P)
Multiple System Atrophy (MSA)- cerebellar type (C)
Corticobasal ganglionic degeneration (CBD)

5.70 Another study\textsuperscript{59} found non-concordance between neuroradiological diagnosis and clinical diagnosis in 2/21 people with PD, 5/14 people with MSA-P and 1/4 people with MSA-C. Level DS II

5.71 One study\textsuperscript{68} reported only 15\% of people with PD and 24\% of those with PSP had abnormal T2 hypointensity in the posterolateral putamen
and none had abnormal putaminal proton density hyperintensity. **Level DS Ib**

5.72 One study\(^6^7\) found two false negatives in the PSP group (one had a diagnosis of clinically probable PSP and one clinically definite PSP) and five false positives (two were non-diseased controls and three had a diagnosis of PD). **Level DS II**

*Evidence to recommendation*

5.73 Whilst in expert hands structural MRI has proved of some value in differentiating PD from other types of parkinsonism, further research is required before it can be recommended in routine clinical practice.

*Recommendation*

5.74 **R11** Structural MRI should not be used in the diagnosis of Parkinson’s disease. **Grade B (DS)**

5.75 **R12** Structural MRI may be useful in the differential diagnosis of parkinsonian syndromes. **Grade D (DS)**

*Magnetic resonance volumetry*

5.76 Magnetic resonance volumetry uses the same principles as structural MRI to measure the size of three-dimensional volumes of tissue. This technique has been used to examine the size of various structures involved in the pathology of PD.

5.77 Can magnetic resonance volumetry be used in the differential diagnosis of parkinsonism?

*Methodology*

5.78 Two studies\(^6^9,7^0\) addressed the diagnostic effectiveness of magnetic resonance volumetry against retrospective clinical diagnosis in determining an accurate diagnosis in people with parkinsonian syndrome.

*Evidence statement*

5.79 One study\(^7^0\) (n= 61) found no differences between people with PD and controls on any of the magnetic resonance volume measures. However, individuals with PSP were distinguished from people with PD and controls with a sensitivity of 95.2% and specificity of 90.9% (mainly due to frontal grey matter volume measure). **Level DS Ib**

5.80 Another study\(^6^9\) (n=53) found the mean superior cerebellar peduncle (SCP) volume atrophy on visual image analysis differentiated PSP from PD, MSA and controls with a sensitivity of 74% and a specificity of 94%, whereas in quantitative analysis the best sensitivity and specificity of the volumetric analysis was 74% and 77%. **Level DS II**
Evidence to recommendation

5.81 Whilst two studies suggest that volumetric MRI can help in the differentiation of PD from other types of parkinsonism, further work is required before it can be recommended.

Recommendation

5.82 **R13** Volumetric MRI should not be used in the differential diagnosis of parkinsonian syndromes, except in the context of clinical trials. **Grade D (DS)**

Magnetic resonance spectroscopy

5.83 Proton magnetic resonance spectroscopy (MRS) measures the concentrations of intermediary metabolites in small volumes of brain tissue. N-acetylaspartate (NAA) is found in the highest concentration in neurones and their processes, whereas creatine (Cr) is a marker of energy status and choline (Cho) is an indicator of membrane synthesis and degradation.

5.84 Can MRS be helpful in the correct diagnosis of parkinsonism?

Methodology

5.85 A systematic review\(^7\) of mixed study designs assessed the diagnostic accuracy of MRS against a clinical diagnosis of a range of parkinsonian syndromes.

Evidence statements

5.86 The review\(^7\) concluded that due to the heterogeneous nature of the available evidence no comments on the variability in metabolite concentrations and ratios between people with parkinsonian disorders could safely be made. **Level DS II**

Evidence to recommendation

5.87 Contradictory results have been found on the value of MRS in differentiating PD from controls and other types of parkinsonism.

Recommendation

5.88 **R14** Magnetic resonance spectroscopy should not be used in the differential diagnosis of parkinsonian syndromes. **Grade B (DS)**

Acute levodopa and apomorphine challenge tests

5.89 Many people with PD respond to single doses of oral levodopa and/or subcutaneous apomorphine.
5.90 Can such responses be assessed using clinical rating scales to provide a diagnostic test for PD?

**Methodology**

5.91 A systematic review\textsuperscript{72} and an additional diagnostic study\textsuperscript{73} addressed the effectiveness of acute levodopa and apomorphine testing in determining an accurate diagnosis of people with a parkinsonian syndrome. Another review\textsuperscript{74} published prior to the included systematic review\textsuperscript{72} was excluded because it summarised the same papers.

**Evidence statements**

5.92 The systematic review\textsuperscript{72} included 13 studies, four of which examined people with de novo PD and nine others which examined people with well-established PD and with other parkinsonian syndromes. These two groups are presented separately in Exhibits 5F and 5G. The diagnostic study\textsuperscript{73} followed people with PD for three years to investigate whether an acute challenge of carbidopa/levodopa had better diagnostic accuracy compared to the acute apomorphine challenge test. These results are also included in Exhibit 5G.

5.93 The systematic review used logistic regression analysis to determine if there was a significant difference between the three tests for the mis-classification of participants. Two studies\textsuperscript{75,76} demonstrated no significant difference between the acute apomorphine challenge test and chronic levodopa therapy. However, two other studies\textsuperscript{75,77} provided evidence that there was a difference between the acute levodopa challenge test and chronic levodopa therapy, in favour of chronic levodopa (p<0.001). \textbf{Level DS II}

5.94 The diagnostic study\textsuperscript{73} commented on the adverse reactions to acute apomorphine challenges. Drowsiness, nausea, vomiting, hypotension, and sweating were reported to such an extent that these effects prevented an increased dosage in some people with PD. Levodopa was better tolerated than apomorphine, with vomiting and nausea still occurring, but infrequently. No statistics were provided on whether the better tolerance of the levodopa challenge over the apomorphine challenge was significant. \textbf{Level DS III}

**Exhibit 5F: Diagnostic accuracy of acute apomorphine and levodopa challenge testing in de novo PD cases\textsuperscript{72}**

<table>
<thead>
<tr>
<th>Test</th>
<th>(N=)</th>
<th>Positive predictive value; 95% Confidence Interval</th>
<th>Grade</th>
</tr>
</thead>
<tbody>
<tr>
<td>Acute APO (1.5-5 mg)</td>
<td>187</td>
<td>0.63 (95% CI 0.56 to 0.70)</td>
<td>DS II</td>
</tr>
<tr>
<td>Acute LD (125-275 mg)</td>
<td>67</td>
<td>0.69 (95% CI 0.59 to 0.80)</td>
<td></td>
</tr>
<tr>
<td>Chronic LD (&lt;1000 mg)</td>
<td>209</td>
<td>0.76 (95% CI 0.70 to 0.82)</td>
<td></td>
</tr>
</tbody>
</table>

Apomorphine (APO)
Levodopa (LD)
Exhibit 5G: Diagnostic accuracy of acute apomorphine and levodopa challenge testing in established PD cases\textsuperscript{72,73}

<table>
<thead>
<tr>
<th>Test</th>
<th>(N=)</th>
<th>Sensitivity (%)</th>
<th>Specificity (%)</th>
<th>Grade</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>PD</td>
<td>Non-PD</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>236</td>
<td>126</td>
<td>86 (95% CI 0.78</td>
<td>85 (95% CI 0.74</td>
</tr>
<tr>
<td>Acute APO 0.7-10 mg\textsuperscript{72}</td>
<td></td>
<td></td>
<td>0.94 to 0.96)</td>
<td>0.74 to 0.96)</td>
</tr>
<tr>
<td>Acute LD 275 mg\textsuperscript{72}</td>
<td>135</td>
<td>39</td>
<td>75 (95% CI 0.64</td>
<td>87 (95% CI 0.77</td>
</tr>
<tr>
<td>Chronic LD &lt;1000 mg\textsuperscript{72}</td>
<td>155</td>
<td>47</td>
<td>0.85 to 0.85)</td>
<td>0.77 to 0.97)</td>
</tr>
<tr>
<td>Acute carbidopa/LD 250/25 mg\textsuperscript{73}</td>
<td>83</td>
<td>51</td>
<td>77.1</td>
<td>71.7</td>
</tr>
<tr>
<td>Acute APO 1.5 mg\textsuperscript{73}</td>
<td>83</td>
<td>51</td>
<td>70.5</td>
<td>65.9</td>
</tr>
<tr>
<td>3 mg\textsuperscript{73}</td>
<td>83</td>
<td>51</td>
<td>76.5</td>
<td>63.9</td>
</tr>
<tr>
<td>4.5 mg\textsuperscript{73}</td>
<td></td>
<td></td>
<td>76.5</td>
<td>66.7</td>
</tr>
</tbody>
</table>

Evidence to recommendation

5.95 The evidence demonstrates that acute challenge tests with levodopa and apomorphine add nothing to standard chronic levodopa therapy in the differentiation of established cases of PD from other causes of parkinsonism. Furthermore, when used in the early stages of the disease, as they would be in clinical practice, acute challenges with levodopa and apomorphine are less discriminatory than the standard practice of treating people with levodopa as an out-patient. This does not preclude the use of acute apomorphine challenges to assess whether a person with later PD will still respond to dopaminergic medication.

Recommendation

5.96 R15 Acute levodopa and apomorphine challenges should not be used in the differential diagnosis of parkinsonian syndromes. \textbf{Grade B (DS)}

Objective smell testing

5.97 Around 80% of people with PD may have an impaired sense of smell (hyposmia).\textsuperscript{78}

5.98 Since smell can be objectively tested with a battery of different odours, is it possible that objective smell identification may be useful in PD differential diagnosis?
Methodology

5.99 We found six diagnostic studies looking at the effectiveness of smell testing in PD differential diagnosis. Two techniques were employed: the ‘Sniffin Sticks’ test\textsuperscript{79} and the University of Pennsylvania Smell Identification Test (UPSIT) test. The tests were used to differentiate between parkinsonian syndromes\textsuperscript{79-81} and people with PD from healthy controls.\textsuperscript{78,82,83}

Evidence statements

5.100 A separate summary of the five diagnostic accuracy studies is listed in Exhibits 5H and 5I. One study\textsuperscript{83} found the discriminatory test scores decreased as a function of age for each of the participant groups and that, on average, lower UPSIT scores are needed to clinically define PD in males than females. \textbf{Level DS II}

5.101 Another study\textsuperscript{82} reported that of the 40 odorants in the UPSIT test, the combined smell of pizza and wintergreen was the best discriminator. As well, pizza (oregano smell) alone specifically indicates anosmia for people with PD with a very high sensitivity and specificity (Exhibit I). \textbf{Level DS II}

5.102 A third study\textsuperscript{78} found abnormal olfactory function in 82\% of the PD participants tested compared to 23\% of controls. \textbf{Level DS II}
### Exhibit 5H: Diagnostic accuracy of smell testing techniques in differentiating parkinsonian syndromes

<table>
<thead>
<tr>
<th>Technique</th>
<th>Groups (N=)</th>
<th>Mean age (years)</th>
<th>Disease duration (yrs)</th>
<th>Cut-off score (%)</th>
<th>Sensitivity (%)</th>
<th>Specificity (%)</th>
<th>Grade</th>
</tr>
</thead>
<tbody>
<tr>
<td>‘Sniffin’ Sticks&lt;sup&gt;79&lt;/sup&gt;</td>
<td>PD (7) vs. MSA (8)</td>
<td>57.7</td>
<td>5.8</td>
<td>19.5</td>
<td>78</td>
<td>100</td>
<td>DS Ib</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>24.8</td>
<td>100</td>
<td>63</td>
<td></td>
</tr>
<tr>
<td>UPSIT Test&lt;sup&gt;80&lt;/sup&gt;</td>
<td>PD (118) vs. MSA (29), PSP (15) and CBD (7)</td>
<td>59.4</td>
<td>63.7</td>
<td>-</td>
<td>25</td>
<td>77</td>
<td>85</td>
</tr>
<tr>
<td>UPSIT test&lt;sup&gt;81&lt;/sup&gt;</td>
<td>PD (18) vs. VP (14)</td>
<td>70.6</td>
<td>4.1</td>
<td>&gt;22</td>
<td>85.7</td>
<td>88.9</td>
<td>DS II</td>
</tr>
<tr>
<td>UPSIT test&lt;sup&gt;81&lt;/sup&gt;</td>
<td>PD (NR) vs. VP (8)</td>
<td>65-75</td>
<td>-</td>
<td>≤23</td>
<td>100</td>
<td>85.7</td>
<td>DS II</td>
</tr>
<tr>
<td>UPSIT test&lt;sup&gt;81&lt;/sup&gt;</td>
<td>PD (NR) vs. VP (6)</td>
<td>76-88</td>
<td>-</td>
<td>≤22</td>
<td>85.7</td>
<td>80</td>
<td>DS II</td>
</tr>
<tr>
<td>Vascular Parkinsonism (VP)</td>
<td>Not reported (NR)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

### Exhibit 5I: Diagnostic accuracy of smelling testing techniques in differentiating parkinsonian syndromes from non-parkinsonian syndromes

<table>
<thead>
<tr>
<th>Technique</th>
<th>Groups</th>
<th>Mean age (years)</th>
<th>Disease duration (yrs)</th>
<th>Cut-off score (%)</th>
<th>Sensitivity (%)</th>
<th>Specificity (%)</th>
<th>Grade</th>
</tr>
</thead>
<tbody>
<tr>
<td>B-SIT test&lt;sup&gt;78&lt;/sup&gt;</td>
<td>PD (N=49) vs. Control (N= 52)</td>
<td>68</td>
<td>5</td>
<td>-</td>
<td>82</td>
<td>82</td>
<td>DS II</td>
</tr>
<tr>
<td>UPSIT Test&lt;sup&gt;83&lt;/sup&gt;</td>
<td>Male: PD (N=52) vs. Controls (N=76)</td>
<td>61 to 70</td>
<td>5 (3 mo-48 yrs)</td>
<td>25</td>
<td>81</td>
<td>82</td>
<td>DS II</td>
</tr>
<tr>
<td>UPSIT Test&lt;sup&gt;83&lt;/sup&gt;</td>
<td>Female: PD (N=20) vs. control (N=104)</td>
<td>61 to 70</td>
<td>See above</td>
<td>30</td>
<td>80</td>
<td>88</td>
<td>DS II</td>
</tr>
<tr>
<td>UPSIT Test&lt;sup&gt;83&lt;/sup&gt;</td>
<td>Male: PD (N=32) vs. controls (N=128)</td>
<td>≤ 60</td>
<td>See above</td>
<td>31</td>
<td>91</td>
<td>88</td>
<td>DS II</td>
</tr>
<tr>
<td>UPSIT Test&lt;sup&gt;83&lt;/sup&gt;</td>
<td>Female: PD (N=28) vs. control (N=112)</td>
<td>≤ 60</td>
<td>See above</td>
<td>33</td>
<td>79</td>
<td>85</td>
<td>DS II</td>
</tr>
<tr>
<td>UPSIT Test&lt;sup&gt;83&lt;/sup&gt;</td>
<td>Male: PD (N=25) vs. controls (N=100)</td>
<td>≥ 71</td>
<td>See above</td>
<td>22</td>
<td>76</td>
<td>78</td>
<td>DS II</td>
</tr>
<tr>
<td>UPSIT Test&lt;sup&gt;83&lt;/sup&gt;</td>
<td>Female: PD (N=23) vs. control (N=92)</td>
<td>≥ 71</td>
<td>See above</td>
<td>25</td>
<td>78</td>
<td>82</td>
<td>DS II</td>
</tr>
<tr>
<td>Pizza and wintergreen&lt;sup&gt;82&lt;/sup&gt;</td>
<td>IPD (N=96) vs. controls (N=96)</td>
<td>62</td>
<td>45.6</td>
<td>Not stated</td>
<td>NA</td>
<td>90</td>
<td>86</td>
</tr>
<tr>
<td>Pizza (oregano smell) only&lt;sup&gt;82&lt;/sup&gt;</td>
<td>IPD (N=96) vs. controls (N=96)</td>
<td></td>
<td></td>
<td></td>
<td>76</td>
<td>90</td>
<td>DS II</td>
</tr>
</tbody>
</table>
Evidence to recommendation

5.103 Objective smell testing has a moderate sensitivity and specificity in differentiating people with PD from controls. However, there is little data on its ability to differentiate PD from other parkinsonian syndromes. Smell is also diminished in Alzheimer's disease. At present, smell identification adds little in the differential diagnosis of parkinsonism but this situation may change with further research.

Recommendation

5.104 **R16** Objective smell testing should not be used in the differential diagnosis of parkinsonian syndromes, except in the context of clinical trials. **Grade B (DS)**
6. Neuroprotection

Introduction

6.1 This chapter outlines:
- The definitions used in the field of neuroprotection
- Details of previous trial designs and outcome measures used to evaluate disease progression
- The mechanisms by which agents may slow disease progression
- Potential neuroprotective agents
- Neuroprotective agents chosen for review:
  - Vitamin E
  - Co-enzyme Q₁₀
  - Dopamine agonists
  - MAO-B inhibitors

Definitions

6.2 Neuroprotection is a process in which a treatment beneficially affects the underlying pathophysiology of PD (Exhibit 6A). This is preferred here to ‘disease modifying therapy’ since the latter may encompass processes, which lead to modification of clinical outcomes without any effect on the underlying pathophysiology of the condition. Good examples of this are drugs which delay the onset of motor complications in PD such as dopamine agonists. This outcome is not necessarily due to a neuroprotective effect; it may arise from a variety of pharmacokinetic and pharmacodynamic mechanisms.⁸⁶,⁸⁷

6.3 Neurorescue refers to the salvage of dying neurones; this may mean a stabilising of the condition with prevention of further cell loss rather than any progressive increase in cell number (Exhibit 6A).⁸⁶,⁸⁷

6.4 Neurorestoration refers to increasing the numbers of dopaminergic neurones by techniques such as cell implantation or nerve growth factor infusion (Exhibit 6A). Such surgical techniques are discussed but not reviewed in the chapter on ‘Surgery for Parkinson's disease’.⁸⁶,⁸⁷

6.5 Neuromodulation has been used by some to refer to deep brain stimulation procedures in PD such as bilateral subthalamic stimulation.⁸⁶,⁸⁷
Exhibit 6A: Schematic representation of neuroprotective processes

Pathogenesis of disease modification

6.6 Detailed discussion of this topic is beyond the scope of this guideline. However, the main pathophysiological mechanisms upon which agents may be neuroprotective are listed below:

- Mitochondrial complex-1 deficiency
- Free radical damage and oxidative stress
- Proteasomal dysfunction
- Apoptosis
- Inflammation (microglial activation).

Measuring disease progression

6.7 Considerable debate surrounds how to measure the rate of progression of PD in clinical trials of neuroprotective therapies. The measures used to date are detailed in Exhibit 6B along with a summary of their potential benefits and drawbacks.
6.8 The majority of previous neuroprotection trials have been parallel group design and placebo controlled. A washout period at the end of the study was often included to remove the symptomatic effects of the active agent. In general, clinical rating scales have been seen as the most acceptable measure of disease modification. One study used a delayed start design to reduce the numbers of people with PD given placebo. With this technique one group is randomised to active treatment from the outset but one or more other groups are randomised to start active drug after a period on placebo (Exhibit 6C). If the drug has a symptomatic effect then clinical outcome measures in the groups will merge together, given sufficient follow up. If the drug delays disease progression then clinical ratings will remain different between the groups.

Exhibit 6B: Outcome measures used in neuroprotection trials in PD.
(Adapted from refs:90,92) .

<table>
<thead>
<tr>
<th>Outcome measures</th>
<th>Benefits</th>
<th>Problems</th>
</tr>
</thead>
<tbody>
<tr>
<td>Quality of life</td>
<td>Patient-rated so more meaningful to them.</td>
<td>Open to symptomatic effects of therapy. Likely to have low sensitivity unless agent has large treatment effect.</td>
</tr>
<tr>
<td>Clinical rating scales</td>
<td>Standard method used for many years.</td>
<td>Open to symptomatic effects of therapy unless evaluated after drug withdrawal.</td>
</tr>
<tr>
<td>Mortality</td>
<td>Has direct relevance to people with PD.</td>
<td>Open to symptomatic effects of therapy. Studies need to be large or long term to have adequate power.</td>
</tr>
<tr>
<td>SPECT and PET imaging</td>
<td>Intuitively a good biomarker for the disease. May improve diagnostic accuracy at start of trials May be more sensitive than clinical outcomes.</td>
<td>People who have PD clinically but have normal baseline scan. People with PD with abnormal baseline radionuclide studies may have PSP or MSA. Lack of clinical correlation of neuroprotection in radionuclide studies to date. Poor sensitivity to change and reproducibility of radionuclide studies. Differential regulation of ligand pharmacokinetics by medication.</td>
</tr>
<tr>
<td>Delaying motor complications</td>
<td>Has direct relevance to people with PD.</td>
<td>More likely to be a pharmacokinetic or dynamic effect than neuroprotection.</td>
</tr>
</tbody>
</table>
Exhibit 6C: Schematic representation of delayed start design trial. At time points T1 and T2 people with PD are randomised to drug or placebo. With neuroprotective drugs, outcome scores will be parallel but with drugs that have a symptomatic effect the curves come together.  

Methodological limitations of neuroprotective studies

6.9 When reviewing the evidence on neuroprotective agents, the following methodological issues should be considered:
- Wide range in sample size
- Lack of statistical detail on power of small studies
- No methods on allocation concealment
- Comparability of results from different centres in multi-site studies
- Drug regimen varied between trials (drug, dose, frequency)

Potential neuroprotective agents

6.10 The many agents suggested to have neuroprotective properties have undergone systematic review by the NINDS. They developed a short list of 12 candidate drugs for neuroprotection trials, which are listed in Exhibit 6D. In addition, Vitamin E has been examined for neuroprotective potential.
6.11 On the basis of the evidence available, the GDG chose to review the four classes of potential neuroprotective drugs for PD based on the human studies:
- Vitamins
- Co-enzyme Q10
- Dopamine agonists
- Monoamine oxidase B inhibitors

**Vitamin E**

6.12 If the generation of free radicals is a significant pathophysiological process in PD, then the anti-oxidant vitamins E and C may be neuroprotective. No trials with vitamin C have been done in PD.

6.13 Does Vitamin E have neuroprotective properties in PD?

**Methodology**

6.14 Three papers were found, which analysed data from the same cohort recruited into the DATATOP study. The DATATOP study (n=800) was a randomised controlled study, which addressed whether vitamin E (tocopherol 2000 IU) was effective in reducing the progression of PD.

**Evidence statements**

6.15 All of the studies failed to demonstrate a significant benefit of vitamin E in slowing the progression of PD. **Level 1++**
6.16 One report\textsuperscript{94} examined 24 months follow-up data and showed:
- The probability of reaching end-point (onset of disability prompting administration of levodopa) was not reduced in people with PD receiving tocopherol
- There was no significant change in UPDRS variables for the tocopherol treatment groups
- There was no evidence of any beneficial effect of $\alpha$-tocopherol (2000 IU per day) in either slowing functional decline or ameliorating the clinical features of PD. \textbf{Level 1++}

6.17 Another report\textsuperscript{96} looked at 24 months follow-up data and showed:
- No significant benefit of tocopherol in reducing the likelihood of reaching end-point (requiring levodopa therapy)
- No significant benefit on any of the secondary outcome measures (UPDRS, Hoehn and Yahr scale, Schwab and England Activities of Daily Living Scale, and neuropsychological testing, Hamilton depression scale). \textbf{Level 1++}

6.18 A third report\textsuperscript{95} looked at 14 months follow-up data and showed no significant effects for tocopherol on the annualised rates of change of any cognitive measure after adjustment for multiple comparisons. \textbf{Level 1+}

\textit{Evidence to recommendation}

6.19 The DATATOP evidence shows that vitamin E taken as 2000 IU of tocopherol daily is not neuroprotective in PD.

\textit{Recommendation}

6.20 \textbf{R17 Vitamin E should not be used as a neuroprotective therapy in PD. Grade A}

\textbf{Co-enzyme Q\textsubscript{10}}

6.21 Mitochondrial complex I activity is reduced in post mortem substantia nigra and in the platelets of people with PD. \textsuperscript{98,99} Co-enzyme Q\textsubscript{10} is the electron acceptor for complexes I and II and as a result is a potent antioxidant. The level of co-enzyme Q\textsubscript{10} is reduced in platelet mitochondria in PD.\textsuperscript{100} Oral supplementation with co-enzyme Q\textsubscript{10} reduced dopaminergic neurone loss in MPTP-treated mice.\textsuperscript{101}
6.22 In view of this positive pre-clinical work, is there any clinical trial evidence that co-enzyme Q₁₀ has neuroprotective properties in PD?

Methodology

6.23 Two studies\textsuperscript{102,103} examined the effectiveness of co-enzyme Q₁₀ in reducing the rate of progression of PD. The methodological limitations included the lack of detail concerning randomisation and allocation concealment in one study\textsuperscript{102}, and a small sample size without power calculations in both studies\textsuperscript{102,103}.

Evidence statements

6.24 The two studies\textsuperscript{102,103} used validated clinical rating scales as the outcome measures to assess benefit from co-enzyme Q₁₀.

6.25 One trial\textsuperscript{103} (n=80) compared three different doses (300 mg/d, 600 mg/d and 1200 mg/d) of co-enzyme Q₁₀ to placebo using total UPDRS scale as the primary outcome measure. The primary analysis was a test for trend between placebo and all doses of co-enzyme Q₁₀. This showed a significant difference (5.30; 95% CI 0.21 to 10.39) at the \( p=0.09 \) level. In a pre-specified secondary analysis, which compared each of the dosages to placebo, only the 1200mg/d group had a significant effect compared to placebo (\( p=0.04 \)). \textbf{Level 1++}

6.26 This trial\textsuperscript{103} also found:

- People with PD taking co-enzyme Q10 displayed a worsening on the Schwab and England Scale as assessed by the examiner (\( p=0.04 \)) but not by the person with PD (\( p=0.81 \)).
- Co-enzyme Q10 did not have a significant effect on the scores for the Hoehn and Yahr Scale or the timed tapping task. \textbf{Level 1++}

6.27 Another trial\textsuperscript{102} (n=28) compared a low dose (360 mg/day) of co-enzyme Q₁₀ to placebo and showed:

- The UPDRS total score was in favour of co-enzyme Q10 treatment (\( p=0.012 \)).
- A benefit of co-enzyme Q10 supplementation on the Visual Function Test (\( p=0.008 \)) measured with the Farnsworth-Munsell 100 Hue Test (FMT). \textbf{Level 1+}
Evidence to recommendation

6.28 The small neuroprotection trials performed with co-enzyme Q₁₀ in PD so far have been encouraging, but further evidence is required before it can be recommended routinely.

Recommendation

6.29 **R18** Co-enzyme Q₁₀ should not be used as a neuroprotective therapy in PD, except in the context of clinical trials. **Grade B**

Dopamine agonists

6.30 A considerable body of pre-clinical work has suggested that dopamine agonists are neuroprotective in cell culture and various animal models of PD.¹⁰⁴,¹⁰⁵

6.31 What clinical evidence is there that dopamine agonists have neuroprotective properties in PD?

Methodology

6.32 Eight studies³⁵,⁵⁴,¹⁰⁶-¹¹¹ were found which addressed the neuroprotective effects of dopamine agonists versus levodopa therapy in PD.

6.33 One trial¹⁰⁷ was excluded due to the lack of reporting drug dosages used during the trial, which limits the comparability with other trials to show consistency of effect.

6.34 GDG members found a related abstract¹¹² on pergolide therapy, but this abstract was excluded, as the results have not been published in a full paper.

6.35 Of the six studies included in the evidence-base, half of them were designed as open-trials. Usually, this would be a serious methodological issue as open-trials are subject to increased performance bias. However, one of the main outcome measures was mortality, which cannot be influenced by the open-trial design. In addition, the long-term follow-up of 4.5 and 10 years is practical justification for an open-trial design.³⁵,¹¹⁰,¹⁰⁸

6.36 There were specific methodological issues associated with the imaging studies. One study reported at baseline that 11% of the people who had been clinically diagnosed with PD had normal scans.⁵⁴ Another study did not include a washout period in order to distinguish between the symptomatic and neuroprotective effects of the drugs administered.¹⁰⁶
Evidence statements

6.37 With respect to clinical rating scales, the ropinirole REAL-PET (n=162) study found UPDRS motor scores during treatment at two years was superior with levodopa compared with ropinirole (95% CI 3.54 to 9.14).\(^\text{54}\) **Level 1++**

6.38 Non-significant results reported by the studies included:
- CALM-PD\(^\text{106}\) (pramipexole) (n=82) mean total and mean motor UPDRS **Level 1++**
- REAL-PET\(^\text{54}\) (ropinirole) Clinical Global Impression (CGI) improvement scale **Level 1++**
- UK-PDRG study\(^\text{35}\) (bromocriptine) (n=782) mean Webster disability scores **Level 1+**
- Cabergoline study\(^\text{111}\) UPDRS factor III (disability) (n=412) and factor II (activities of daily living). **Level 1+**

6.39 With respect to mortality:
- The PRADO study\(^\text{108}\) (n=587) was terminated when 18 deaths were reported in the levodopa (LD) group vs. eight deaths in the levodopa/bromocriptine (LD/BR) group (p=0.07; adjusted for age and sex p=0.02). The risk ratio of death in the LD group compared to the LD/BR group was 2.7, a reduction of 63%. **Level 1+**
- All three of the bromocriptine studies\(^\text{45,109,110}\) found no significant differences between treatment groups. **Level 1+**
- The cabergoline study\(^\text{111}\) found no significant difference between treatment groups. **Level 1+**

6.40 With respect to imaging, several analytical measures found benefit of ropinirole and pramipexole over levodopa, these are summarised in Exhibit 6E.
Exhibit 6E: Percentage rate of decline (Level 1++)

<table>
<thead>
<tr>
<th>Variable</th>
<th>% Change levodopa (SE)</th>
<th>% Change dopamine (SE)</th>
<th>Significance</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ropinirole (REAL-PET)</td>
<td>13.4% (2.14)</td>
<td>20.3% (2.35)</td>
<td>RD 34% (95%CI 0.65 to 13.06; P=0.022)</td>
</tr>
<tr>
<td>Region-of-interest analysis (reduction in putamen Ki over 2 years)</td>
<td>14.1% (1.58)</td>
<td>22.9% (1.70)</td>
<td>RD 38% (95%CI 4.24 to 13.3; p&lt;0.005)</td>
</tr>
<tr>
<td>Statistical parametric mapping (reduction in putamen)</td>
<td>4.3% (3.67)</td>
<td>-7.5% (3.94)</td>
<td>MD 11.9 (95%CI 1.3 to 22.4; P=0.025)</td>
</tr>
<tr>
<td>Amplitudes of change (substantia nigra)</td>
<td>-7.1 (9.0)</td>
<td>-13.5 (9.6)</td>
<td>P=0.004</td>
</tr>
<tr>
<td>Pramipexole (CALM-PD)</td>
<td>-10.9 (11.8)</td>
<td>-19.6 (12.4)</td>
<td>P=0.009</td>
</tr>
<tr>
<td>At 34 months</td>
<td>-16.0 (13.3)</td>
<td>-25.5 (14.1)</td>
<td>P=0.01</td>
</tr>
<tr>
<td>Striatal $[^{123}I] \beta$-CIT (rate of decline) at 22 months</td>
<td>-7.1 (9.0)</td>
<td>-13.5 (9.6)</td>
<td>P=0.004</td>
</tr>
<tr>
<td>At 34 months</td>
<td>-10.9 (11.8)</td>
<td>-19.6 (12.4)</td>
<td>P=0.009</td>
</tr>
<tr>
<td>At 46 months</td>
<td>-16.0 (13.3)</td>
<td>-25.5 (14.1)</td>
<td>P=0.01</td>
</tr>
</tbody>
</table>

RD: Relative difference  
Ki: influx constant  
SE: standard error  
MD: mean difference

6.41 With respect to motor complications:
- The REAL-PET study$^{54}$ found:
  - Development of dyskinesia favoured ropinirole (odds ratio 0.09, 95% CI 0.02 to 0.29, p<0.001)
  - Time to develop dyskinesias favoured ropinirole (hazard ratio 8.2, 95% CI 2.46 to 27.93, p<0.001). **Level 1++**

- The PRADO study$^{108}$ found the incidence of dyskinesias favoured bromocriptine (rate ratio: 0.73, 95% CI 0.57 to 0.93). **Level 1+**

- The cabergoline versus levodopa study$^{111}$ found:
  - Risk of developing motor complications favoured cabergoline treatment (p<0.02)
  - The relative risk of developing motor complications was >50% lower with cabergoline compared to levodopa
  - Cabergoline-treated people requiring levodopa were at the same risk of developing motor complications as those on a stable levodopa dose. **Level 1+**
**Evidence to recommendation**

6.42 The apparent reduction in the rate of tracer loss in the ropinirole and pramipexole trials shown by radionuclide imaging raised the prospect that these agonists are neuroprotective. However, there are a number of methodological problems with these studies (as shown in Exhibit 6B). Clinical motor rating scales were better in levodopa treated individuals with PD or no different. The delaying of motor complications by the agonists may be due to a pharmacokinetic or pharmacodynamic effect rather than by slowing disease progression.

**Recommendations**

6.43 **R19** Dopamine agonists should not be used as neuroprotective therapies in PD, except in the context of clinical trials.  

**Grade B**

**MAO-B Inhibitors**

6.44 The propargylamines selegiline and rasagiline are monoamine oxidase inhibitors thereby reducing the turnover of dopamine and hopefully reducing free radical generation. However, they may also have an anti-apoptotic effect.  

6.45 What in vivo evidence is there that MAO-B inhibitors are neuroprotective in PD?  

**Methodology**

6.46 One meta-analysis and an RCT were found, which addressed the effectiveness of MAO-B inhibitors in reducing the rate of progression of PD.

6.47 The meta-analysis included 3525 people with PD in 17 randomised trials; 13 trials were on selegiline, three trials were on lazabemide and one trial was on rasagiline therapy. Only selegiline and rasagiline (to be licensed in the UK in 2005) are licensed for use in the UK. The results of the lazabemide studies were consistent with the results of the other two therapies, so the full meta-analysis was included in the evidence base.

6.48 The RCT consisted of 404 people with PD randomised to rasagiline or placebo-delayed rasagiline therapy. The delayed-start design (see Exhibit 6C) consisted of randomising them to one of three groups:

- Rasagiline 1mg/d for one year,
- rasagiline 2 mg/d for one year,
- Placebo for six months, followed by rasagiline 2mg/d for six months.
Evidence statements

6.49 The meta-analysis\(^{113}\) combined the available data from six trials of selegiline therapy. All trials showed significantly improved scores in favour of selegiline versus controls for UPDRS scores at three months as follows:

- Total score: 2.7 (95%CI 1.4 to 4.1, p=0.00009)
- Motor score: 1.8 (95%CI 0.8 to 2.7, p=0.004)
- Activities of Daily Living scores: 0.9 points (0.5 to 1.4, p=0.00007)

Level 1++

6.50 Although the large DATATOP study accounted for over 79% of people with PD in the MAO-B inhibitors versus placebo comparison, the combined results from the other studies were consistent with those from DATATOP (p=0.004). Level 1++

6.51 The rasagiline trial\(^{91}\) showed that:

- Total UPDRS scores for rasagiline 1 mg/d for one year versus delayed-start rasagiline 2mg/d for six months was significant –1.82 (95% CI -3.64 to 0.001 units, p=0.05) in favour of longer treatment.
- Rasagiline 2mg/d for one year versus delayed-start rasagiline 2mg/d for six months was significant –2.29 (95% CI –4.11 to –0.48 units, p=0.01) in favour of longer treatment.
- Activities of daily living score for rasagiline 2mg/d for one year versus delayed-start rasagiline 2mg/d for six months significantly favoured the longer treatment (p=0.005).
- The comparisons of other UPDRS subscales were not significant. Level 1++

6.52 The meta-analysis\(^{113}\) assessed mortality rates by combining all of the available data from nine trials of selegiline and one trial of lazabemide therapy. The results in eight trials (excluding UK-PDRG), showed:

- No excess in mortality between MAO-B inhibitor treated individuals with PD and controls (p=0.8).
- In the UK-PDRG study there were significantly more deaths in the selegiline arm versus the levodopa arm (odd ratio=1.57, 95% CI 1.09 to 2.30, p=0.015).
- By taking all available data, 20% of deaths occurred in the MAO-B inhibitor group compared 21% in the controls (p=0.2).
- No significant heterogeneity was found between trials (p=0.6) even including the UK-PDRG study. Level 1++

6.53 The meta-analysis\(^{113}\) found five trials, which reported data on motor complications. The combined results showed:

- A 25% reduction in motor fluctuations in MAO-B inhibitor group (0.75, 95% CI 0.59 to 0.95, p=0.02).
- No difference in the incidence of dyskinesia between treatment groups (0.97, 95% CI 0.75 to 1.26, p=0.8) compared to non-MAO-B inhibitors group. Level 1++
Evidence to recommendation

6.54 The benefits of MAO-B inhibitors versus control in terms of clinical rating scales were consistent with a known short-term symptomatic effect. There does not seem to be any clear increase or decrease in mortality with MAO-B inhibitors. The delayed onset of motor fluctuations with MAO-B inhibitors is comparable to the delayed motor complications with dopamine agonists but is likely to represent a levodopa-sparing effect involving pharmacokinetic or pharmacodynamic factors.

6.55 The sustained difference in total UPDRS in the rasagiline versus placebo delayed start design trial suggests this agent may be neuroprotective. However, the relatively short follow up in this trial may not have been long enough to see the UPDRS scores in the different trial groups merge, as would be seen with a symptomatic effect.

6.56 Further larger trials with longer-term follow-up are required to assess whether the MAO-B inhibitors have neuroprotective properties in PD.

Recommendation

6.57 **R20** Monoamine oxidase B inhibitors should not be used as neuroprotective therapies in PD, except in the case of clinical trials.  
Grade B
7. Symptomatic pharmacological therapy in PD

Introduction

7.1 Symptomatic therapies for PD treat the symptoms of the disease but do not necessarily slow the rate of progression of the condition. In this guideline the symptomatic pharmacological therapies have been classified on the basis of the clinical manifestations of a person with PD. Thus:

- Early disease has been used to refer to people with PD who have developed functional disability and require symptomatic therapy
- Later disease has been used to refer to people on levodopa who have developed motor complications.

7.2 Clinical trials and regulatory authorities define the term 'later disease' in the same way. However, since motor complications can occur soon after starting levodopa, particularly if large doses are used, 'later disease' is something of a misnomer. The term is generally preferred to the alternative ‘advanced disease’.

Methodological limitations of symptomatic therapy studies

7.3 When reviewing the symptomatic therapy evidence the following methodological issues should be considered:

- Trial duration is often too short
- Drug regimen varied between trials (type of drug, dose, frequency)
- Small sample size which limits generalisability and sensitivity of tests to detect outcome differences between groups.
- Lack of reporting methods of randomisation and allocation concealment
- Lack of washout periods between treatment arms in crossover studies
- Lack of reporting results of first arm from crossover studies which leads to risk of carryover effect
- Lack of intention-to-treat analyses
- Lack of defining the clinical criteria for diagnosis.

"None of the pills I take gives me even a mild buzz, but the freedom of movement and the interlude of physical grace they provide are intoxicating."--patient
7.4 Most of the poorly designed trials were performed in the 1970s and 1980s when trial design was in its infancy. Drugs evaluated in such trials may not have been found to be efficacious in this review. However, this does not mean that they are ineffective. In such cases, clinical experience may be the only appropriate judge of efficacy and safety.

7.5 The Cochrane reviews included in this chapter have received a 1++ grading for the methodology of the systematic review as applied by the Cochrane group but this grading does not apply to the trials contained within these reviews. Although the methodologies of the systematic reviews were of good quality, the trials contained within the reviews sometimes suffered from methodological limitations. The results of these trials should be treated with caution due to the inherent methodological limitations. In light of this, it was felt to be inappropriate to present evidence statements based on the individual trial data.

7.6 Efficacy outcome measures in later disease trials are considerably different from those in early disease. The people with PD in such trials have already developed motor complications and the aim of adjuvant therapy is to reduce the time the person with PD spends ‘off’ and to reduce the dose of levodopa which has played some part in the generation of the complications in the first place. ‘Off’ time is measured from patient-completed 30 minute epoch ‘on’/’off’ diary cards which are usually averaged over a three day period. Levodopa dose is recorded throughout the trial. Usually the UPDRS scale components are also noted during late disease trials. (See also Appendix J: Glossary of Terms)

**Early Pharmacological Therapy**

7.7 In this section consideration is given to:
- Symptomatic therapies for early PD:
  - Levodopa
  - Modified-release levodopa
  - Dopamine agonists
  - Monoamine oxidase B (MAO-B) inhibitors
  - Adrenergic antagonists (beta-blockers)
  - Amantadine
  - Muscarinic antagonists (anticholinergics).
- Comparisons between drug classes:
  - Dopamine agonists versus levodopa
  - MAO-B inhibitors versus levodopa
  - MAO-B inhibitors versus dopamine agonists
  - Choice of initial therapy in early PD.
Levodopa

7.8 The standard symptomatic therapy for PD for more than 30 years has been levodopa. This is the precursor of dopamine which is deficient in PD. Levodopa is readily converted into dopamine by dopa decarboxylase. To reduce peripheral metabolism of levodopa, it is combined with a peripheral dopa decarboxylase inhibitor (i.e. carbidopa or benserazide). This increases the amount of levodopa which crosses the blood-brain barrier.

7.9 However, levodopa preparations contribute to the development of motor complications in PD. These are comprised of abnormal involuntary movements or dyskinesias, such as chorea and dystonia, along with response fluctuations in which people experience ‘wearing off’ of the drug’s effects and/or unpredictable switching between the ‘on’ and the ‘off’ state.

7.10 To avoid motor complications, the strategy of delaying the introduction of levodopa has developed. This approach requires initial therapy with an alternative that is as effective as levodopa which does not cause motor complications. A number of drug classes have been examined for such properties.

Methodology

7.11 Only one RCT \(^{55}\) (ELLDOPA) was found which addressed the effectiveness of levodopa (plus a decarboxylase inhibitor) versus placebo. The other trials found included studies on levodopa monotherapy versus placebo and were published between 1969 to 1971. These were not reviewed as levodopa is no longer used without a decarboxylase inhibitor.

7.12 The RCT \(^{55}\) was a large multi-centre study including 361 early PD people randomly assigned to four groups, consisting of three different doses of levodopa/carbidopa (105/37.5 mg/day, 300/75 mg/day, or 600/150 mg/day) or placebo.

7.13 All people included in the trial had received a diagnosis of PD within the past two years and no one was on any antiparkinsonian medication at the time of enrolment. The trial duration was 40 weeks which was followed by a two-week withdrawal period at the end of the trial.

7.14 There were two primary outcome measures: clinical assessment using UPDRS and measurement of the dopamine transporter with \(^{123}\)I-CIT SPECT.
Evidence statements

7.15 With respect to clinical rating scales:\(^55\)
- Levodopa in a dose-dependent pattern reduced the worsening of symptoms of PD.
- Changes in UPDRS scores from baseline to week 42 (versus placebo):
  - Total score (p<0.001)
  - ADL component (p<0.001)
  - Motor component (p<0.01)
  - Mental component (non-significant)
- The UPDRS scores in the 3 levodopa groups worsened during the 2-week washout period but did not deteriorate to placebo levels.
- The group receiving the highest dose of levodopa had the best result. Level 1++

7.16 With respect to \(^{123}\)\(\beta\)-CIT (neuroimaging) outcomes:\(^55\)
- The percentage decrease in striatal \(^{123}\)\(\beta\)-CIT uptake over 40 weeks was greater among participants in levodopa than placebo groups and although this is non-significant, almost 15% of people had a putaminal uptake of more than 75% of age-matched controls.
- Analysis of the results after exclusion of the 19 people without dopaminergic deficit on imaging showed a significantly greater decrease in uptake among those receiving levodopa than those receiving placebo (p=0.036). Level 1++

7.17 With respect to adverse events: \(^55\)
- Side effects were more common in 600mg group than placebo for dyskinesias (p<0.001), nausea (p=0.001), infection (p=0.01), hypertonia (p=0.03) and headache (p=0.03).
- And other findings were non-significant between other levodopa doses and placebo. Level 1++

7.18 With respect to withdrawal rates: \(^55\)
- Of the total 361 participants enrolled- 317 (88%) took the study medication for 40 weeks and 311 (86%) completed the 2 weeks of washout.
- The percent of dropouts per group included: placebo (22%), 150mg/d (15%), 300mg/d (6%) and 600mg/d (11%).
- The main reasons for withdrawal were worsening of symptoms and adverse events. Level 1++

Evidence to recommendation

7.19 The clinical impression that levodopa is a most effective treatment for PD has been confirmed in the large ELLDOPA trial. Short-term dopaminergic adverse effects are infrequent and usually settle with time. However, long-term levodopa therapy precipitates motor complications such as dyskinesias and motor fluctuations. Questions
remain regarding the possibility that levodopa may be toxic or even protective to the remaining nigrostriatal dopaminergic neurones. Further work is required to clarify this issue.

Recommendation

7.20 R21 Levodopa can be used as a symptomatic treatment in early PD. Grade A

Modified-release levodopa

7.21 It has been suggested that levodopa induces motor complications because of its short duration of action and thus the pulsatile stimulation of dopamine receptors. To avoid this, modified or slow-release formulations of levodopa were developed.

7.22 What is the evidence that modified-release levodopa preparations delay the onset of motor complications?

Methodology

7.23 Four studies\textsuperscript{114-117} were found which addressed the effectiveness of modified-release levodopa versus immediate-release levodopa in the treatment of early Parkinson’s disease.

7.24 One study\textsuperscript{114} was excluded due to lack of important information on drug dosages, randomisation methods, method of outcomes measurement and clinical criteria for the patient group. Another study was excluded as it was an open-trial design and therefore had increased potential for bias.\textsuperscript{116}

7.25 One of the two included studies\textsuperscript{115} examined the efficacy of immediate-release co-beneldopa (Madopar; levodopa and benserazide) versus modified-release (Madopar HBS/CR), while the other study examined immediate-release co-careldopa (Sinemet; levodopa and carbidopa) versus modified-release (Sinemet CR) formulation.\textsuperscript{117}

Evidence statements

7.26 With respect to clinical rating scales of quality of life:

- The co-careldopa study\textsuperscript{117} (n=134) found:
  - Activities of daily living scores (UPDRS scale) were in favour of the modified-release preparation (p=0.006 year one; p=0.031 year five).
  - Nottingham Health Profile was in favour of modified-release for emotional reaction and social isolation (p<0.05). Level 1+

7.27 Both studies\textsuperscript{115,117} found no significant differences between the treatment groups for the following outcome measures of motor impairment:

- NYUPDS
• NUDS
• UPDRS
• Hoehn and Yahr scales
• Schwab and England scores. **Level 1+**
7.28 One study\textsuperscript{117} reported no significant difference between treatment groups for motor fluctuations (primary endpoint) either by diary data or by questionnaire.

7.29 With respect to drug dosage, one study\textsuperscript{117} (n=618) found the average number of daily doses was in favour of the modified-release preparation (p<0.005), while the other study\textsuperscript{115} found no differences. \textbf{Level 1+}

7.30 With respect to adverse effects one study\textsuperscript{115} reported no significant differences between the two groups. \textbf{Level 1+}

7.31 With respect to withdrawal rates one study\textsuperscript{117} found the number of withdrawals was higher in the immediate-release group (p=0.007). \textbf{Level 1+}

\textit{Evidence to recommendation}

7.32 This evidence strongly suggests that there is no value in using the existing modified-release levodopa preparations to delay the onset of motor complications.

\textit{Recommendation}

7.33 \textbf{R22} Modified-release levodopa preparations should not be used to delay the onset of motor complications in early PD. \textbf{Grade A}

\textbf{Dopamine Agonists}

7.34 The dopamine receptor agonists mimic the effect of dopamine by binding directly with the post-synaptic dopaminergic receptors. They were introduced as adjuvant therapy to levodopa in later disease, but more recently trials have examined their effects as initial monotherapy in the hope that they may delay the onset of motor complications.

7.35 What is the effectiveness of dopamine agonists versus placebo in the treatment of functionally disabled early Parkinson’s disease?

\textit{Methodology}

7.36 Six randomised controlled trials\textsuperscript{118-123} were found which compared the effectiveness of dopamine agonists versus placebo for the treatment of people with early PD who are functionally disabled. The sample size for most of these studies was quite large (range n=55 to 335, mean 177).

\textit{Evidence statements}

7.37 The following outcomes were reported to be significantly in favour of dopamine-agonists:


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- UPDRS total score\textsuperscript{118,119}
- UPDRS motor scores\textsuperscript{118,120-123}
- UPDRS > 30\% reduction in motor scores\textsuperscript{118,120,123}
- UPDRS ADL scores\textsuperscript{118,121,122}
- Schwab and England ADL scores\textsuperscript{118}
- Clinical Global Impression 'very much improved' score\textsuperscript{118,120,123}
- Requirement of levodopa supplementation\textsuperscript{120}
- Withdrawal rates\textsuperscript{120} Level 1+

7.38 The following adverse events were found to be significantly increased (p<0.05) in the treatment group:
- Nausea\textsuperscript{118,121,123}
- Somnolence\textsuperscript{118,121,123}
- Dizziness\textsuperscript{118,123}
- Insomnia, constipation, hallucinations\textsuperscript{121}
- Anorexia, vomiting\textsuperscript{118} Level 1+

7.39 The following outcomes were reported as non-significant:
- Incidence of reporting adverse events\textsuperscript{118-123}
- Incidence of withdrawals\textsuperscript{118,123} Level 1+

\textit{Evidence to recommendations}

7.40 Dopamine agonists are an effective treatment for the motor features of early PD. However, agonists generate significant dopaminergic adverse events. The latter do not lead to drug withdrawal which suggests that they are mild and that tolerance develops. These conclusions apply to the relatively young people included in these studies. Further work on the efficacy and safety of dopamine agonists in older people is required.

7.41 Ergot-derived dopamine agonists (bromocriptine, cabergoline, lisuride and pergolide) are well known to cause rare serosal reactions such as pleural, pericardial and peritoneal effusion and/or fibrosis.\textsuperscript{124} Recently, two echocardiographic series have suggested that pergolide can also cause a cardiac valvulopathy.\textsuperscript{125,126} As a result of these reports, the pergolide Summary of Product Characteristics has been changed to include:
- Pergolide is to be used as second-line after a non-ergot dopamine agonist
- The dose of pergolide should not exceed 5 mg per day
- An echocardiogram must be obtained before initiating therapy and should be repeated regularly thereafter to monitor for valvulopathy
- Pergolide is contra-indicated in anyone with anatomical evidence of cardiac valvulopathy.

7.42 Reports of serosal reactions with non-ergot dopamine agonists (pramipexole and ropinirole) are few and these are possibly due to previous exposure to ergot-derived agonists. However, the patient
years of exposure to these newer agonists is low, so firm conclusions cannot be reached.

Recommendations

7.43  **R23**  Dopamine agonists can be used as a symptomatic treatment in early PD. **Grade A**
Monoamine oxidase B inhibitors

7.44 Monoamine oxidase type B inhibitors (MAO-B inhibitors) block the metabolism of dopamine thereby increasing its level in the striatum. MAO-B inhibitors do not cause a reaction after consuming tyramine rich foods (“tyramine” or “cheese” effect) and are therefore safer to use than non-selective inhibitors.

7.45 MAO-B inhibitors were introduced as a symptomatic therapy in later PD. After encouraging pre-clinical and one retrospective clinical trial they were used for a time in early PD in the hope that they might have a neuroprotective effect in addition to a symptomatic effect (See Chapter 6).

7.46 What is the evidence that MAO-B inhibitors are an effective and safe symptomatic treatment in early PD?

Methodology

7.47 One meta-analysis and two RCTs which addressed the effectiveness of MAO-B inhibitors in treating people with early Parkinson’s disease were included.

7.48 The meta-analysis included 3525 people with PD from 17 randomised trials; 13 trials were on selegiline, three trials were on lazabemide and one trial was on rasagiline therapy. Although only selegiline and rasagiline are licensed for use in the UK, the results of the lazabemide studies were consistent with the results of the other two therapies. Thus, the meta-analysis which combined the results of all MAO-B inhibitors trials, was included in the evidence base. All of the selegiline trials used the standard oral preparation rather than the lyophilised buccal preparation (Zelapar® selegiline).

7.49 One RCT consisted of 15 people with PD. The small sample size could explain the non-significant results, when compared to the large meta-analysis. The other RCT consisted of 56 people with PD, divided into 3 rasagiline dose groups (1,2 or 4 mg/d) and a placebo group. This authors of this study reported that the trial was inadequately powered for assessing anti-parkinsonian efficacy of the study drug.

Evidence statements

7.50 The large DATATOP study accounted for over 65% of the people with PD analysed for UPDRS scores and over 79% of people with PD in the MAO-B inhibitor versus placebo comparison. The combined results from the other two studies of MAO-B inhibitor versus placebo were
consistent with those from DATATOP and were significant independently \( (p=0.004) \). **Level 1**

7.51 With respect to clinical rating scales the meta-analysis\(^{113}\) reported:
- UPDRS scores at three months from six trials (all used selegiline for MAO-B inhibitor intervention):
  - Total score: treatment difference 2.7 (95% CI 1.4 to 4.1, \( p=0.00009 \))
  - Motor score: treatment difference 1.8 (95% CI 0.8 to 2.7, \( p=0.0004 \))
  - Activities of daily living score: treatment difference 0.9 (95% CI 0.5 to 1.4, \( p=0.00007 \))
  - All of the above quoted outcomes favoured selegiline over controls. **Level 1**

7.52 The randomised cross-over trial\(^{129}\) reported no significant differences for the Webster rating scale (total scores) for people with PD on co-beneldopa/selegiline versus people with PD on co-beneldopa/placebo. **Level 1**

7.53 The other RCT\(^{128}\) reported:
- Total UPDRS score during 10-week period (\( p<0.05 \)) for rasagiline 2mg but not for 1mg and 4mg groups compared to placebo
- A responder analysis showed that 28% of people (12/43) receiving rasagiline had an improvement in total UPDRS score of more than 30% compared with none of the people receiving placebo (\( p<0.05 \))
- No evidence of drug effect was noted with respect to the CGIC scale, Hoehn and Yahr stage, Schwab and England ADL scale, or BDI. **Level 1**

7.54 With respect to need for levodopa therapy the meta-analysis\(^{113}\) found:
- Eight trials reported data on the need for levodopa (MAO-B inhibitor v placebo). The combination of these trial results showed a highly significant reduction in need for levodopa in people with PD randomised to a MAO-B inhibitor compared to placebo (0.57, 95% CI 0.48 to 0.67, \( p<0.00001 \)). **Level 1**

7.55 With respect to motor complications, the meta-analysis\(^{113}\) found five trials. The combined results showed:
- 25% reduction in motor fluctuations in MAO-B inhibitor group, treatment difference 0.75 (95% CI 0.59 to 0.95, \( p=0.02 \))
- No significant difference in the incidence of dyskinesia between treatment groups compared to non-MAO-B inhibitor group. **Level 1**

7.56 The meta-analysis\(^{113}\) found more side effects were reported in:
- People with PD randomised to an MAO-B inhibitor, treatment difference 1.36 (95% CI 1.02 to 1.80, \( p=0.04 \))
7.57 The RCTs\textsuperscript{128,129} found minimal or no side effects reported in either treatment group. \textbf{Level 1+}

7.58 The meta-analysis\textsuperscript{113} found more people in the MAO-B inhibitor group withdrew due to adverse events than the non-MAO-B inhibitor group, treatment difference 2.16 (95% CI 1.44 to 3.23, \(p=0.0002\)). \textbf{Level 1+}

\textit{Evidence to recommendation}

7.59 The trial evidence supports the ability of MAO-B inhibitors in PD to improve motor symptoms, improve activities of daily living, delay the need for levodopa and delay the onset of motor fluctuations but not dyskinesia. This is at the expense of more dopaminergic adverse events and, as a result, more withdrawals from treatment.

7.60 \textbf{R24 Monoamine oxidase B inhibitors can be used as a symptomatic treatment in early PD. Grade A}

\textbf{Beta-adrenergic antagonists (beta-blockers)}

7.61 Beta-adrenergic antagonists (e.g. propanolol and oxprenolol) are well established in the treatment of the tremor seen in essential tremor and thyrotoxicosis.

7.62 Are beta-adrenergic antagonists effective in reducing the symptoms of PD?

\textit{Methodology}
7.63 A Cochrane systematic review\textsuperscript{130} included four randomised controlled trials. Only 72 people with PD were included in these studies. All trials were randomised double blind crossover studies.

7.64 Three of the cross-over trials\textsuperscript{131, 132, 133} in the systematic review did not present data from the end of the first arms. Since there is a carry-over risk, the systematic review did not analyse the data from these trials. One trial that did report data from the first arm\textsuperscript{134}, however the trial did not state baseline scores, numbers of patients in each group, or standard deviations.

\textit{Evidence statements}

7.65 The systematic review was methodologically sound and hence it could technically be given a grading of 1++ / 1+. However the methodological limitations of individual studies contained within the review meant that there was insufficient robust data from which to derive evidence statements.

7.66 The only evidence reported by the review was from a single trial\textsuperscript{134} which found no significant difference between oxprenolol and placebo in mean total score for tremor.

7.67 Details of the data analysis were not given so it was not possible for the systematic review to determine whether the non-significance was based on comparison between the first and second arms (which could have been affected by a possible cross-over effect) or between the therapy and placebo groups at the end of each arm.

\textit{Recommendation}

7.68 There is insufficient trial evidence for the efficacy or safety of beta-adrenergic antagonists in PD. However, the GDG felt that for selected people with PD with postural tremor they could be useful and safe.

\textit{Recommendation}

7.69 \textbf{R25} Beta-adrenergic antagonists can be used in the symptomatic treatment of selected people with postural tremor in PD, but they should not be the drugs of first choice. \textbf{Grade D (GPP)}

\textbf{Amantadine}

7.70 Amantadine was initially investigated as an anti-viral agent but found to be effective in PD by chance. The mechanism(s) of action of amantadine in PD are unclear.

7.71 What evidence is there to support the use of amantadine in early PD?

\textit{Methodology}
7.72 A Cochrane systematic review\textsuperscript{135} was found which compared the effectiveness of amantadine versus placebo or levodopa in the treatment of people with early PD who are functionally disabled. The review included six studies, with a total sample size of 215 people with PD.

7.73 An additional randomised cross-over trial\textsuperscript{136} was found but excluded due to the following methodological limitations: methods of randomisation and allocation concealment not stated, limited patient characteristics given, not intention-to-treat analysis and no power calculations provided for the small sample size (n=29).

7.74 Due to inadequate reporting of trial data, only two of the six trials within the systematic review had results that could be examined. However, in these two trials\textsuperscript{137,138} only data for the trials ‘means’ were given and thus no statistical analysis of the significance of the changes due to amantadine could be undertaken.

Evidence statements

7.75 The systematic review was methodologically sound and hence it could technically be given a grading of 1++ / 1+. However the methodological limitations of individual studies contained within the review meant that there was insufficient robust data from which to derive evidence statements”.

Evidence to recommendation

7.76 There is limited trial data to document the efficacy and safety of amantadine in early PD. This can be explained by its development in the 1970s when trial design was in its infancy. The GDG concluded that, whilst amantadine should be available for the treatment of mild PD symptoms, other drug classes (i.e. levodopa, dopamine agonists) are more appropriate treatments for the early stages of the disease.

Recommendation

7.77 \textbf{R26} Amantadine can be used as a treatment for early PD but is not a drug of first choice. \textbf{Grade D (GPP)}
Anticholinergics

7.78 Anticholinergics have been used to treat PD for over 100 years. They were introduced in the late 19th century after Charcot’s work with hyoscine (scopolamine). In the mid-20th century, the selective centrally active muscarinic receptor antagonists were developed which had fewer peripheral side effects. These agents proliferated in the absence of more effective pharmacotherapy, but the most commonly used for PD are benzhexol and orphenadrine.

7.79 What is the evidence that selective muscarinic antagonists are effective and safe treatments for PD?

Methodology

7.80 A Cochrane review\textsuperscript{139} and an additional RCT\textsuperscript{140} were found which addressed the effectiveness of anticholinergics in early Parkinson’s disease.

7.81 One study\textsuperscript{141} was excluded on the basis that the methodology did not constitute a randomised design between anticholinergic and levodopa treatment groups.

7.82 The Cochrane review included nine double blind randomised crossover trials, with a total of 221 people. All of the trials compared the effectiveness of anticholinergics versus placebo or no treatment. The RCT\textsuperscript{140} was a single-blind study with a total of 82 people randomised to 3 groups: anticholinergics, levodopa, and bromocriptine.

7.83 The Cochrane review authors highlighted that the outcome measures varied widely amongst the trials and the scales used to measure effectiveness were either the author’s own or no longer in current clinical use. The numerous methodological issues associated with these trials included: rating scales not being defined in detail, incomplete reporting of methodology and results and heterogeneous study designs which precluded any analysis of the results.

Evidence statements

7.84 The RCT\textsuperscript{140} showed the three anti-parkinsonian medications (anticholinergics, bromocriptine or levodopa) did not have qualitatively different effects upon various parkinsonian symptoms. The authors suggested that this may have been due to low level of disease severity. Level 1+

7.85 The systematic review was methodologically sound and hence it could technically be given a grading of 1++ / 1+. However the methodological limitations of individual studies contained within the review meant that there was insufficient robust data from which to derive evidence statements.
7.86 The authors of the review conclude that as monotherapy or as an
drug of first choice due to limited efficacy and the propensity for
neuropsychiatric side effects. 

Evidence to recommendation:

7.87 There is insufficient data from randomised controlled trials on the
efficacy and safety of anticholinergics in PD. This is particularly true of
the claimed efficacy of this class in the treatment of tremor. However,
the GDG concluded that anticholinergics should be available for the
treatment of mild parkinsonian symptoms in people with no cognitive
dysfunction. Their use should be regularly reviewed but withdrawal
can be difficult due to the re-emergence of motor impairments.

Recommendation

7.88 R27 Anticholinergics can be used as a symptomatic treatment typically
in young people with early PD and severe tremor, but are not a drug of
first choice due to limited efficacy and the propensity for
neuropsychiatric side effects. 

Comparisons of drug classes

7.89 Whilst proving the efficacy and safety of a drug class in placebo-
controlled trials is important, particularly from the regulatory point of
view, clinicians are keen to know how each class compares with one
another so that evidenced-based treatment recommendations can be
made for individual people. Such active comparator trials are rare in
PD.

7.90 Recommendations will be presented at the end of this section for all
drug comparisons.

Dopamine agonists versus levodopa

7.91 How effective and safe are dopamine agonists compared with levodopa
in the treatment of functionally disabled early Parkinson’s disease?

Methodology

7.92 Twelve randomised controlled trials were found which
addressed whether dopamine agonists were more effective than
levodopa in treating people with early PD who are functionally
disabled.

7.93 Eight of these papers were randomised double blind studies. One of these studies was single-blind and three were
open trial designs. Two of the papers included were by
the same group of investigators, the more recent publication reported 10-year follow-up outcomes for the same cohort of people.
7.94 The sample sizes ranged from 18 to 782 (median 82) and the trial durations ranged from 5.8 months to 120 months (median 44.4 months or 3.7 years).

Evidence statements

7.95 The results from the eight trials are summarised in Exhibit 7A.

Exhibit 7A: Dopamine versus levodopa (Level 1+)

<table>
<thead>
<tr>
<th>Outcome</th>
<th>DA v LD</th>
</tr>
</thead>
<tbody>
<tr>
<td>Quality of Life (PDQUALIF and EuroQol scores)</td>
<td>NS 150</td>
</tr>
<tr>
<td>UPDRS total</td>
<td>NS 142, PPX 150</td>
</tr>
<tr>
<td>UPDRS motor (III)</td>
<td>NS 143, PPX 150, RP 144</td>
</tr>
<tr>
<td>UPDRS ADL (II)</td>
<td>NS 144, 111, PPX 150</td>
</tr>
<tr>
<td>Hoehn and Yahr</td>
<td>NS 145, 146</td>
</tr>
<tr>
<td>Columbia Score</td>
<td>NS 143, 147, BR 145</td>
</tr>
<tr>
<td>NUDS</td>
<td>NS 147, BR 145</td>
</tr>
<tr>
<td>Webster Scale</td>
<td>NS 146, BR 35</td>
</tr>
<tr>
<td>Risk of developing motor complications</td>
<td>CB 111, BR 148, 150, PPX 150</td>
</tr>
<tr>
<td>Risk of dyskinesias</td>
<td>NS 144, 145, 148, 150, PPX 150</td>
</tr>
<tr>
<td>Risk of wearing-off</td>
<td>NS 143, 147, PPX 150</td>
</tr>
<tr>
<td>Risk of dystonia</td>
<td>NS 143, 150, BR 145</td>
</tr>
<tr>
<td>Need for supplemental LD</td>
<td>PPX 150</td>
</tr>
<tr>
<td>Adverse events (all)</td>
<td>NS 111, 142-144, 148-148</td>
</tr>
<tr>
<td>Somnolence, oedema, hallucinations</td>
<td>PPX 150</td>
</tr>
<tr>
<td>Mortality</td>
<td>NS 148, BR 35</td>
</tr>
<tr>
<td>Withdrawals</td>
<td>NS 111, 142-144, 148, 149</td>
</tr>
</tbody>
</table>

PPX/RP/BR/CB in favour (p<0.05) of dopamine treatment
LD in favour (p<0.05) of levodopa treatment
NS non-significant difference between treatment groups
7.96 What is the effectiveness of dopamine-agonists plus levodopa versus levodopa monotherapy in the treatment of functionally disabled early Parkinson’s disease?

Methodology

7.97 Eight papers\(^{108,143,146,149,151-154}\) were found which compared the effectiveness of dopamine agonists combined with levodopa versus levodopa monotherapy. Five of these studies\(^{108,143,146,152,153}\) were included in a Cochrane review\(^{155}\), but these papers were reviewed independently for additional outcomes and follow-up studies.

7.98 Five of the trials\(^{108,149,151,152,154}\) were open-label for the majority of the follow-up, one trial\(^{146}\) was single blind and one trial\(^{143}\) was double blind.

7.99 The sample size ranged from 20 to 587 people (median 78) and the trial duration ranged from 12 months to 5 years.

7.100 Five articles were appraised (see Exhibit7B) and met quality criteria\(^ {156-160}\). No UK studies were identified.

Health economic methodology

7.101 An American study assessed the cost-effectiveness of pramipexole versus no pramipexole in early PD by estimating the cost per QALY during a life-time horizon\(^ {156}\).

7.102 One study estimated the incremental cost per QALY of initial pramipexole treatment versus initial levodopa treatment in early PD based on a 2-year US and Canadian multicentre randomised controlled trial\(^ {157}\).

7.103 A Canadian study derived the costs per day per patient to substitute levodopa plus benserazide by ropinirole over a 5-year time horizon in a cost-minimisation analysis\(^ {158}\).

7.104 A German study evaluated cabergoline versus levodopa monotherapy by estimating the cost per decreased UPDRS score based on a Markov model with a 10-year time horizon and the incremental costs per additional motor complication-free patient\(^ {159}\).

7.105 A Swedish study evaluated the cost-effectiveness of early cabergoline treatment compared to levodopa in the early treatment of PD by estimating the cost per year of motor complications over 5 years\(^ {160}\).

7.106 A cost-minimisation analysis of dopamine agonist versus levodopa in initial PD therapy was estimated from the perspective of the NHS over a 1-year period [APPENDIX F].
**Evidence statements**

7.107 The results from the eight trials are summarised in Table 7B below:

**Exhibit 7B: Dopamine plus levodopa versus levodopa monotherapy (Level 1+)**

<table>
<thead>
<tr>
<th>Outcome variable</th>
<th>Significance</th>
</tr>
</thead>
<tbody>
<tr>
<td>Clinical rating scales</td>
<td></td>
</tr>
<tr>
<td>UPDRS total</td>
<td>NS&lt;sup&gt;149&lt;/sup&gt;</td>
</tr>
<tr>
<td>UPDRS II (activities of daily living)</td>
<td>NS&lt;sup&gt;143,152&lt;/sup&gt;, Li/LD&lt;sup&gt;151&lt;/sup&gt;</td>
</tr>
<tr>
<td>UPDRS III (motor)</td>
<td>Li/LD&lt;sup&gt;151,153&lt;/sup&gt;, BR/LD&lt;sup&gt;153&lt;/sup&gt;</td>
</tr>
<tr>
<td>UPDRS IV</td>
<td>NS&lt;sup&gt;151,153&lt;/sup&gt;</td>
</tr>
<tr>
<td>UPDRS addendum (motor complications) scores</td>
<td>Li/LD&lt;sup&gt;151&lt;/sup&gt;</td>
</tr>
<tr>
<td>‘On’ time during day</td>
<td>NS&lt;sup&gt;153&lt;/sup&gt;</td>
</tr>
<tr>
<td>Hoehn and Yahr</td>
<td>NS&lt;sup&gt;146,151,152,154&lt;/sup&gt;, LD&lt;sup&gt;153&lt;/sup&gt;</td>
</tr>
<tr>
<td>Webster score</td>
<td>NS&lt;sup&gt;146,153&lt;/sup&gt;</td>
</tr>
<tr>
<td>Columbia University Rating Scale (CURS)</td>
<td>BR/LD&lt;sup&gt;153&lt;/sup&gt;</td>
</tr>
<tr>
<td>Modified CURS</td>
<td>NS&lt;sup&gt;143&lt;/sup&gt;</td>
</tr>
<tr>
<td>Schwab and England Score</td>
<td>Li/LD&lt;sup&gt;151&lt;/sup&gt;</td>
</tr>
<tr>
<td>Northwestern University Disability Score (NUDS)</td>
<td>LD&lt;sup&gt;153&lt;/sup&gt;</td>
</tr>
<tr>
<td>Adverse events</td>
<td></td>
</tr>
<tr>
<td>All events</td>
<td>NS&lt;sup&gt;143,146&lt;/sup&gt;</td>
</tr>
<tr>
<td>Mortality</td>
<td>BR/LD&lt;sup&gt;108&lt;/sup&gt;</td>
</tr>
<tr>
<td>Nausea/vomiting</td>
<td>LD&lt;sup&gt;153&lt;/sup&gt;</td>
</tr>
<tr>
<td>Fatigue/weakness</td>
<td>LD&lt;sup&gt;153&lt;/sup&gt;</td>
</tr>
<tr>
<td>Hallucinations/confusion</td>
<td>LD&lt;sup&gt;153&lt;/sup&gt;</td>
</tr>
<tr>
<td>Withdrawal rates</td>
<td></td>
</tr>
<tr>
<td>Number of drop-outs</td>
<td>NS&lt;sup&gt;143,146,149&lt;/sup&gt;, Li/LD&lt;sup&gt;151&lt;/sup&gt;</td>
</tr>
</tbody>
</table>

LD Levodopa Li Lisuride BR Bromocriptine
LD in favour (p<0.05) of levodopa monotherapy
Li or BR/LD in favour (p<0.05) combination therapy
NS non-significant

**Health economic evidence statements**

7.108 Evidence in people with early PD, the incremental cost-effectiveness for pramipexole versus no pramipexole is $8,837 in US$ 1997 (approximately £5,514) per QALY from a societal perspective and $34,423 (approximately £21,477) per QALY without including productivity gains from pramipexole. However, cost-effectiveness results were sensitive to changes in the model’s parameters, resulting in cost per QALYs of $3,883 (approximately £2,423) when direct medical costs are 50% higher, $46,468 (approximately £28,993) when
the rate of change of UPDRS after levodopa is 0.5 (versus 1.375 base-line) and $908,308 (approximately £566,719) when no-pramipexole treatment includes pergolide as adjunct.

7.109 One study estimated the incremental cost-effectiveness of initial pramipexole treatment versus initial levodopa treatment in early PD over a two-year period costs $106,900 in US$ 2002 (approximately £65,219) per QALY derived by the EQ-5D 157. However, the pramipexole strategy is dominated by levodopa strategy when using the EQ-VAS to derive the health utilities 157.

7.110 Assuming equivalent clinical effectiveness, the cost of replacing levodopa plus benserazide with ropinirole in a Canadian setting gives a net incremental cost of $4.14 (£2.38) per patient day. From a societal perspective, productivity and caregiver utilisation savings offset the drug acquisition cost for ropinirole. Varying the key parameters: nursing home admission rates, cost of caregiver time and proportion of people with disabling dyskinesias who lost their jobs, by 15-20%, did not change the direction of the results158.

7.111 In people > 60 years of age, cabergoline monotherapy was estimated to cost approximately an additional €1,031 in Euro 2002 (approximately £718) per unit decrease in UPDRS score. This value was robust to changes in the discount rate, cost data and mortality assessed in the sensitivity analysis. Levodopa monotherapy dominated cabergoline monotherapy in people < 60 years of age. Incremental costs per additional motor complication-free patient were estimated at €104,400 (approximately £72,710) in people < 60 years of age and €57,900 (approximately £40,325) in people > 60 years of age based on sub-samples of the clinical trial used for data analysis159.

7.112 Study estimated an incremental cost-effectiveness of €13,863 (approximately £9,655) per year of motor complications avoided with cabergoline treatment 160.

7.113 The base-line estimates result in an incremental cost of £2,394 for pramipexole treatment over a one-year period. The unit cost of pramipexole had the most impact on the incremental costs and resulted in the widest range of all the incremental cost estimates (£1,883 to £2,644). On the basis of equivalent quality of life between the treatments, the levodopa strategy is the less costly option [APPENDIX F].

Evidence to recommendation

7.114 There is a wealth of evidence from dopamine agonist versus levodopa trials that agonists delay the onset of motor complications. However, there is some evidence that levodopa treats motor impairments and disability better. Agonists also lead to more adverse events such as
somnolence, oedema and hallucinations but this does not lead to an excess of withdrawals from the trials.

7.115 It is more difficult to interpret the generally older dopamine agonist combined with levodopa versus levodopa trials. There is some suggestion of combination therapy treating motor impairments and disability better than levodopa but at the expense of more adverse events such as nausea, vomiting, fatigue, hallucinations and confusion. There is little data on motor complications.

7.116 The implication is that to delay motor complications, dopamine agonists should be used initially without levodopa. However, patient’s motor function will not be treated as well and they may suffer more side effects. This issue requires further clarification in trials using patient-rated quality of life as the primary outcome measure. The GDG decided that on the basis of the benefits and drawbacks, the treatments are clinically equivalent. This assumption was used in the economic model which indicated the levodopa strategy is the less costly option.

**Monoamine oxidase type B inhibitors versus levodopa**

7.117 How effective are MAO-B inhibitors compared with levodopa in managing people with early PD?

**Methodology**

7.118 One meta-analysis\(^\text{113}\) and a randomised cross-over trial\(^\text{129}\) which addressed the effectiveness of MAO-B inhibitors in treating people with early Parkinson’s disease were included.

7.119 The meta-analysis\(^\text{113}\) compared MAO-B’s versus controls (and did not differentiate between levodopa and placebo controls). In many of the included trials, the MAO-B inhibitors were not given alone but were in combination with levodopa therapy. The RCT\(^\text{129}\) also compared people on levodopa plus selegiline versus levodopa plus placebo.

7.120 The meta-analysis\(^\text{113}\) included 3525 people with PD from 17 randomised trials. The randomised crossover trial consisted of 15 people with PD. The small sample size may have underpowered the study and could be reflective of the non-significant results, when compared to the large meta-analysis.

**Evidence statements**

7.121 With respect to clinical rating scales:

- Only one study\(^\text{35}\) in the meta-analysis\(^\text{113}\) reported mean Webster disability scores. The trial reported that the difference was non-significant between groups on levodopa plus selegiline versus levodopa alone (no p values given). **Level 1+**
• The randomised cross-over trial\textsuperscript{129} reported no significant differences between scores for the Webster rating scale (total scores) between people with PD on levodopa plus selegiline versus levodopa alone. \textbf{Level 1++}

7.122 With respect to motor complications only one study\textsuperscript{148} in the meta-analysis\textsuperscript{113} reported the following:
• Motor fluctuations were more frequent among levodopa-treated people (29.7\%) than selegiline-treated people (18.7\%)
• People assigned to selegiline were significantly less likely to experience motor fluctuations (non-significant, no p value stated)
• Dyskinesias occurred less frequently in the selegiline group (20.7\%) than the levodopa group (27.1\%) \textbf{Level 1+}

7.123 With respect to need for levodopa therapy the combined trials in the meta-analysis\textsuperscript{113} found:
• The dose of levodopa required for adequate symptom control was 67mg lower in the selegiline arm (95\% CI 14 to 119; p=0.01). \textbf{Level 1+}

7.124 With respect to withdrawal rates:
• Only one study\textsuperscript{148} in the meta-analysis\textsuperscript{113} reported data on withdrawal rates. The trial found the probability of people ceasing treatment in the selegiline group was about three-fold higher than in those assigned to levodopa.
• Most of these withdrawals occurred after the first 6 months and were due to people' or physicians determination of inefficacy (two people stopped because of sleep disturbance side effects). \textbf{Level 1+}

7.125 With respect to mortality:
• One study\textsuperscript{35} in the meta-analysis\textsuperscript{113} reported the following between levodopa monotherapy and levodopa plus selegiline therapy:
  o For all deaths unadjusted hazard ratio of 1.22 (95\%CI 0.95 to 1.55, no p value stated)
  o First 5 years of study unadjusted hazard ratio of 1.41 (95\%CI 0.92 to 2.17, p=0.27)
• Another study\textsuperscript{148} in the meta-analysis found no difference between rates of mortality. \textbf{Level 1+}

\textit{Evidence to recommendation}

7.126 Selegiline delays the onset of motor complications and the need for levodopa but at the expense of more withdrawals due to lack of efficacy. There is little trial data on selegiline’s effect on motor impairments and none on quality of life. The clinical experience of the GDG suggests that selegiline is less effective than levodopa in the treatment of functional impairments and disability in PD. There is no
trial data or clinical experience on the comparative efficacy and safety of rasagiline. Further trials to compare MAO-B therapy with levodopa are required.

Monoamine oxidase type B inhibitors versus dopamine agonists

7.127 How effective are MAO-B inhibitors compared with dopamine agonists in the treatment of early PD?

Methodology

7.128 Only two randomised controlled trials\textsuperscript{148,35} were found which compared the effectiveness of MAO-B inhibitors and dopamine agonists in the treatment of early PD.

7.129 Both studies included a third levodopa therapy arm. Most of the disability and motor function analysis in the UK-PDRG study\textsuperscript{35} involved the comparison of bromocriptine versus levodopa. Similarly, the other trial\textsuperscript{148} used the levodopa group as the reference group and did not provide statistical analysis of the results for the comparison of selegiline and dopamine agonists.

7.130 The UK-PDRG study\textsuperscript{35} consisted of 782 people with PD, and compared the effectiveness of levodopa, levodopa and selegiline and bromocriptine. The other study\textsuperscript{148} consisted of 473 people with PD, and compared the effectiveness of selegiline, levodopa and dopamine agonists (bromocriptine and lisuride). It is important to note selegiline in the UK-PDRG trial\textsuperscript{35} was combined with levodopa therapy, whereas the other study\textsuperscript{148} used selegiline as a monotherapy (levodopa could be added if physician deemed selegiline alone to be ineffective).

Evidence statements

7.131 In the UK-PDRG study\textsuperscript{35}, after nine years of follow-up, the there was a non-significant difference in Webster scores (adjusted for baseline score) between the bromocriptine group and the levodopa plus selegiline group. \textbf{Level 1+}

7.132 With respect to motor complications, one study\textsuperscript{148} found no significant differences in:

- Motor fluctuations
- Mean time to motor fluctuation
- Frequency of dyskinesias
- Difference in time to dyskinesia between dopamine agonist and MAO-B inhibitor groups. \textbf{Level 1+}
7.133 With respect to mortality the UK-PDRG study\textsuperscript{35} found non-significant
differences in mortality between levodopa plus selegiline and
bromocriptine groups:
- Unadjusted hazard ratio for overall deaths (non-significant)
- Unadjusted hazard ratio in first five years was \( p=0.27 \). \textbf{Level 1+}

7.134 The other study\textsuperscript{148} found no significant difference in mortality between
the dopamine agonist groups and the selegiline group. \textbf{Level 1+}

7.135 With respect to withdrawal rates one study\textsuperscript{148} reported the following:
- Most people with PD withdrew from dopamine agonists because of:
  - nausea/vomiting or postural hypotension or both (43/53 people)
- Most of the withdrawals in the selegiline group occurred in the first
  six months of treatment and were due to lack of efficacy
- Combination therapy was started in 40.7\% of people on dopamine
  agonists and 63.9\% of people on selegiline
- The initiation of levodopa therapy was delayed for a median of 30
  months in dopamine agonist group and 15 months in selegiline
  group. \textbf{Level 1+}

\textit{Evidence to recommendation}

7.136 Whilst there was no difference in the delaying of motor complications
between MAO-B inhibitors and dopamine agonists, there is a
suggestion that agonists are more effective than MAO-B inhibitors in
delaying the need for levodopa. More people with PD withdraw from
MAO-B inhibitors because of lack of efficacy, however, this evidence is
based on just two studies and all of the data relates to selegiline.

\textbf{Choice of initial pharmacological therapy in early PD}

7.137 \textbf{R28} It is not possible to identify a universal first choice drug therapy for
people with early PD. The choice of drug first prescribed should take
into account:
- Clinical and lifestyle characteristics
- Patient preference, after being informed of the short and long term
  benefits and drawbacks of the drug classes. \textbf{Grade D (GPP)}
Later Disease

7.138 Since most people with PD will eventually need levodopa, they will all with time develop motor complications. Whilst the latter can be mild and not interfere with a person’s quality of life, for some they can be severely incapacitating. Adjuvant drugs to take with levodopa have been developed with the aim of reducing these complications and improving quality of life.

7.139 The previous section (see 7.3 to 7.6) contains a statement about the methodological limitations of symptomatic therapy studies and recommendations about symptomatic pharmacological therapies for both early and later disease.

7.140 The GDG was concerned that the old practice of withdrawing PD patients from medication in the hope of improving motor complications is dangerous. Such ‘drug holidays’ can lead to severe immobility with secondary chest infection, neuroleptic malignant syndrome and death. This practice is rarely performed now and, because of the dangers, it should be abandoned.

7.141 In this section consideration is given to:

- Symptomatic adjuvant therapies for later PD, namely:
  - Modified-release levodopa
  - Dopamine agonists
  - Monoamine oxidase B (MAO-B) inhibitors
  - Catechol-O-methyl transferase (COMT) inhibitors
  - Amantadine
  - Apomorphine.
  - Comparisons between drug classes, namely:
  - Dopamine agonists versus MAO-B inhibitors
  - Dopamine agonists versus COMT inhibitors
  - Dopamine agonists versus amantadine
  - Choice of adjuvant therapy in later PD.

Modified-Release Levodopa

7.142 Wearing off of the effects of levodopa and peak dose dyskinesia are largely caused by pulsatile stimulation of dopamine receptors, which is related to the intermittent administration of exogenous immediate-release levodopa. One potential way to overcome this is to prolong the effect of each dose of levodopa by administering controlled or...
modified-release levodopa preparations. Such preparations of co-careldopa (Sinemet CR®) and co-beneldopa (Madopar HBS/CR®) have been developed.

7.143 Can modified-release preparations of levodopa reduce motor complications compared with immediate-release preparations?

**Methodology**

7.144 Eleven randomised controlled trials\(^{161-171}\) comparing the effect of controlled-release (CR) 50/500mg levodopa (LD) versus immediate-release (IR) 25/100 LD in later PD were found. The sample size (range 19- 202, mean 57) and mean age of people (range 58 to 67 years, mean 62.8) varied between trials.

7.145 Most of the included studies\(^{161-169,171}\) used the co-careldopa formulation of either 25/100 or 50/200 for the immediate-release and controlled-release tablets, respectively. Only one trial\(^{170}\) used 25/200 for the immediate-release dosage, but administered 50/200 for controlled-release. None of the included trials used the co-beneldopa formulation.

7.146 Only one trial reported a washout period between trials\(^{170}\), all other trials analysed data either from the end of the trial arms or at week 2 or later in each arm.

7.147 All of the included trials started with an open label titration phase in which the optimal antiparkinsonian dose and inter-dose interval for each treatment was determined. In many of the trials a large percentage of people withdrew (35%\(^{170}\), 31%\(^{166}\), 26%\(^{161}\), 24%\(^{164}\), 18%\(^{171}\), 17%\(^{162}\)) during the open phase because of inconsistencies with response, delayed onset of drug action or because of adverse events. Due to the already small sample size (average 60), lack of power calculations and intention-to-treat analysis, these studies were highly biased towards a pre-selected patient population. The trial duration was also very short with a range of 8 to 24 weeks.
### Evidence Statements

#### Exhibit 7C: Controlled versus immediate-release levodopa

<table>
<thead>
<tr>
<th>Outcome measures</th>
<th>Results</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total number of trials</td>
<td>11</td>
</tr>
<tr>
<td>Total sample size (n=)</td>
<td>646</td>
</tr>
<tr>
<td>Clinical rating scales</td>
<td></td>
</tr>
<tr>
<td>UPDRS motor Score</td>
<td>CR 164</td>
</tr>
<tr>
<td>Hoehn and Yahr Score</td>
<td>CR 168</td>
</tr>
<tr>
<td>NYUPDS Score (after 6 months treatment)</td>
<td>CR 168</td>
</tr>
<tr>
<td>SEALD Score</td>
<td>CR 162</td>
</tr>
<tr>
<td>Patient-rated global improvement</td>
<td>CR 160</td>
</tr>
<tr>
<td>Physician-rated global improvement</td>
<td>CR 168</td>
</tr>
<tr>
<td>Patient-reported helpfulness of medication and improvement in clinical fluctuations</td>
<td>CR 162</td>
</tr>
<tr>
<td>Motor complications</td>
<td></td>
</tr>
<tr>
<td>‘On’ time</td>
<td>CR 164, 166, 169, 170 IR 164</td>
</tr>
<tr>
<td>‘Off’ time</td>
<td>CR 164, 168, 170</td>
</tr>
<tr>
<td>Dyskinesia duration</td>
<td>IR 169</td>
</tr>
<tr>
<td>Levodopa dose</td>
<td></td>
</tr>
<tr>
<td>Mean doses per day</td>
<td>CR 161, 163, 164, 166, 171</td>
</tr>
<tr>
<td>Mean interdose interval</td>
<td>NS 168</td>
</tr>
<tr>
<td>Mean daily LD dose (mg/d)</td>
<td>CR 161, 164, 171</td>
</tr>
<tr>
<td>NS 168</td>
<td></td>
</tr>
<tr>
<td>IR 162-165, 167, 169-172</td>
<td></td>
</tr>
</tbody>
</table>

CR Favouring (p<0.05) CR - Not reported                                          |
IR Favouring (p<0.05) IR - Non-significant (p>0.05) IR - Non-significant (p>0.05) NS

### 7.148 With respect to adverse events:

- Most common adverse events for both treatments included: dizziness, dyskinesia, dystonia, headache, hallucinations, nausea, vomiting, hypotension and confusion 162,167,168
- There was no significant difference in the reported incidence of adverse events between the two treatment groups162,165,171
- One study168 reported people treated with CR had a higher incidence of self-reported adverse events (p<0.05) but not a higher frequency **Level 1**

### 7.149 With respect to withdrawal rates:

- Two studies162,163 found 52-54% of people preferred CR over 27-33% of people who preferred IR
- Two studies found high numbers of people continuing CR therapy after the completion of their trials (100%170 and 87%171)
Common reasons for withdrawal include: adverse events, insufficient therapeutic response, lack of compliance, or missing follow-up appointments. \textsuperscript{167,168} **Level 1**

**Evidence to recommendation**

7.150 The trial evidence suggests that modified-release levodopa preparations can satisfactorily reduce motor complications. However, the GDG had considerable reservations about the design of many of the trials. Subsequent clinical practice has found that switching directly from immediate- to modified-release levodopa leads to an increase in off time. This is probably due to poorer absorption of modified-release preparations from the gut. As a result, modified-release levodopa is rarely used to manage motor complications. Modified-release preparations are also more expensive than immediate-release formulations. The GDG concluded that combinations of modified- and immediate-release levodopa could be useful in a small number of people with motor complications.

7.151 **R29** Modified-release levodopa preparations can be used to reduce motor complications in later PD but are not drugs of first choice. **Grade B**

**Dopamine agonists**

7.152 Whilst recent trial work has concentrated on the use of dopamine agonists as initial therapy in PD, these agents were originally introduced as adjuvant therapy to reduce motor complications in later disease.

7.153 How effective and safe are dopamine agonists as adjuvant therapy in later PD?

**Methodology**

7.154 Nine papers which included six Cochrane reviews\textsuperscript{173-178} and three additional RCTs\textsuperscript{179-181}, were found that addressed the effectiveness of adding dopamine-agonists compared with placebo in the treatment of motor complications in people with later Parkinson’s disease. Sample sizes of these trials are listed in Exhibit 7D. No RCTs were found on lisuride effectiveness.

7.155 There were several issues for consideration with the trials included in the Cochrane reviews\textsuperscript{173-178}, such as:

- Inclusion of phase II and III studies and unpublished papers
- Additional unpublished data obtained from investigators or manufacturers sought by the Cochrane authors
7.156 The three RCTs\textsuperscript{179-181} that were published since the Cochrane reviews were well designed and had sound methodologies.

Evidence Statements

7.157 With respect to quality of life:

- Two trials, one\textsuperscript{182} included in the Cochrane review\textsuperscript{177} and another published after the review\textsuperscript{179} reported the following outcomes in favour of pramipexole:
  - Functional Status Questionnaire (FSQ) Basic ADL
  - Mental Health Scales
  - European Quality of Life (EuroQol) scale
  - Patient diaries (impairment of daily living and severity of tremor ($p<0.0001$)).

7.158 With respect to clinical rating scales, motor complications and levodopa dose reduction improvement was found to be in favour of the dopamine agonists (bromocriptine, cabergoline, pergolide, pramipexole and ropinirole) in most of the included trials (Exhibit 7D).
### Exhibit 7D: DA versus Placebo in Late PD

<table>
<thead>
<tr>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>No. of Trials</strong></td>
<td>7</td>
<td>3</td>
<td>1</td>
<td>7</td>
<td>3</td>
</tr>
<tr>
<td><strong>Sample size</strong></td>
<td>400</td>
<td>268</td>
<td>376</td>
<td>1228</td>
<td>263</td>
</tr>
<tr>
<td><strong>Clinical rating scales</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>UPDRS II</td>
<td></td>
<td>DA 192</td>
<td>NS 190</td>
<td>DA 182,194-196</td>
<td>180,181</td>
</tr>
<tr>
<td>UPDRS III</td>
<td></td>
<td>DA 192</td>
<td>NS 190</td>
<td>DA 182,194-196</td>
<td>180,181</td>
</tr>
<tr>
<td>UPDRS IV</td>
<td></td>
<td></td>
<td></td>
<td>DA 194,195</td>
<td>182,196</td>
</tr>
<tr>
<td>Hoehn and Yahr</td>
<td></td>
<td>NS 191,192</td>
<td>DA 193</td>
<td>DA 194</td>
<td>NS 182</td>
</tr>
<tr>
<td>S &amp; E</td>
<td></td>
<td>NS 190,191</td>
<td></td>
<td>A 194</td>
<td>NS 182</td>
</tr>
<tr>
<td>MCR *</td>
<td></td>
<td></td>
<td>DA 193</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td><strong>Global rating</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Clinician</td>
<td></td>
<td>DA 191</td>
<td>-</td>
<td>DA 195, 179,181</td>
<td>DA 198</td>
</tr>
<tr>
<td>Motor complication</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Dyskinesia</td>
<td>LD 189</td>
<td>-</td>
<td>LD 193</td>
<td>-</td>
<td>LD 198</td>
</tr>
<tr>
<td>Off time</td>
<td>NS 186,188</td>
<td>NS 190,191</td>
<td>DA 193</td>
<td>DA 182,194-196</td>
<td>DA 198</td>
</tr>
<tr>
<td>Impairment</td>
<td>DA 186,187</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>DA 198</td>
</tr>
<tr>
<td>Wearing-off</td>
<td>DA 187</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Levodopa (LD)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>LD dose reduction</td>
<td>NS 187</td>
<td>DA 192</td>
<td>DA 193</td>
<td>DA 192,194,196</td>
<td>DA 198</td>
</tr>
<tr>
<td>Adverse events</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hallucination</td>
<td>-</td>
<td>NS 190-192</td>
<td>P 193</td>
<td>P 192,194,196</td>
<td>-</td>
</tr>
<tr>
<td>Dyskinesia</td>
<td>-</td>
<td>NS 190-192</td>
<td>P 193</td>
<td>DA 182,194,195</td>
<td>P 196</td>
</tr>
<tr>
<td>Hypotension</td>
<td>NS</td>
<td>DA 190-192</td>
<td>-</td>
<td>NS 182,194-196</td>
<td>-</td>
</tr>
<tr>
<td>Withdrawal rate</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>All cause</td>
<td>NS 190-192</td>
<td>NS 193</td>
<td>DA 182,194</td>
<td>NS 182</td>
<td></td>
</tr>
<tr>
<td>Adverse events</td>
<td>-</td>
<td>-</td>
<td>P 193</td>
<td>-</td>
<td>-</td>
</tr>
</tbody>
</table>

DA = Favouring dopamine agonist (p<0.05)  
P = Favouring (p<0.05) placebo  
- = Not reported  
NS = Non-significant (p>0.05)

(References for papers included in Cochrane reviews)
Evidence to recommendation

7.159 In people with PD and motor complications, adjuvant dopamine agonist therapy reduces off time, levodopa dose and improves motor impairments and activities of daily living. This is at the expense of increased dopaminergic adverse events including dyskinesia, hallucinations and postural hypotension. These conclusions are based on short-term trials and the long-term acceptability of adjuvant agonist therapy remains to be evaluated.

7.160 Concerns regarding serosal reactions with ergot-derived dopamine agonists have been considered earlier in this chapter. (see 7.41)

Recommendations

7.161 **R30** Dopamine agonists can be used to reduce motor complications in later PD. **Grade A**

Monoamine Oxidase B Inhibitors

7.162 The monoamine oxidase B inhibitor selegiline was first used as a symptomatic treatment for PD before it was evaluated as a possible neuroprotective therapy (Chapter 6). More recently, rasagiline has become available as another MAO-B inhibitor with symptomatic effects in PD.

7.163 How effective and safe are these MAO-B inhibitors in treating the motor complications of later PD?

Methodology

7.164 Ten randomised double-blind placebo-controlled trials\(^{200-209}\) were found which addressed the effectiveness of MAO-B inhibitors as an adjunct to levodopa treatment in people with late PD and motor complications. Of these nine trials six were parallel group studies and three were crossover trials.

7.165 All of the trials, apart from three\(^{200,208,209}\), investigated the effectiveness of conventional selegiline treatment. Two RCTs\(^{208,209}\) investigated the effectiveness of rasagiline, while the other\(^{200}\) assessed the effectiveness of Zelapar selegiline, a formulation that dissolves on contact with saliva and undergoes pregastric absorption.

7.166 A common methodological issue in all the conventional selegiline trials was the lack of sample size calculations. Most of these trials failed to demonstrate a significant difference in many of the outcomes measures investigated between active treatment and placebo. The small sample sizes (range 19 to 96, mean 54.6) and the short-term
duration (range 3 to 8 weeks, mean 6.7 weeks) need to be taken into consideration.

7.167 One large (n=460) and well designed RCT (LARGO)\textsuperscript{208} compared rasagiline with entacapone and placebo over 18 weeks. Another well designed RCT (PRESTO)\textsuperscript{209} with a large sample size (n=472) and duration of 26 weeks compared two different doses of rasagiline (0.5 or 1 mg) with placebo.

7.168 The Zelapar selegiline study\textsuperscript{200} was a large (n=140) study of 12 weeks duration. The only shortcoming of this trial was the lack of a conventional selegiline arm to directly compare the two formulations.

7.169 Most of the studies using conventional selegiline used a dose of 10 mg/day. One study\textsuperscript{205} used a dosing sequence of 0-5-10 mg/day in a random order, another study\textsuperscript{202} started with 5mg/day in the first 4 weeks and increased to 10 mg/day for the final 4 weeks, and only one study\textsuperscript{201} used 5mg/day for the entire trial duration of 8 weeks. The rasagiline study administered a dose of 1mg/d for 18 weeks. The study on Zelapar selegiline used a dose of 1.25-2.5 mg/day for 12 weeks.
### Evidence Statements

#### Exhibit 7E: MAO-B inhibitor versus placebo

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Conventional Selegiline</th>
<th>Rasagiline</th>
<th>Zelapar Selegiline</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number of trials</td>
<td>7</td>
<td>2</td>
<td>1</td>
</tr>
<tr>
<td>Sample size (n=)</td>
<td>169</td>
<td>932</td>
<td>140</td>
</tr>
<tr>
<td>Quality of Life</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>PDQUALIF scores</td>
<td></td>
<td>R(^{209})</td>
<td></td>
</tr>
<tr>
<td>Clinical Rating Scales</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>UPDRS Total</td>
<td></td>
<td>R(^{208})</td>
<td></td>
</tr>
<tr>
<td>UPDRS- motor (on)</td>
<td></td>
<td>R(^{208,209})</td>
<td></td>
</tr>
<tr>
<td>UPDRS- ADL (off)</td>
<td></td>
<td>R(^{208,209})</td>
<td></td>
</tr>
<tr>
<td>UPDRS subscores</td>
<td></td>
<td>R(^{208,209})</td>
<td></td>
</tr>
<tr>
<td>Schwab and England ADL</td>
<td></td>
<td>R(^{209})</td>
<td></td>
</tr>
<tr>
<td>Patient diaries: proportion of people</td>
<td>MAO-B 203,203,204</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>with improvement</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Clinician Global Impression Scale</td>
<td></td>
<td>R(^{208,209})</td>
<td>MAO-B 200</td>
</tr>
<tr>
<td>Patient Global Impression Scale</td>
<td></td>
<td>-</td>
<td>MAO-B 200</td>
</tr>
<tr>
<td>Motor complications</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>‘On-off’ episodes</td>
<td>MAO-B 201</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>‘On’ time</td>
<td>MAO-B 205</td>
<td>R(^{208,209})</td>
<td>MAO-B 200</td>
</tr>
<tr>
<td>‘Off’ time</td>
<td>MAO-B 205</td>
<td>R(^{208,209})</td>
<td>MAO-B 200</td>
</tr>
<tr>
<td>‘On’ time with dyskinesia (increased)</td>
<td>P(^{205}) NS R(^{209})</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Tremor</td>
<td>MAO-B 206</td>
<td>R(^{208})</td>
<td></td>
</tr>
<tr>
<td>Daily Levodopa dose</td>
<td>MAO-B 202,202,206,207</td>
<td>R(^{208})</td>
<td></td>
</tr>
<tr>
<td>Levodopa dose reduction</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Any adverse events</td>
<td>NS</td>
<td>NS(^{218})</td>
<td>NS(^{210})</td>
</tr>
<tr>
<td>All cause withdrawal rates</td>
<td>NS</td>
<td>NS(^{205,209})</td>
<td>NS(^{210})</td>
</tr>
</tbody>
</table>

MAO-B Favouring MAO-B inhibitor (p<0.05)   P Favouring (p<0.05) placebo
R Favouring Rasagiline (p<0.05)            - Not reported NS Non-significant (p>0.05)

7.170 Other outcomes of interest, which favoured (p<0.05) conventional selegiline were:
- Physician preference\(^{202}\)
- Webster Rating scale \(^{202}\)
- Modified Columbia Rating Sale: 5/22 items (dressing, dysarthria, hypomimia, sialorrhea, tremor)\(^{203}\)
- Disability Scale: 2/22 items (facial expression and resting tremor)\(^{204}\)
Investigator’s Global Subjective Opinion: more likely to have experienced improvement than worsened or no change\textsuperscript{204} Level 1+

7.171 With respect to patient observations of conventional selegiline:
- At the end of the 6-week treatment period 76% of people reported themselves to be improved in the selegiline group and only 26% in the placebo group\textsuperscript{203}
- People reported the following while in selegiline treatment: dose of levodopa lasted longer, transitions between on and off periods were less abrupt, on periods were better, off periods were less severe.\textsuperscript{207} Level 1+

7.172 With respect to long-term follow-up:
- One study\textsuperscript{206} performed a long-term blinded follow-up. People selected the treatment period they preferred during the randomised short-term trial and they were maintained on that preferred treatment for about 16 months on average. The follow-up study found:
  - Average levodopa dose was significantly lower (p<0.001) in selegiline treated people
  - The average dosing frequency was also lower in the selegiline group (p<0.01). Level 2+

7.173 One rasagiline RCT\textsuperscript{209} reported a significant (p<0.05) increase in adverse events in the treatment group:
- Dyskinesias were reported as an adverse event by 10% receiving placebo and by 18% receiving either dose of rasagiline
- Weight loss, vomiting and anorexia in 1.0 mg/d group
- Balance difficulty and depression in 0.5 mg/d Level 1++
Evidence to recommendation

7.174 The size and quality of the adjuvant selegiline trials was poor, so it is impossible to reach firm conclusions about its efficacy and safety in later PD. The more recent study with the buccal formulation of selegiline and two large oral rasagiline trials provide more convincing evidence for the efficacy and safety of MAO-B inhibitors in later PD. However, all studies were of short duration, so no comments on the long-term benefits and drawbacks of these agents can be made.

Recommendations

7.175 **R31** Monoamine oxidase B inhibitors can be used to reduce motor complications in later PD. **Grade A**

Catechol-O-Methyl Transferase Inhibitors

7.176 Levodopa is now always combined with carbidopa (co-careldopa) or benserazide (co-beneldopa) to block its metabolism by dopa decarboxylase. This increases levodopa bioavailability by two- to three-fold and reduces peripheral side effects. However, only 5-10% of each levodopa dose crosses the blood-brain barrier, the rest being metabolised to 3-O-methyldopa by catechol-O-methyl transferase (COMT). The aim of COMT inhibitors is to further reduce the metabolism of levodopa and thus increase the amount crossing into the brain.

7.177 Two COMT inhibitors are available: entacapone and tolcapone. These lead to a 30-50% increase in levodopa half-life (t½) and a 25-100% increase in the levodopa concentration versus time curve (area under the curve, AUC); they do not increase the maximum plasma concentration of levodopa (tmax). Most of this occurs because of peripheral inhibition but tolcapone also has a central effect in the brain.

7.178 Tolcapone was the first COMT inhibitor to enter clinical practice in England and Wales but its European product licence was withdrawn in November 1998 after three cases of fatal hepatic toxicity. However, after further clinical experience in other markets and a forced switch from entacapone to tolcapone study, it has recently been re-introduced in Europe. It is currently licensed for people who have failed on entacapone at a dose of 100 mg three times a day with mandatory liver function test monitoring at two week intervals for the first year of treatment.

7.179 Entacapone has been combined with the levodopa plus carbidopa combination (co-careldopa) as a triple combination called Stalevo®.

7.180 How effective are these COMT inhibitors in reducing the motor complications of later PD?
Methodology

7.181 A Cochrane review\textsuperscript{211} was found which addressed the effectiveness of COMT inhibitors tolcapone and entacapone versus placebo in people with Parkinson’s disease suffering from motor complications.

7.182 Two additional RCTs\textsuperscript{208,212} were found after the Cochrane search date. One RCT\textsuperscript{208} compared entacapone (200mg) with placebo (LARGO). The study\textsuperscript{208} had a large (n=456) sample size and a trial duration of 18 weeks. The other RCT\textsuperscript{212} compared entacapone (200 mg) plus levodopa to levodopa monotherapy. The study sample size was large (n=270) and the trial duration was 13 weeks. The methodological limitations of this study were lack of reported methods of randomisation and allocation concealment.

7.183 An additional RCT\textsuperscript{213} was also found but excluded on the basis of patient characteristics. The people included in this trial could not experience end-of-dose wearing off within 4 hours of levodopa use, and had on average disease duration of 4.5 years. The results of this trial were not included due to the absence of motor complications.

7.184 The Cochrane review consisted of 14 trials (13 phase III, 1 phase II) and 2566 patents with PD and motor fluctuations. Eight trials\textsuperscript{214-221} examined entacapone versus placebo (n=1560) and six trials\textsuperscript{222-227} examined tolcapone versus placebo (n=1006). Two of the included entacapone papers\textsuperscript{219,220} included were abstracts, however the results were consistent with the full publications.

7.185 Issues for consideration with the Cochrane entacapone studies included: lack of randomisation and allocation concealment methods, lack of methodological detail available from the abstracts, and two studies did not state the method of data analysis. In addition, one of the entacapone studies\textsuperscript{218} was a crossover design (n=26) without a washout period, and the results were presented as a combination of the two trial arms. The review did not use the results of this study in the meta-analysis. Finally, for both the Cochrane tolcapone and entacapone studies, the review authors needed to contact the manufacturers to obtain additional detail on results and analysis.
### Evidence statements

#### Exhibit 7F: Meta-analysis of COMT inhibitors versus placebo

<table>
<thead>
<tr>
<th></th>
<th>Entacapone</th>
<th>Tolcapone</th>
<th>Combined meta-analysis</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total number of trials</td>
<td>9</td>
<td>6</td>
<td>14</td>
</tr>
<tr>
<td>Sample size (n=)</td>
<td>2016</td>
<td>1006</td>
<td>2566</td>
</tr>
</tbody>
</table>

**Efficacy**

<table>
<thead>
<tr>
<th></th>
<th>Entacapone</th>
<th>Tolcapone</th>
<th>Combined meta-analysis</th>
</tr>
</thead>
<tbody>
<tr>
<td>Levodopa dose reduction</td>
<td>COMT 208,214-217,220</td>
<td>COMT * 222-227</td>
<td>COMT</td>
</tr>
<tr>
<td></td>
<td>COMT 208,214-217</td>
<td>COMT 222,223,225,226</td>
<td>COMT</td>
</tr>
<tr>
<td>Off’ time (hours)</td>
<td>COMT 208,214-217</td>
<td>COMT 222,223,225,226</td>
<td>COMT</td>
</tr>
<tr>
<td>On’ time (hours)</td>
<td>COMT 208,214-217</td>
<td>COMT 222,223,225,226</td>
<td>COMT</td>
</tr>
<tr>
<td>UPDRS ADL</td>
<td>COMT 208,215-217,221</td>
<td>COMT ** 224</td>
<td>-</td>
</tr>
<tr>
<td>UPDRS motor score</td>
<td>COMT 208,215-217,221</td>
<td>COMT ** 223</td>
<td>-</td>
</tr>
</tbody>
</table>

**Adverse events**

<table>
<thead>
<tr>
<th></th>
<th>Entacapone</th>
<th>Tolcapone</th>
<th>Combined meta-analysis</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dyskinesia</td>
<td>P 214-217,221, NS 208</td>
<td>P * 222-227</td>
<td>P</td>
</tr>
<tr>
<td>Nausea</td>
<td>P 214-217,221, NS 208</td>
<td>P * 222-227</td>
<td>P</td>
</tr>
<tr>
<td>Vomiting</td>
<td>P 215,215, NS 208</td>
<td>P * 222-227</td>
<td>P</td>
</tr>
<tr>
<td>Diarrhoea</td>
<td>P 214-217, NS 208</td>
<td>P ** 223-225,227</td>
<td>P</td>
</tr>
<tr>
<td>Constipation</td>
<td>P 214-216, NS 208</td>
<td>NS 224-227</td>
<td>P</td>
</tr>
<tr>
<td>Hallucinations</td>
<td>NS 208,214-217</td>
<td>P ** 222-227</td>
<td>P</td>
</tr>
</tbody>
</table>

**Withdrawal rates**

<table>
<thead>
<tr>
<th></th>
<th>Entacapone</th>
<th>Tolcapone</th>
<th>Combined meta-analysis</th>
</tr>
</thead>
<tbody>
<tr>
<td>Due to adverse events</td>
<td>P 214-217,221, NS 208</td>
<td>NS 222-227</td>
<td>P</td>
</tr>
<tr>
<td>Due to all causes</td>
<td>P 214-217,221, NS 208</td>
<td>NS 222-227</td>
<td>P</td>
</tr>
</tbody>
</table>

COMT Favouring COMT inhibitor (p<0.05) P Favouring (p<0.05) placebo NS Non-significant (p>0.05)

- Not reported
* Significant for 50, 100,200 and 400 mg tds doses
** Significant for 200 mg tds doses

Numbers within the table refer to the references of the original papers.

7.186 The additional RCT which compared entacapone plus LD with LD monotherapy reported the following significant (p<0.05) results in favour of combined therapy:

- Improvement in UPDRS II (ADL) score, treatment difference: −1.6 (95%CI -2.4 to −0.8, p=0.0001)
- UPDRS III (motor) scores decreased, treatment difference −1.9 (95%CI –3.7 to −0.2, p=0.03)
- Mean UPDRS total score decreased, treatment difference −3.6 (95%CI –6.0 to −1.2, p=0.004)
• Fluctuation sum score (UPDRS IVb) decreased, treatment difference: -0.3, (95%CI -0.5 to –0.1, p=0.02)
• Global Assessment scores by study investigator increased (p<0.001) and the proportion of participants who improved was greater.

7.187 The RCT\textsuperscript{212} also reported the following non-significant outcomes between treatment groups:
• PDQ-39 summary index scores and subscores
• SF-36 variables and EQ-5D self-rating questionnaire utility score
• Patient home diaries: mean 'off' time and mean 'on' time
• UPDRS I (mentation, behaviour and mood) scores
• Dyskinesia sum score (UPDRS IVA)
• Severity of PD (UPDRS part V; Hoehn and Yahr staging)
• UPDRS IV (Schwab and England)
• Mean daily dose of LD

7.188 The RCT\textsuperscript{212} reported the following in relation to adverse events:
• 113 (65%) entacapone plus LD and 47 (49%) of LD monotherapy people reported adverse events
• A total of 311 adverse events occurred in entacapone plus LD (2.8 events per participant) and 104 in LD monotherapy group (2.2 events per participant)
• The most frequently reported adverse events significantly (p<0.05) in favour of levodopa monotherapy were: nausea, diarrhoea, aggravated parkinsonism and constipation
• A frequently reported adverse event was also dyskinesia but there was no significant difference between treatment groups.

7.189 The RCT\textsuperscript{212} reported the following results in relation to withdrawal rates:
• 45 (17%) of participants discontinued prematurely (27/174 entacapone plus LD and 18/96 LD monotherapy)
• Reported reasons for discontinuation: adverse events for 26 (10%) of people, an unsatisfactory response to treatment for 14 (5%) of people, a wish to discontinue for three participants (1%) and other reasons for 2 participants (1%)

Evidence to recommendation

7.190 The placebo-controlled COMT inhibitor trials document the efficacy of these agents in reducing off time and levodopa dose, whilst improving on time, motor impairments and disability. This is at the expense of increased dopaminergic adverse events such as nausea, vomiting and dyskinesia.
7.191 Tolcapone has caused rare cases of fatal hepatic toxicity and neuroleptic malignant syndrome. As a result, it can only be used in England and Wales after a patient has failed on entacapone and its use requires intensive monitoring of hepatic function (see Summary of Product Characteristics).

**Recommendation**

7.192 **R32** Catechol-O-methyl transferase inhibitors can be used to reduce off time in later PD.\(^6\) **Grade A**

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\(^6\) Tolcapone is only licensed for use in patients for whom entacapone has failed and it requires intensive monitoring of liver function
Amantadine

7.193 When originally introduced, amantadine was used as an early therapy for PD. It fell into disuse as more effective agents such as levodopa and dopamine agonists became available. In the last few years, amantadine has had a revival after several small trials suggested it may have an anti-dyskinetic effect in people with late PD and motor complications.

7.194 How effective and safe is amantadine in managing the motor complications of later PD?

Methodology

7.195 A Cochrane review\(^{228}\) and an RCT\(^{229}\) (published after the review) were found which compared the effectiveness of adding amantadine versus placebo in the treatment of people with late PD and motor complications.

7.196 The Cochrane review\(^{228}\) included three studies with a total of 53 people. Whilst the RCT\(^{229}\) included a total of 40 people.

7.197 Issues for consideration included a lack of reporting: allocation concealment, washout periods in cross-over design trials, clinical criteria for PD diagnosis, and intention-to-treat analysis. The trials were generally of small sample size (range 11-40) and short trial duration (range 4 weeks up to 6 weeks). A dose of 100-400 mg/d of Amantadine was used.

7.198 The three trials\(^{230-232}\) included in the review\(^{228}\) were all crossover designs, in which none had reported the results of the first treatment arms. Two of the trials\(^{231,232}\) did not incorporate a washout period, thus data from these trials was not reported.

Evidence Statements

7.199 The RCT\(^{229}\) found the results of key outcome measures changed over time (see Exhibit 7G below). **Level 1+**

**Exhibit 7G: Amantadine versus placebo at different time points**\(^{229}\)

<table>
<thead>
<tr>
<th></th>
<th>After 15 and 30 days treatment</th>
<th>After 8 months treatment</th>
<th>After one month withdrawal</th>
</tr>
</thead>
<tbody>
<tr>
<td>Clinical rating scale</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>UPDRS items 32-34 (self-assessment)</td>
<td>A</td>
<td>NS-B</td>
<td>NS</td>
</tr>
<tr>
<td>Motor complications</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>IGA scores of dyskinesia</td>
<td>NS-A</td>
<td>NS-B</td>
<td>NS</td>
</tr>
<tr>
<td>DRS total scores</td>
<td>NS-A</td>
<td>NS-B</td>
<td>NS</td>
</tr>
</tbody>
</table>

A favours (p<0.05) amantadine  
NS no differences between groups  
Non-significant improvement in amantadine  
Non-significant worsening in amantadine
7.200 With respect to motor complications:
- Only one trial from the systematic review \(^{230}\) reported the outcome of dyskinesia severity following levodopa challenge. This trial reported that dyskinesia was reduced after oral amantadine treatment by 6.4 points (41\%) when compared to placebo arm (after 2 weeks of amantadine treatment).

7.201 With respect to adverse events:
- Only one trial \(^{230}\) from the systematic review \(^{228}\) reported adverse events for patients while on amantadine medication, these included: confusion, worsening of hallucinations, reappearance of palpitations, nausea, reversible oedema, dry mouth and constipation.
- Only one trial \(^{229}\) from the review reported adverse events following amantadine withdrawal, these included: an abrupt increase of dyskinesia to 100\% of daily time, hypothermia, and severe confusion (amantadine was re-introduced). Level 1+

7.202 With respect to withdrawal rates
- Reasons for withdrawal from amantadine treatment included: mild and transient adverse events \(^{232}\), tachycardia (n=1) \(^{229}\), psychosis and livedo reticularis (n=2) \(^{229}\).
- Reasons for withdrawal from placebo group included: dizziness \(^{229}\), somnolence \(^{229}\), poor compliance \(^{231}\).

Evidence to recommendation

7.203 Whilst there is some encouraging trial evidence that amantadine can be used as an anti-dyskinesia agent, data on its long-term effects are lacking. The evidence from one small trial suggests that amantadine’s anti-dyskinetic effect is substantially reduced after 8 months of therapy. Further work is required in this area.

Recommendation

7.204 R33 Amantadine can be used for the reduction of disabling dyskinesia in later PD. Grade C

Apomorphine

7.205 Apomorphine is a dopamine agonist which is not effective orally due to extensive first pass metabolism in the liver. Early studies in PD lead to severe emesis and pre-renal failure. Its further development was facilitated by the availability of the antiemetic domperidone which in
doses of 10-30 mg tds can prevent most of the gastrointestinal side effects of apomorphine.

7.206 There are currently two distinct methods of administering apomorphine: subcutaneous bolus doses or continuous infusion. People with a maximum of five or six off periods per day are suitable for intermittent bolus injections. Initially, the threshold dose of apomorphine (usual range 2 to 4 mg) is established as an inpatient using clinical examination and motor rating scales. The patient is then trained to use a pre-filled apomorphine injection system in which the agreed threshold dose can be dialled up more easily by the patient when in the off state.

7.207 Subcutaneous infusions of apomorphine are appropriate for PD people with so many off periods that repeated bolus injections are inappropriate. Apomorphine is administered by a portable syringe driver connected via a butterfly cannula sited in the abdominal wall or subcutaneous tissue of the thighs. The programmable pump delivers 50-120 mg of apomorphine over the 16 hour waking day or the whole 24 hour period. Usually, oral medication can be reduced according to the patient’s response. Considerable adjustment of the infusion dose is required once the patient is in the home environment. This can be facilitated by a Parkinson's Disease Nurse Specialist.

7.208 What is the evidence that apomorphine injections and infusions are effective and safe treatments for motor complications in later PD?

Intermittent Subcutaneous Apomorphine Injections

Methodology

7.209 Two randomised controlled trials\textsuperscript{233,234} were found which addressed the effectiveness of subcutaneous injections of apomorphine versus placebo. The people included in these trials were all classified as late PD and had mean disease duration of 9-12 years.

7.210 Both of these studies\textsuperscript{233,234} were placebo-controlled, but one was an eight-day crossover design\textsuperscript{234} (4 days per arm), while the other was a four-week parallel design\textsuperscript{233}. The sample sizes of both trials were relatively small with n=29 in one trial\textsuperscript{233,234} and n=22 in the other\textsuperscript{233,234}.

7.211 No controlled trials were found which looked at apomorphine versus standard oral treatment, and no controlled trials were found of continuous subcutaneous apomorphine infusions.
Evidence statements

Exhibit 7H: Effectives of subcutaneous apomorphine injections

<table>
<thead>
<tr>
<th>Clinical rating scales</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>UPDRS (I, II, III, IV) scores</td>
<td>NS&lt;sup&gt;234&lt;/sup&gt;</td>
</tr>
<tr>
<td>UPDRS motor (III) score</td>
<td>APO&lt;sup&gt;233&lt;/sup&gt;</td>
</tr>
<tr>
<td>Patient diaries for hand-tapping test</td>
<td>APO&lt;sup&gt;233&lt;/sup&gt;</td>
</tr>
<tr>
<td>Patient diaries for Webster step-seconds scores</td>
<td>P&lt;sup&gt;233&lt;/sup&gt;</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Motor complications</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean daily duration of 'off' periods</td>
<td>Staff-rating</td>
</tr>
<tr>
<td>(min/day)</td>
<td>APO&lt;sup&gt;234&lt;/sup&gt;</td>
</tr>
<tr>
<td></td>
<td>Patient-rating</td>
</tr>
<tr>
<td></td>
<td>APO&lt;sup&gt;234&lt;/sup&gt;</td>
</tr>
<tr>
<td>Mean daily numbers of 'off' periods</td>
<td>Staff-rating</td>
</tr>
<tr>
<td></td>
<td>P&lt;sup&gt;234&lt;/sup&gt;</td>
</tr>
<tr>
<td></td>
<td>Patient-rating</td>
</tr>
<tr>
<td></td>
<td>NS&lt;sup&gt;234&lt;/sup&gt;</td>
</tr>
<tr>
<td>Distribution of severity of 'off'</td>
<td>APO&lt;sup&gt;234&lt;/sup&gt;</td>
</tr>
<tr>
<td>periods</td>
<td></td>
</tr>
<tr>
<td>Patient diaries (Out of 10 parameters):</td>
<td></td>
</tr>
<tr>
<td>‘Off’ state events aborted per patient</td>
<td>APO&lt;sup&gt;233&lt;/sup&gt;</td>
</tr>
<tr>
<td>Onset latency (min)</td>
<td>APO&lt;sup&gt;233&lt;/sup&gt;</td>
</tr>
<tr>
<td>Total time ‘off’ per day</td>
<td>APO&lt;sup&gt;233&lt;/sup&gt;</td>
</tr>
<tr>
<td>Incidence of dyskinesia</td>
<td>P&lt;sup&gt;233&lt;/sup&gt;</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Adverse events</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Yawning</td>
<td>P&lt;sup&gt;233&lt;/sup&gt;</td>
</tr>
<tr>
<td>Mean daily duration of involuntary movements</td>
<td>P&lt;sup&gt;233&lt;/sup&gt;</td>
</tr>
<tr>
<td>Mean daily numbers of involuntary movements</td>
<td>P&lt;sup&gt;233&lt;/sup&gt;</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>APO Favouring dopamine agonist (p&lt;0.05)</th>
<th>P Favouring (p&lt;0.05) placebo</th>
</tr>
</thead>
<tbody>
<tr>
<td>- Not reported</td>
<td>NS Non-significant (p&gt;0.05)</td>
</tr>
</tbody>
</table>

7.212 With respect to a correlation analysis<sup>233</sup>:

- Levodopa dose (the single dose that produced the effect to which APO responses were matched) was not predictive of the required APO dose
- Total daily LD dose was also not predictive of APO dose (p=0.32)
- Inpatient response was correlated with and predictive of outpatient efficacy (p<0.001).

7.213 With respect to clinical global impressions<sup>234</sup>:

- 86% of people who completed the apomorphine eight-week follow-up (maintenance phase) reported ‘much’ or ‘very much’ improvement at the last visit
- No people reported to have worsened during the follow-up.
7.214 With respect to withdrawal rates\textsuperscript{233,234}:
- Reasons for withdrawal included: failure to demonstrate a significant response to the levodopa challenge, adverse events (nausea and vomiting, hypotension, exanthema), lack of motivation.

7.215 With respect to adverse events:
- Common events: Injection site complaints, drowsiness, yawning, dyskinesias, nausea or vomiting, chorea, sweating and warmth, dizziness, headache, rhinitis\textsuperscript{233,234}
- There were no significant changes in other safety measures (blood tests, ECG, physical exam)\textsuperscript{233}

\textit{Apomorphine Infusions}

\textit{Methodology}

7.216 There were no randomised or controlled trials, which assessed the effectiveness of chronic apomorphine infusion in people with late PD. Nine retrospective case series\textsuperscript{235-243} were found which investigated the benefit of chronic apomorphine treatment versus pre-treatment evaluations.

7.217 Most of the included studies used a hospital/clinic database to identify people who had received apomorphine for the treatment of severe motor fluctuations or dyskinesia, but who were refractory to optimum oral medication. From the included studies, the follow-up ranged from 3 months to 5 years, the sample size ranged from 7 to 64 people, and the average age ranged from 56 to 65 years.

7.218 The methodological limitations of these studies included were in accordance with a retrospective trial design, such as: lack of prospective protocols, non-randomisation of people, lack of control groups, small sample sizes, and lack of patient and/or investigator blinding.
**Evidence statements**

**Exhibit 7I: Effectiveness of continuous apomorphine infusions (Level 3)**

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Before versus after treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Clinical rating scales</td>
<td></td>
</tr>
<tr>
<td>UPDRS total and subscores</td>
<td>APO(^{236})</td>
</tr>
<tr>
<td>Hoehn and Yahr scores (off and on states)</td>
<td>APO(^{239})</td>
</tr>
<tr>
<td>Schwab and England Scale (off and on states)</td>
<td>APO(^{239})</td>
</tr>
<tr>
<td>Motor complications</td>
<td></td>
</tr>
<tr>
<td>Decrease in 'off' time</td>
<td>APO(^{235-237,239-242})</td>
</tr>
<tr>
<td>Dyskinesias</td>
<td>NS(^{236,237,239})</td>
</tr>
<tr>
<td>Levodopa</td>
<td></td>
</tr>
<tr>
<td>Daily dose of levodopa</td>
<td>APO(^{235-239,241})</td>
</tr>
<tr>
<td>Number of levodopa doses per day</td>
<td>APO(^{241})</td>
</tr>
<tr>
<td>APO favouring apomorphine treatment (p&lt;0.05)</td>
<td>NS non-significant</td>
</tr>
</tbody>
</table>

7.219 With respect to clinical global rating scales\(^{239}\):
- Patient rating: no patient described overall worsening, three felt unchanged, six experienced slight improvement, and sixteen had a clear improvement\(^{239}\).
- Physician rating: no patient worsened, two people were unchanged (the same who described themselves as unchanged), seven slightly improved, and sixteen had a clearly improved. **Level 3**

7.220 With respect to drug dosage\(^{241}\):
- Larger doses of apomorphine produced a longer duration of antiparkinsonian effect (p<0.001). **Level 3**

7.221 Two studies\(^{242,243}\) looked at the anti-dyskinetic effect of monotherapy, which means these people received no oral antiparkinsonian drug treatment from the time when the apomorphine pump was started in the morning to when it was turned off at night. There was an overlap in the patient populations included in these studies, therefore only the results of one\(^{242}\) will be reported below.

7.222 With respect to motor complications\(^{242}\):
- Mean maximum reduction of dyskinesia per patient of 64% (p<0.005)
- Mean time to achieve maximum dyskinesia improvement was 12.1 months
- Increase in ‘on’ time of 55% (p<0.005) **Level 3**
7.223 With respect to treatment management:\textsuperscript{242}:
- 25\% of people managed treatment independently, 50\% managed with family help, 25\% required nurse input
- Greater success rate (p<0.05, 81\%) amongst people managing the pump system independently or with help from family than those requiring outside help (e.g. nurse). \textbf{Level 3}

7.224 With respect to neuropsychiatric problems:\textsuperscript{242}:
- 40\% improvement (specially in people with depressive-type symptoms) (p<0.05) \textbf{Level 3}

7.225 With respect to adverse events:\textsuperscript{235-242}
- All people developed subcutaneous nodules
- Other effects: rhinorrhea, nausea and hiccups, recurrent diarrhoea, confusion and emotional lability, euphoria and dysarthria, worsening of dyskinesia, orthostatic hypotension, psychosis, hallucinations, intermittent illusions, confusion, sleepiness, vertigo, eosinophilia, increased appetite, increased libido, visual delusions, diurnal agitation, immune haemolytic anaemia. \textbf{Level 3}

7.226 With respect to withdrawal rates:\textsuperscript{235,237,239-242}:
- People withdrew due to side effects (psychiatric effects, insufficient therapeutic effects or adverse effects) \textbf{Level 3}

\textit{Evidence to recommendation}

7.227 The evidence base for the use of both intermittent injections and continuous infusions of apomorphine is relatively poor but both techniques are licensed for use in England and Wales. The GDG considers these to be useful treatment modalities for people with severe off periods which are not responsive to changes in oral medication. However, the risk of triggering serious side effects such as confusion, hallucinations and injection site reactions is considerable.

7.228 Long-term continuous apomorphine infusions can dramatically reduce both off periods and dyskinesia and allow withdrawal of oral medication.

7.229 The use of apomorphine should be restricted to expert units with the availability of a home monitoring system by a suitably trained health professional such as a Parkinson’s Disease Nurse Specialist.

\textit{Recommendations}
7.230 **R34** Intermittent apomorphine injections can be used to reduce off time and dyskinesia in people with PD with severe motor complications. **Grade B**

7.231 **R35** Continuous subcutaneous infusions of apomorphine can be used to reduce off time and dyskinesia in people with PD with severe motor complications. Its use should be restricted to specialist units with facilities for home monitoring. **Grade D**

**Comparisons of Drug Classes**

7.232 Whilst it is valuable to know that various drug classes are effective agents in managing the motor complications seen in later PD, clinicians are particularly keen to know whether one class is better than another so that rational decisions about the order in which adjuvant therapies are used can be made.

**Dopamine agonists versus MAO-B inhibitors**

7.233 How effective are dopamine agonists compared with MAO-B inhibitors in the management of later PD?

*Methodology*

7.234 No trials were found which compared dopamine-agonists with MAO-B inhibitors in the treatment of people with late PD and motor complications.

*Evidence to recommendation*

7.235 In the absence of any evidence, no firm conclusions on the comparative efficacy and safety of dopamine agonists versus MAO-B inhibitors can be made. Further trials are required to compare these two drug classes.

**COMT inhibitors versus dopamine agonists**

7.236 How effective are dopamine agonists compared with COMT inhibitors in the management of later PD?

*Methodology*

7.237 One Cochrane review\textsuperscript{244}, was found which compared the effectiveness of dopamine-agonists versus COMT inhibitors.
7.238 Two RCTs were included in the review. One trial\textsuperscript{245} (n=205) compared tolcapone with pergolide and the other trial\textsuperscript{246} (n=146) compared tolcapone with bromocriptine.

\textit{Evidence statements}

7.239 With respect to quality of life\textsuperscript{245}:
- PDQ-39 improved more with tolcapone than pergolide (p=0.005)
- Sickness Impact Profile (SIP) was non-significant. \textbf{Level 1++}

7.240 With respect to clinical rating scales\textsuperscript{245,246}:
- Both studies found a non-significant difference in UPDRS ADL scores and UPDRS motor scores. \textbf{Level 1++}

7.241 With respect to levodopa dose (LD) reduction:
- One trial\textsuperscript{246} found the total daily LD dose decreased significantly with tolcapone compared to bromocriptine (124 mg versus 30 mg, p<0.01).
- The other trial\textsuperscript{245} found a non-significant difference between tolcapone and pergolide (mean of 108 mg versus 92 mg) \textbf{Level 1++}

7.242 With respect to total “on” and “off” time
- One trial\textsuperscript{246} found a non-significant difference in “off” and “on” time between tolcapone and bromocriptine. \textbf{Level 1++}

7.243 With respect to adverse events:
- The combined results of both trials showed more nausea (odds ratio=0.42, p=0.0003), constipation (OR=0.26, p=0.00007) and orthostatic complaints (OR=0.24, p=0.0002) in pergolide and bromocriptine groups than tolcapone groups. \textbf{Level 1++}

7.244 With respect to withdrawal rates:
- One of the studies\textsuperscript{245} reported, due to adverse events, there was a trend towards more pergolide withdrawals (Peto OR=0.34, p=0.02). Neither study showed any significant differences for all cause withdrawal. \textbf{Level 1++}

\textit{Evidence to recommendation}

7.245 Whilst there is some evidence of the superiority of tolcapone over bromocriptine and pergolide, this is insufficient to recommend the use of COMT inhibitors ahead of dopamine agonists. Further trials are required to compare these classes of adjuvant therapy.
Dopamine-agonists versus amantadine

7.246 How effective are dopamine agonists compared with amantadine in the management of later PD?

Methodology

7.247 No trials were found which compared adding dopamine-agonists versus amantadine to levodopa therapy in the treatment of people with late PD and motor complications.

Evidence to recommendation

7.248 In the absence of any evidence, no conclusions on the comparative efficacy and safety of dopamine agonists versus amantadine can be made. Further trials are required to compare these two drug classes.

Choice of adjuvant therapy in later PD

7.249 **R36** It is not possible to identify a universal first choice adjuvant drug therapy for people with late PD. The choice of adjuvant drug first prescribed should take into account:

- Clinical and lifestyle characteristics
- Patient preference, after being informed of the short and long term benefits and drawbacks of the drug classes. **Grade D (GPP)**
8. Surgery for Parkinson's disease

Introduction

8.1 Recognition of the limitations of dopaminergic therapy and the need to treat motor complications were the prime movers in the revival of functional stereotactic surgery for PD. This was aided by technological advances in the fields of imaging and computing. The introduction of CT and MRI scanning allowed surgeons to visualise and directly target deep brain structures without the need for indirect calculations from atlases based on cadaveric dissections. Modern engineering methods and computer technology resulted in easily used and reliable stereotactic hardware. Further advance came with the development of technology for deep brain stimulation (DBS) which has become the mainstay of movement disorder surgery.

8.2 Better understanding of the pathophysiology of movement disorders and of the basal ganglia circuitry has refined the surgical targets used in movement disorder surgery.

8.3 The ventrolateral nucleus of the thalamus has been one of the commonly used target sites for surgery in PD. Cells firing at tremor frequency can be identified in the ventralis intermedius (Vim) part of the thalamus and lesions or stimulators placed at this target can dramatically improve tremor.

8.4 The serendipitous observation of the effects of accidental ligation of the anterior choroidal artery focused attention on the globus pallidus (GP) as a target for surgery. One trial group identified the ventral and posterior parts of the internal segment (GPI) as the optimal site for surgical ablation. This group revived this procedure and it was in widespread use in the early 1990s. While pallidotomy significantly reduced dyskinesia, it had a lesser effect on tremor and akinesia. The morbidity of bilateral lesions and the introduction of subthalamic nucleus deep brain stimulation reduced the use of pallidotomy. However, deep brain stimulation of the pallidum has a role in dystonia and some patients with PD.
8.5 Experimental studies using the MPTP primate model showed increased cellular activity in the subthalamic nucleus (STN) and lesions or stimulation of the STN can reverse the cardinal features of parkinsonism. However, surgeons were reluctant to lesion the STN in humans because of the risk of inducing hemiballismus. It was then shown that electrical stimulation of the subthalamic nucleus (STN-DBS) produced dramatic improvement in parkinsonian symptoms in PD. STN-DBS has since become the most widely undertaken surgical procedure for PD.

8.6 Surgical techniques vary between centres but it is generally performed in three stages: radiological localisation; physiological localisation; and then either an ablation or stimulation procedure.

8.7 Radiological localisation involves the rigid fixation to the skull under local anaesthesia of a stereotactic base ring onto which a fiducial array can be mounted. In the past ventriculography (i.e. outlining the ventricles of the brain by instilling air or contrast medium) was the radiological technique used, but this has been largely replaced by CT and MRI. It is now possible to identify most of the targets on MRI and their position in stereotactic space is calculated using sophisticated computer programmes.

8.8 When the radiological data has been acquired and analysed the patient is moved to the operating theatre and the radiological localiser is
replaced with a stereotactic arc system that allows the surgeon to pass electrodes through a small opening in the skull with a high degree of precision. This is usually undertaken under local anaesthesia to allow the surgeon to evaluate responses from the patient, though some centres now carry this out under general anaesthesia and depend on recording of cellular activity for final localisation of the target. Microelectrode recording of cellular activity is widely used for physiological localisation, but there is no consensus on the added value of this technique. Further confirmation of accurate identification of the target is usually made by evaluating the patient’s response to electrical stimulation of the target.

8.9 When the target has been identified the options are of either using radiofrequency current for thermal ablation of the area or the introduction of a system for chronic electrical stimulation. Ablation has the advantage of being an inexpensive single procedure that does not require long term follow up for maintenance of implanted hardware. These advantages are largely negated by the irreversibility of the procedure and higher morbidity. Ablation has therefore largely been replaced by chronic deep brain stimulation.

8.10 For DBS the initial target localization is similar to that used for ablative procedures. Once the target has been identified the test electrode is replaced with an implantable quadripolar electrode which is anchored to the skull. A period of stimulation using an external stimulator is sometimes used and when the efficacy has been confirmed the system is internalised. Under general anaesthesia fine cables are connected to the electrodes and tunnelled subcutaneously to a programmable pulse generator usually placed in the chest wall. The pulse generator is similar to a cardiac pacemaker with a high degree of programmability by an external device. It is possible to provide the patient with a degree of control of the stimulator. The pulse generator has a battery within it and depending on usage will have to be replaced in a simple surgical procedure every 3-5 years.

Methodological limitations of surgery trials

8.11 The included trials all had methodological limitations common to non-analytical study designs. Firstly, none of the included trials were randomised into surgical or non-surgical intervention groups. Secondly, none of the trials were performed under blinded conditions, either single or double. None of the trials were controlled with a cohort of non-surgical patients for longitudinal comparison over time.

8.12 There was also a general lack of inclusion/exclusion criteria which could lead to pre-selected patient populations, lack of multi-centre comparative results analysis, and lack of sample size calculations. The mean follow-up of most trials was 7-12 months and the patient
population tended to be younger with an average age of approximately 60 years.

8.13 What is the effectiveness and safety of any deep brain stimulation procedure versus standard medical therapy in the treatment of motor complications in patients with PD?

**STN stimulation**

**Methodology**

8.14 No randomised or controlled trials were found on the effectiveness of any DBS procedure versus standard medical therapy. Therefore, the GDG agreed to include large case series studies with a minimum sample size of 40 patients were to be accepted for review.

8.15 Nine papers were found which reported the effectiveness of STN-DBS versus standard medical therapy.

**Health economic methodology**

8.16 Four health economic studies met our quality criteria\(^{254-257}\). One study\(^{255}\) evaluated the incremental cost effectiveness of bilateral DBS of the STN or the GPI versus best medical management. The study\(^{255}\) estimated the cost per quality adjusted life year (QALY) of bilateral DBS of the STN or GPI (intervention) versus best medical management in the US healthcare context.

8.17 Another study\(^{254}\) evaluated the incremental cost-effectiveness of STN-DBS versus drug treatment. This study\(^{254}\) estimated the extra cost per additional UPDRS-point gained from bilateral high-frequency STN-DBS by comparing STN-DBS and drug treatment to drug treatment alone in the German healthcare context.

8.18 One study\(^{256}\) evaluated the costs of STN-DBS. The study\(^{256}\) estimated the total health service cost per patient including preoperative assessment, STN-DBS and postoperative management over a 5-year period in the UK healthcare context.

8.19 Another study\(^{257}\) evaluated the change in medication costs after bilateral STN-DBS. This study\(^{257}\) estimated the antiparkinsonian medication (APMED) costs pre- and post-operatively at 1 and 2 years after bilateral STN-DBS in a US healthcare context.

8.20 A simplified cost-effectiveness analysis of bilateral DBS-STN was estimated from the perspective of the NHS over 5-year period [APPENDIX F].
Evidence statements

8.21 With respect to quality of life\textsuperscript{258}:

- Parkinsonian symptoms, systemic symptoms, emotional functioning and social functioning all improved post-operatively (p<0.001)
- The improvement in the score of UPDRS II correlated with the improvement in total PDQL score (p<0.001). Level 3

8.22 With respect to efficacy, see Exhibit 8B below. Level 3

**Exhibit 8B: Bilateral STN stimulation (stimulator ‘on’)**

<table>
<thead>
<tr>
<th></th>
<th>3 months</th>
<th>6 months</th>
<th>1 year</th>
<th>2 year</th>
<th>3 year</th>
<th>5 year</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Quality of Life</strong></td>
<td></td>
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<td></td>
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<tr>
<td>PDQL</td>
<td></td>
<td></td>
<td>S\textsuperscript{258}</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td><strong>Clinical rating scales</strong></td>
<td></td>
<td></td>
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<td></td>
<td></td>
</tr>
<tr>
<td>Hoehn and Yahr</td>
<td>-</td>
<td>S\textsuperscript{259,260}</td>
<td>S\textsuperscript{260}</td>
<td>S\textsuperscript{260}</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>UPDRS I</td>
<td>-</td>
<td>-</td>
<td>NS\textsuperscript{258}</td>
<td>-</td>
<td>B\textsuperscript{261}</td>
<td>-</td>
</tr>
<tr>
<td>UPDRS II</td>
<td>S\textsuperscript{261,262}</td>
<td>S\textsuperscript{259,260}</td>
<td>S\textsuperscript{258,260,260-262}</td>
<td>S\textsuperscript{260,260,260}</td>
<td>-</td>
<td>S\textsuperscript{264}</td>
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<tr>
<td>UPDRS III</td>
<td>S\textsuperscript{261,262}</td>
<td>S\textsuperscript{259}</td>
<td>S\textsuperscript{258,260,260-262}</td>
<td>S\textsuperscript{260}</td>
<td>-</td>
<td>S\textsuperscript{264}</td>
</tr>
<tr>
<td>UPDRS IV</td>
<td>S\textsuperscript{262}</td>
<td>S\textsuperscript{259}</td>
<td>S\textsuperscript{258,260,260-262}</td>
<td>S\textsuperscript{260}</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>SEALD</td>
<td>S\textsuperscript{261}</td>
<td>S\textsuperscript{260}</td>
<td>S\textsuperscript{258,260,260,261,264}</td>
<td>S\textsuperscript{260}</td>
<td>S\textsuperscript{264}</td>
<td>S\textsuperscript{264}</td>
</tr>
<tr>
<td>BDI</td>
<td>-</td>
<td>-</td>
<td>S\textsuperscript{258,261}</td>
<td>-</td>
<td>S\textsuperscript{261}</td>
<td>NS\textsuperscript{264}</td>
</tr>
<tr>
<td><strong>Motor complications</strong></td>
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<tr>
<td>Tremor</td>
<td>S\textsuperscript{261}</td>
<td>S\textsuperscript{260}</td>
<td>S\textsuperscript{260,261}</td>
<td>S\textsuperscript{260}</td>
<td>-</td>
<td>S\textsuperscript{264}</td>
</tr>
<tr>
<td>Dyskinesias (on drug)</td>
<td>-</td>
<td>S\textsuperscript{260}</td>
<td>S\textsuperscript{258,260,260-262}</td>
<td>S\textsuperscript{260}</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Dystonia</td>
<td>-</td>
<td>S\textsuperscript{260}</td>
<td>S\textsuperscript{258,260,260-262}</td>
<td>S\textsuperscript{260}</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Akinesia and rigidity</td>
<td>S\textsuperscript{261}</td>
<td>S\textsuperscript{260}</td>
<td>S\textsuperscript{258,260,260-262}</td>
<td>S\textsuperscript{260}</td>
<td>-</td>
<td>S\textsuperscript{264}</td>
</tr>
<tr>
<td>Axial symptoms (^{A})</td>
<td>-</td>
<td>S\textsuperscript{259,260}</td>
<td>S\textsuperscript{259,260}</td>
<td>S\textsuperscript{260}</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Fluctuations</td>
<td>-</td>
<td>S\textsuperscript{259}</td>
<td>S\textsuperscript{263}</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Medication</td>
<td></td>
<td></td>
<td></td>
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<td></td>
<td></td>
</tr>
<tr>
<td>Levodopa-dose</td>
<td>S\textsuperscript{262}</td>
<td>S\textsuperscript{259,260}</td>
<td>S\textsuperscript{258,260,260-264}</td>
<td>S\textsuperscript{260,262}</td>
<td>S\textsuperscript{264}</td>
<td>-</td>
</tr>
</tbody>
</table>

\textsuperscript{S} improvement in favour of STN stimulation (p<0.05)
\textsuperscript{B} worsening of symptoms after surgery (p<0.05)
\textsuperscript{NS} non-significant
\textsuperscript{*} Patients > 70 years of age
\textsuperscript{^{A}} Axial symptoms: speech, postural stability and gait (items 18,28,29 and 30 of UPDRS III)
\textsuperscript{\dagger} Off-medication
8.23 With respect to predictive factors, the following results were observed (Exhibit 8C):

- One study\textsuperscript{262} found: ‘the younger the age at the moment of operation and the shorter the duration of disease, the better the clinical outcome’. Another study\textsuperscript{259} reported: no significant correlation between age at time of surgery or disease duration and post-op clinical outcome. \textbf{Level 3}

- One study\textsuperscript{263} found: UPDRS motor scores off medication were improved but less in patients over 70 (< 70 vs. > 70, p<0.02), and changes in UPDRS motor scores (on medication) worsened in patients over 70 and improved in patients under 70 (p<0.05). Whereas, another study\textsuperscript{262} found: no significant difference between patients older and younger than 60 years of age for UPDRS II, III and IV scores, and no significant difference in mean daily levodopa dosage at follow-up. \textbf{Level 3}

\begin{center}
\textbf{Exhibit 8C: Correlations between pre-op and post-op factors}
\end{center}

<table>
<thead>
<tr>
<th>Pre-operative factor</th>
<th>Correlation</th>
<th>Post-operative outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age \textsuperscript{263}</td>
<td>-</td>
<td>Improvement from stimulation (p&lt;0.01)</td>
</tr>
<tr>
<td>Age of patients\textsuperscript{261}</td>
<td>-</td>
<td>Frontal score (p&lt;0.001) and initiation subset of Mattis DRS (p=0.007)</td>
</tr>
<tr>
<td>Age of patients \textsuperscript{261}</td>
<td>-</td>
<td>Item 2 of UPDRS thought disorders (p=0.023)</td>
</tr>
<tr>
<td>Age or disease duration (p&lt;0.005 and p&lt;0.007 respectively) \textsuperscript{259}</td>
<td>+</td>
<td>Motor disability score in the ‘on’ stimulation and ‘on’ drug conditions</td>
</tr>
<tr>
<td>Younger patients and shorter disease duration \textsuperscript{259}</td>
<td>+</td>
<td>Residual ADL, motor disability, and axial scores</td>
</tr>
<tr>
<td>Low motor disability and high neuropsychological status \textsuperscript{259}</td>
<td>+</td>
<td>Improvement in motor disability</td>
</tr>
<tr>
<td>Less severe axial motor symptoms \textsuperscript{259}</td>
<td>+</td>
<td>Improvement in axial motor disability</td>
</tr>
<tr>
<td>L-dopa challenge \textsuperscript{263}</td>
<td>+</td>
<td>Results from STN DBS (p&lt;0.02)</td>
</tr>
<tr>
<td>Improvement from L-dopa \textsuperscript{263}</td>
<td>+</td>
<td>Improvement from STN DBS (p&lt;0.0001)</td>
</tr>
<tr>
<td>L-dopa response in an individual symptom \textsuperscript{263}</td>
<td>+</td>
<td>Stimulation response for that same symptom (akinesia, tremor, rigidity, postural instability, gait and pull test (p&lt;0.001))</td>
</tr>
<tr>
<td>Improvement from L-dopa in Hoehn and Yahr and Schwab and England global ratings \textsuperscript{263}</td>
<td>+</td>
<td>Improvement from stimulation in the same rating (p&lt;0.001)</td>
</tr>
</tbody>
</table>

+ Positively correlated (i.e. increase in factor 1 leads to an increase in factor 2)
- Negatively correlated (i.e. increase in factor 1 leads to a decrease in factor 2)
8.24 With respect to adverse events, the following were reported:
- Neuropsychological events including: confusion, mania, delusion, depression, hypomania, aggressive behaviour, hallucinations, attentional and cognitive deficit, dementia, panic attack and apathy, which in some impaired activities of daily living.
- Other adverse events including: hypophonia, transitory eye opening apraxia, thrombophlebitis, subcutaneous infection, haematomas, focal cerebral contusions, infections of the system, dysarthria, disequilibrium, dystonia, weight-gain, connection wound dehiscence, leads repositioning, air embolus, seizure and dyskinesias.
- Stimulator-induced events including: electrode replacement due to unsatisfactory results, local pain at the implantation site of the pulse generator, reversible stimulation-induced dyskinesias after an increase in voltage, minor intracerebral bleeding at the site of the trajectory lead, dislocation of the impulse generator from site of implantation, transient paresthesias associated with adjustment of stimulation parameter. **Level 3**

8.25 With respect to withdrawal rates:
- Two studies reported suicide attempts: one study reported patients with depression (3) who then attempted suicide (2)\(^{258}\) and the other study reported four patients who attempted suicide post-operatively (one died)\(^{261}\).
- In a third study\(^ {265}\), three patients died from causes unrelated to surgery or stimulation and in a fourth study\(^ {264}\), 3 (7%) deaths were reported. **Level 3**

*Health economic evidence statements*

8.26 Bilateral STB or GPI DBS costs an additional $49,194 in US$ 2000 (approximately £31,112) per QALY in comparison to best medical management\(^ {255}\). The study’s results suggest deep brain stimulation may therefore be cost effective if the quality of life after the procedure is improved by 18% or more compared to best medical management.

8.27 Bilateral STN-DBS costs approximately an additional DM1,800 (UK £580) in 2002 prices per unit improvement in UPDRS total score derived from German costs and patient data\(^ {254}\). However, the costs will decrease further over the long-term (> 1 year study period) from reduced drug expenditure and improved patient functioning. Therefore, the direct and indirect costs need to be assessed over the long-term to sufficiently evaluate the cost-effectiveness of DBS.

8.28 The total health service costs of deep brain stimulation of the subthalamic nucleus, including preoperative assessment, surgery and post-operative management over a 5 year period, was recently evaluated in the UK.\(^ {256}\) The estimated total cost per patient was
£32,526 for the bilateral procedure and £30,447 for the unilateral procedure (£2002).256

8.29 A US study evaluated the change in antiparkinsonian medication costs two years after bilateral STN-DBS. The study found the medication costs had significantly decreased by 32% (p<0.01) from the one-year pre-operative costs and 39% reduction after two years.257 Pre-operatively, the average daily cost of PD medication was $19.53 ± 10.41 in US$ 2002 (approximately £11.92 ± 6.35) per patient. Post-operatively, this fell to $13.25 ± 5.41 (approximately £8.08 ± 3.30) per patient257.

8.30 The economic modelling performed for this guideline [APPENDIX G] suggests that STN-DBS costs approximately £19,500 per QALY over a 5-year period in comparison to standard PD care in the UK (£1998). The results are relatively robust based on one-way sensitivity analysis.

Evidence-to-recommendation

8.31 In the absence of randomised controlled trials, any conclusions on the efficacy and safety of bilateral STN stimulation must be tentative. Most of the patients in the open label non-controlled trials described above were relatively young (aged around 60 years) so the results may not be generalisable to all those with the condition. Follow up was for around 12 months only which may not record later complications.

8.32 In spite of these limitations, what evidence is available supports the efficacy of this technique in reducing off time, dyskinesia and levodopa dose, improving motor impairments and disability, and improving quality of life.

8.33 There is a small but significant risk of permanent neurological disability as a consequence of this operation, due mostly to cerebral infarction or haemorrhage. This can, in a small number of patients, lead to death. Most other adverse effects of surgery were transient but concern remains regarding the incidence of neuropsychiatric complications, particularly depression and suicide. It is difficult to comment reliably on such issues in the absence of a control group.

8.34 The procedure requires an experienced well trained multidisciplinary team.

8.35 The high cost of this type of functional neurosurgery in PD is well recognised. No long-term data for clinical trials is available. However, economic modelling over a 5-year period was performed as part of this guideline suggests that bilateral STN-DBS costs £19,500 per QALY in comparison to standard PD care in the UK (£1998).
8.36 NICE published an Interventional Procedure Statement on bilateral STN stimulation in November 2003. This supported the use of the procedure provided normal arrangements for consent, audit and clinical governance are in place.

8.37 The PD SURG trial is evaluating the clinical and cost effectiveness of STN surgery and recruitment is ongoing (http://www.pdsurg.bham.ac.uk/). The NICE Interventional Procedure Statement encouraged clinicians to consider randomising patients in this trial.

Recommendations

8.38 **R37** Bilateral subthalamic stimulation can be used in people with PD who fit the following criteria:

- Motor complications which are refractory to best medical treatment
- Biologically fit with no clinically significant active co-morbidity
- Levodopa responsive
- No clinically significant active mental health problems (e.g. depression) or dementia. **Grade D**

GPI stimulation

Methodology

8.39 No randomised or controlled trials were found on the effectiveness of any GPI DBS procedure versus standard medical therapy. Therefore, large case series designs with a minimum sample size of 40 people were accepted for review.

Evidence statements

8.40 No trials were found which assessed the effectiveness of GPI stimulation in a case series with a minimum sample size of 40 people with PD.

Evidence to recommendation

8.41 Whilst no randomised controlled trials or large case series have evaluated GPI DBS, there are a small number of case series and the comparative trials that suggest the procedure is effective (see section 8.45). However, it is likely to suffer from the same concerns regarding adverse events and costs as STN DBS.

8.42 GPI DBS is rarely performed for PD in the UK at present, though it is sometimes undertaken when STN-DBS is not possible.
**Recommendation**

8.43 **R38** Bilateral globus pallidus stimulation can be used in people with PD who fit the following criteria:
- Motor complications which are refractory to best medical treatment
- Biologically fit with no clinically significant active co-morbidity
- Levodopa responsive
- No clinically significant active mental health problems (e.g. depression) or dementia. **Grade D (GPP)**

**Comparison of different types of deep brain stimulation**

8.44 What is the most effective form of deep brain stimulation procedure in the treatment of motor fluctuations and complications in patients with PD?

**Methodology**

8.45 There were no randomised or controlled trials reporting the most effective form of DBS in the treatment of patients with PD. The majority of trials were retrospective care series, which compared the results of different techniques. Due to the lack of comparative trials in this area, the GDG agreed studies with a sample size minimum of ten patients per arm should be reviewed.

8.46 Five trials 267-271 were found which compared the before and after surgery results of STN, GPI and Vim thalamic DBS.

8.47 The majority of the patient population received bilateral implantation, though results were not reported separately from the unilateral implantation results.

**Evidence statements**

8.48 With respect to clinical efficacy
- The following criteria were significantly (p<0.05) in favour of both STN and GPI DBS:
  - UPDRS I, II (off and on), III (off and on), IV 267,268,270,271
  - Time in off state (UPDRS item 39) 271
  - Hoehn and Yahr scores 270
  - Levodopa equivalent daily dose 267,268,270
  - Dyskinesia scores 267,268
  - Patient and physician global assessments
  - Schwab and England Scale 271
  - Home diary scores (% of time with good mobility and without dyskinesia during the waking day). 268 **Level 3**

- The following criteria were improved in only one DBS technique versus another:
o Motor score improvement was more pronounced in STN patients than G Pi patients (no p values stated)\textsuperscript{270}
o Medication could only be reduced in STN patients and not G Pi patients (no p values stated)\textsuperscript{270}
o Levodopa dose equivalent, though unchanged in the G Pi group, was significantly reduced in STN group (p=0.017)\textsuperscript{271}
o Trail making test (p=0.0013), test B (p=0.0015) and BDI (P<0.0001) improved under STN stimulation and not G Pi\textsuperscript{270}
o Literal (p=0.0018) and total fluency (p=0.0002) decreased under stimulation STN and not G Pi DBS.\textsuperscript{270}o CAPIT dyskinesia rating scale score favoured G Pi (p=0.046) in absolute scores but percentage changes were not significant\textsuperscript{271} Level 3

- Thalamic nucleus stimulation could not be compared directly to other techniques, as the outcome measures used to assess its efficacy are different from other techniques. The main outcome, tremor suppression, was found to be significantly improved with the procedure.\textsuperscript{272} Level 3

8.49 With respect to adverse events, the following was reported:
- No G Pi specific adverse events were reported
- See other sections for events specific to STN (8.14) and thalamic stimulation (8.54) procedures. Level 3

Evidence-to-recommendation

8.50 There is no evidence from randomised controlled trials to compare subthalamic with globus pallidus stimulation. However, observational studies suggest that STN stimulation may lead to greater improvement in motor scores and more reduction in levodopa dose and depression scores. In comparison, G Pi stimulation may lead to less cognitive impairment. Further work is required in this area.

8.51 It is recognised that pallidal stimulation for PD is rarely performed at present, though it is sometimes undertaken when STN-DBS is not possible.

Recommendation

8.52 With the current evidence it is not possible to decide if subthalamic nucleus or globus pallidus stimulation is the preferred surgical option for people with PD. In considering the type of surgery, account should be taken of:
- The clinical condition and the lifestyle of the person with PD
- The views of the person with PD after being informed of the potential benefits and drawbacks of the different surgical procedures. Grade D (GPP)
**Thalamic stimulation**

8.53 How effective and safe is thalamic stimulation for the control of tremor in PD?

**Methodology**

8.54 Three papers\(^{273,272,274}\) reported the effectiveness of chronic stimulation to the ventral intermediate (Vim) thalamic nuclei. The methodological limitations of these papers are similar to those of the STN stimulation (see 8.14).

**Evidence statements**

8.55 With respect to tremor suppression:
- All three studies\(^{273,272,274}\) showed a benefit of thalamic stimulation
- Only one study\(^{272}\) reported statistical analysis and stated that the following outcomes were significantly (p<0.05) improved: face tremor and observed tremor, bradykinesia, rigidity, and ADL score. Level 3

8.56 With respect to adverse events the following were reported:
- Post-operative events: venous infarction with temporary aphasia, intraventricular haemorrhage and cardiovascular problems intraoperatively
- Stimulation-related events that occurred considerably more frequently in patients with bilateral implants (52%) as compared with unilateral (31%)\(^{274}\) included: dystonia, diplopia, sleepiness, altered mental status, paresthesias, mild disturbance of gait and balance, mild dysarthria, increased drooling, nausea, insomnia, dysphagia, depression, wire tightness, and dysarthria. Level 3
- No mortality was reported in any of the trials

8.57 With respect to withdrawal rates:
- Most withdrawals were due to adverse events. Level 3

**Evidence-to-recommendation**

8.58 There is no evidence from randomised controlled trials of the benefit of thalamic stimulation in PD. Data from observational studies suggest that this is an effective method of reducing tremor. The operation carries a risk of serious complications such as cerebral infarction and haemorrhage. The GDG recognised that this form of surgery is rarely performed for tremor in people with PD in England and Wales, having been superseded by STN stimulation.

**Recommendation**

8.59 **R40** Thalamic deep brain stimulation is an option in people with PD who predominantly have severe disabling tremor and where STN DBS cannot be performed. **Grade D**
9. Non-motor Complications of Parkinson's Disease

"...I feel trapped inside my body...as if I'm not in control...almost as if someone or something else is running my life..."—patient

Introduction

9.1 The spectrum of Parkinson's disease includes many problems that do not directly affect motor function. These non-motor complications are of crucial importance to people since they have a major impact on quality of life.21,275

9.2 Non-motor complications are comprised:
- Mental health problems
  - Depression and dementia
- Falls and potential fractures
- Sleep disturbance
- Autonomic disturbance and pain.

9.3 Whilst most people are troubled by these problems in the later stages of their PD, certain non-motor conditions can develop throughout the course of the condition (e.g. depression, anxiety, hypersomnolence) or even precede it (e.g. sleep disturbance, depression, anxiety).

9.4 A recent study reported on the non-motor problems experienced by a group of 149 PD people followed for 15 to 18 years.276 They found the occurrence rates were: falls 81% (with 23% suffering fractures), cognitive decline 84% (48% fulfilling criteria for dementia), hallucinations 50%, depression 50%, choking 50%, symptomatic postural hypotension 35%, and urinary incontinence 41%.

9.5 There have previously been few therapeutic studies examining the effects of treatments for non-motor disorders. However, there is now a real desire to increase research into the non-motor complications of PD having recognised their effect on people’s wellbeing.277

9.6 The non-motor complications of PD considered in the scope of this guideline and thus undergoing literature review include:
- Mental health problems
  - Depression
  - Dementia
  - Psychosis
- Sleep disturbance
  - Hypersomnolence
  - REM sleep behaviour disorder
  - Restless legs syndrome
  - Inverted sleep-wake cycle
  - Nocturnal akinesia
9.7 The non-motor complications of PD not considered in the scope of this guideline include:

- Mental health problems
  - Anxiety
  - Apathy

- Falls

- Autonomic disturbance
  - Bowel dysfunction – including constipation
  - Dysphagia
  - Weight loss
  - Dribbling of saliva
  - Bladder dysfunction
  - Sexual dysfunction
  - Postural hypotension
  - Excessive sweating
  - Postural oedema

- Pain

9.8 Depression, dementia and psychosis are frequent problems in PD and some research has been performed on their treatment. Therefore, these topics were included in the scope of this guideline.

9.9 Other important mental health issues in PD include anxiety and apathy but little work has been done in these areas specific to PD so they were not included in the scope. Standard treatment therefore applies in these areas, see NICE guidance titled: ‘Anxiety: management of anxiety (panic disorder, with or without agoraphobia, and generalised anxiety disorder) in adults in primary, secondary and community care’.278

**Mental Health Problems**

*Depression*

9.10 Depression affects around 40-50% of people with PD.279 It is usually of mild to moderate but can be severe and symptoms of depression can predate motor manifestations.

9.11 The relationship of depression to the pathology of PD is unclear but the inconsistent relationship between mood changes and the severity of motor symptoms indicates that depression should not simply be considered a reaction to motor disability.

9.12 The characteristic features of depression are low mood, loss of interest and enjoyment and fatigue. This is accompanied by various combinations of slowed mental and physical function, motor agitation, poor appetite and sleep, weight loss, other somatic symptoms and disturbance of cognitive function and thought processes.
9.13 The disturbance of cognitive functions and thought processes may result in poor concentration and memory, excessive worry, feelings of worthlessness, hopelessness and guilt, negative views of self and life and thoughts of suicide. Psychological and physical symptoms of anxiety are also common.

9.14 The development of depression creates added burden for the person with PD and their carers and has been shown to be an important determinant of quality of life.\textsuperscript{280}

9.15 Factors relevant to the aetiology of depression that need to be considered are:

- Previous susceptibility to depression
- Neurotransmitter disturbances of PD
- Effects of drug treatments
- Relationship to “on-off” motor fluctuations
- The persons’ adjustment to the diagnosis of PD and their symptoms and life factors including losses
- Other stressors
- Interpersonal relationships.

9.16 What is the effectiveness of antidepressant therapies versus placebo or active comparator in the treatment of depression in PD?

\textit{Methodology}

9.17 A Cochrane review\textsuperscript{281} and two randomised controlled trials\textsuperscript{282,283} (published after the review’s search date) were found which addressed the effectiveness of antidepressant therapies versus placebo or active comparator. No controlled trials were found on electroconvulsive therapy or behavioural therapy for the treatment of depression in Parkinson’s disease people.

9.18 The Cochrane review included three trials: one trial\textsuperscript{284} compared a selective serotonin re-uptake inhibitor (SSRI) to placebo; another study\textsuperscript{285} compared a tricyclic antidepressant (TCA) to placebo; the third trial\textsuperscript{286} compared the effectiveness of an SSRI versus a TCA.

9.19 These trials included small sample sizes (range 22-47). There were several methodological limitations of the included studies: lack of power calculations, lack of baseline characteristics, and no details on methods of randomisation and allocation concealment. The duration of the included trials varied from 16 to 52 weeks (with one study not reporting the trial duration).

9.20 One of the independent RCTs\textsuperscript{282} compared the effectiveness of an SSRI to placebo. The methodological limitations of this study included unclear methods of randomisation and allocation concealment, small sample size (n=12, 6 in each arm) and lack of power calculations. The
study reported that because of the low recruitment the study was terminated after 10 weeks.

9.21 The second independent RCT\textsuperscript{283} compared repetitive transcranial magnetic stimulation (rTMS) versus an SSRI as an effective antidepressant therapy. The methodological limitations included: short trial duration (8 weeks), small sample size (n=42, 21 in each arm) and lack of power calculation.

Evidence statements

9.22 The Cochrane review\textsuperscript{281} reported the following non-significant results:
- Nortriptyline (TCA) improved depressive symptoms in the first half of a crossover trial with no deterioration in Parkinsonian symptoms
- Citalopram (SSRI) provided no additional benefit over placebo in the treatment of depressive symptoms in a parallel trial design
- Fluvoxamine (SSRI) and amitriptyline (TCA) showed similar efficacy in an open-label trial
- Confusion and visual hallucination were infrequently reported in people taking fluvoxamine and amitriptyline, otherwise no other major adverse events were reported.

9.23 One of the independent RCTs\textsuperscript{283} reported no significant difference between sertraline (SSRI) and placebo in terms of ‘response’ to treatment (defined as at least 50% reduction of the pre-treatment Montgomery-Asberg Depression Rating Scale), or UPDRS motor scores. \textbf{Level 1+}

9.24 One of the independent RCTs\textsuperscript{282} reported the following outcomes were improved in both rTMS and fluvoxamine-treated groups: the Hamilton Depression Rating Scale (HDRS) and Beck Depression Inventory (BDI), ADL scores, and Mini-Mental State Examination (MMSE) with no significant differences between groups. However, adverse events were found more frequently in the fluvoxamine-treated group than the rTMS group (p=0.03). \textbf{Level 1+}

Evidence to recommendations

9.25 There is insufficient evidence from randomised controlled trials of the efficacy or safety of any antidepressant therapy in PD. This includes cognitive behavioural therapy, all classes of antidepressant medication and electroconvulsive therapy.

9.26 NICE has recently published guidelines\textsuperscript{16} for the management of depression which include people with physical disorders. Whilst it is tempting to adopt these guidelines for people with PD, there are a number of factors which suggest that the management of depression in PD may require different strategies:
- There are case reports suggesting that some antidepressants may make PD motor symptoms worse\textsuperscript{287}
There are difficulties in diagnosing mild depression in people with PD as the clinical features of depression overlap with the motor features of PD.

There are established interactions between some antidepressants and dopaminergic therapy for PD (e.g. selegiline and SSRIs).

Cognitive behavioural therapy is not widely available to secondary care teams looking after people with PD.

There is an urgent need for further research to establish effective and safe treatments for depression in PD. In the meantime, the GDG adopted a pragmatic approach, based on the NICE guidelines and clinical experience, advising that SSRI class antidepressants should be used before tricyclic antidepressants because they are less likely to be withdrawn due to side effects but they have similar efficacy.

**Recommendations**

**R41** In the absence of any contra-indication, moderate to severe depression in PD should be treated with an SSRI class antidepressant.

*Grade D (GPP)*

**Psychotic symptoms**

Psychotic symptoms indicate a loss of reality testing, that is, the formation of beliefs and sensations without a basis in reason or external sensory stimulus. Delusions (false unshakeable beliefs that cannot be understood from the individual's socio-cultural context) and hallucinations (perceptions in any sensory modality occurring without external sensory stimulus) are the most common symptoms of psychosis.

Psychotic symptoms may occur at any stage in PD. Up to 50% of people with the condition may develop psychotic symptoms and 30% may experience hallucinations within the first five years. Though visual hallucination is the most frequent psychotic symptom a degree of auditory hallucination is found in 40%. Delusions may involve themes of persecution, infidelity and jealousy but these are much less common.

The aetiology of psychotic symptoms in PD is complex. They may arise from the neurotransmitter disturbances of PD but can be caused by any of the drugs used to treat motor symptoms.

The appearance of psychotic symptoms requires careful evaluation. Psychotic symptoms may also occur as part of delirium (caused by other physical illness and drug treatments) or dementia or may indicate the development of a co-morbid mental illness.

Psychotic symptoms are distressing and may be frightening to people with PD and their carers who may not appreciate that they are
symptoms of illness. It is essential to explain the nature of these symptoms to people with PD and their carers.

9.34 What is the effectiveness of atypical antipsychotic therapies versus placebo or active comparator in the treatment of psychotic symptoms in PD?

**Methodology**

9.35 Five randomised controlled trials\(^ {290-294}\) were found which addressed the effectiveness of atypical antipsychotic therapies versus placebo or active comparator in the treatment of psychosis.

9.36 Three trials\(^ {295-297}\) were found that compared two atypical antipsychotic drugs, and these were excluded as within drug class comparisons.

9.37 The methodological limitations for some of the included studies involved: lack of randomisation and allocation concealment methods, lack of multi-centre comparative results analysis, lack of power calculations, small sample sizes (n=31\(^ {298}\), 160\(^ {292}\), 30\(^ {291}\) and 60\(^ {293}\)) short trial duration and not intention-to-treat analysis protocols.

**Evidence statements**

9.38 With respect to psychiatric outcomes:

- Trials which looked at the effectiveness of clozapine versus placebo found the following outcomes in favour of active drug treatment:
  - Clinical Global Impression scale (CGI) (p=0.002)\(^ {290}\), (p=0.001)\(^ {293}\)
  - Brief Psychiatric Rating Scale (BPRS) score (p=0.002)\(^ {290}\)
  - BPRS-Modified score (p=0.003)\(^ {290}\)
  - Scale for the Assessment of Positive Symptoms (SAPS) (p=0.01)\(^ {290}\)
  - ‘Positive and Negative Syndrome Scale’ (PANSS) positive subscore (p<0.001)\(^ {293}\) **Level 1+**

- Trials which looked at the effectiveness of olanzapine versus placebo found no significant differences between groups on a battery of neuropsychological tests\(^ {291,292}\) **Level 1+**

- One trial which looked at quetiapine versus placebo found no significant difference between groups on the Baylor PD Hallucination Questionnaire, the Brief Psychiatric Rating Scale, and a battery of neuropsychological tests.\(^ {294}\) **Level 1+**

9.39 With respect to motor outcomes:

- One trial which looked at clozapine versus placebo reported a beneficial effect of clozapine on UPDRS tremor subscore (p=0.02)\(^ {290}\) **Level 1+**
Other trials which looked at olanzapine versus placebo reported the following outcomes worsened with drug treatment:

- UPDRS total (p=0.007 and p=0.024)\(^{292}\)
- UPDRS motor scores (p=0.023 and p=0.039\(^{292}\) (p<0.05)\(^{291}\)
- Subscores gait (p<0.001) and bradykinesia (p<0.05)\(^{291}\)
- Timed tapping scores (p<0.05)\(^{291}\)
- UPDRS activities of daily living scores (p=0.004 and p=0.009)\(^{292}\) Level 1+

The trial that looked at quetiapine found no differences between placebo and active drug groups on UPDRS activities of daily living or motor scores. There was also no difference found on the Goetz Dyskinesia Rating Scale scores.\(^{294}\) Level 1+

With respect to adverse events:

- The following events were reported as significantly increased in people receiving clozapine treatment:
  - Increase in mean resting heart rate (p=0.046)\(^{290}\)
  - Increased body weight (p=0.005)\(^{290}\)
  - Increased somnolence (53% versus 18%) and worsening of parkinsonism (21.8% versus 4%) (p values not stated)\(^{293}\) Level 1+

- The following events were reported as significantly increased in people receiving olanzapine treatment:
  - Extrapyramidal syndrome (p=0.003)\(^{292}\)
  - Hallucinations (p=0.013)\(^{292}\)
  - Increased salivation (p=0.026)\(^{292}\)
  - No case of agranulosytosis reported\(^{293}\) Level 1+

- There were no significant differences in adverse events reported in the study on quetiapine versus placebo. The study did report that no people on the active drug dropped out secondary to a related adverse event, which included sedation (n=9, 43%), and subjective worsening in PD (n=4, 19%).\(^{294}\) Level 1+

With respect to withdrawal rates:

- Trials on clozapine efficacy reported most withdrawals were due either to treatment failure\(^{293}\) or adverse events\(^{290}\). Level 1+
- Trials which assessed the effectiveness of olanzapine reported:
  - Significantly more people receiving olanzapine discontinued (p=0.029) and mostly due to adverse events (p=0.003) compared to placebo\(^{292}\) Level 1+

- The trial that assessed quetiapine effectiveness reported no significant differences in withdrawal rates. The study found that 81% of the active drug group completed the study, with four patients withdrawing due to serious unrelated illness or lack of effect and poor compliance. In the placebo group 80% of the participants completed
the trial, reasons for withdrawal included unrelated serious illness, resulting in death.\textsuperscript{294} \textbf{Level 1+}

\textit{Evidence to recommendations}

9.42 Psychosis is a common problem in later PD and can be difficult to manage. It may be precipitated by intercurrent illnesses (e.g. infections), addition of new anti-parkinsonian medication or dementia. Correspondingly, the initial treatment of psychosis should include general medical assessment and treatment of any potential causative factor. Consideration should be given to withdrawal of any recently added medication which may have triggered a psychotic reaction. Drugs which are particularly prone to trigger psychosis, such as anticholinergics, selegiline and amantadine, should be withdrawn first. The patient should be evaluated for a fixed cognitive deficit which might suggest the development of dementia.

9.43 For psychosis which does not respond to the above measures, no treatment may be required if psychotic features are not troublesome to the patient or their carers.

9.44 In more severe psychosis, anti-psychotic medication should be considered. Typical anti-psychotics (e.g. phenothiazines and butyrophenones) are well known to exacerbate PD and should not be used. Various atypical anti-psychotics have been evaluated in PD, although none has a product licence for this indication in England and Wales:

- Several randomised placebo-controlled trials have shown that clozapine can reduce psychotic symptoms in PD without exacerbating parkinsonian features. However, the use of clozapine requires intensive monitoring to detect the uncommon but potentially life threatening complication of agranulocytosis. As a result, it is rarely used in PD.
- Limited trial evidence suggests that olanzapine is not effective against psychotic features and makes parkinsonian symptoms worse.
- There are concerns about the safety of olanzapine and risperidone in elderly people with dementia and risk factors for stroke.\textsuperscript{299}
- There is no evidence from randomised controlled trials of the efficacy and safety of quetiapine as an anti-psychotic in PD. However, several trials are ongoing in this area. Quetiapine is thought to be relatively safe and does not require haematological monitoring. As a result, quetiapine has been widely used in PD psychosis.
Recommendations

9.45 R42 All people with PD and psychosis should receive a general medical evaluation and any precipitating condition should be treated. Grade D (GPP)

9.46 R43 Consideration should be given to withdrawing gradually anti-parkinsonian medication which might have triggered psychosis in PD. Grade D (GPP)

9.47 R44 Mild psychotic symptoms in PD may not need to be actively treated if it is well tolerated by the patient. Grade D (GPP)

9.48 R45 Typical anti-psychotic drugs (e.g. phenothiazines, butyrophenones) should not be used in PD as they exacerbate the motor features of the condition. Grade D (GPP)

9.49 R46 Clozapine can be used in the treatment of psychotic symptoms in PD but registration with a mandatory monitoring scheme is required. Grade B

Dementia

9.50 PD is associated with impairment of cognitive function. Compared to people without PD, deficits in visuospatial abilities, category learning, verbal fluency, set switching and executive functions are typically reported.

9.51 Particular attention has focussed on deficits of executive function that may mediate many of the other impairments. Executive functions include working memory, mental flexibility and the ability to initiate and suppress responses.

9.52 Dementia (the progressive loss of global cognitive function) is also common in PD. 48 to 80% of people may develop dementia at some point in the course of the condition.

9.53 In addition to cognitive decline, dementia leads to impairment in activities of daily living and disturbance of behaviour and other psychological functions. Dementia in PD is accompanied by reduced quality of life for the person with PD and their carer.

9.54 Other pathologies commonly causing dementia include Alzheimer's disease, vascular brain disease and dementia with Lewy bodies.

9.55 Traditionally, dementia developing more than one year after the onset of the motor features of PD is referred to as Parkinson's disease with dementia. Dementia developing within one year of the onset of motor features is classified as dementia with Lewy bodies. The relationship between PD with dementia and dementia with Lewy bodies is unclear but many consider them to be a continuum rather than discrete entities.
9.56 Since people with dementia with Lewy bodies may not develop parkinsonism, we have not considered the treatment of this type of dementia in this guideline. The GDG acknowledges that this decision may need to be revisited in the future if new evidence proves that a continuum exists between PD with dementia and dementia with Lewy bodies.

9.57 Rarely, dementia may arise due to a treatable illness. All people with dementia require careful evaluation of their medical condition, treatment and investigations to clarify the diagnosis with attention to potentially treatable conditions. In this context, cognitive decline due to depression, often referred to as depressive “pseudodementia”, should be considered.

9.58 The assessment and management of dementia will require a range of clinical expertise that can only be provided by a multidisciplinary team.

9.59 Are cholinesterase inhibitors effective cognitive enhancement therapies in PD?

Methodology

9.60 Two papers\textsuperscript{302, 303} were found which addressed the effectiveness of cholinesterase inhibitors as cognitive enhancement therapies in PD.

9.61 An additional Cochrane review\textsuperscript{304} was found, which included only one RCT\textsuperscript{305} on rivastigmine versus placebo. This paper was excluded as the patient population was defined as people suffering from dementia with Lewy bodies.

9.62 One RCT\textsuperscript{302} assessed the effectiveness of rivastigmine versus placebo in PD with dementia over a 24-week trial (n=541). Another paper\textsuperscript{303} performed a 15-week trial to look at the effectiveness of donepezil versus placebo (n=16) in PD with dementia.

9.63 One of the studies\textsuperscript{302} had a sound methodology and reported details of their design and analysis. The other RCT\textsuperscript{303} however had a small sample size (n=7 in the active treatment arm) and did not provide a power calculation or state methods of randomisation.

Evidence statements

9.64 One RCT\textsuperscript{302} reported the following outcomes to be significantly (p<0.05) in favour of rivastigmine:

- Neuropsychiatric inventory (10 item version)
- Alzheimer’s disease assessment scale (ASAS-G)
- Alzheimer’s disease cooperative study-clinicians global impression of change (ADCS-CGIC)
- ADCD- activities of daily living
- Mini-Mental State Examination
- Cognitive Drug Research power of attention tests
• Delis-Kaplan Executive Function System\textsuperscript{7}
• Ten-point clock-drawing test\textsuperscript{5} Level 1++

9.65 The other RCT\textsuperscript{303} reported the following outcomes in relation to donepezil efficacy:

• No significant differences between groups on measures of global cognition (MMSE and DRS total scores)
• Significant difference for the DRS Memory subscore (p<0.05)- with an improved score in the donepezil-treated group and a decline in the placebo group
• There were no significant group differences for any other cognitive measure
• Donepezil group displayed a trend towards improvement in psychomotor processing speed and attention in the Trail Making Test- Part A (TMT-A) whereas placebo group was worse at follow-up (p=0.08). Level 1+

9.66 With respect to adverse events:

• The rivastigmine group experienced more adverse events (p<0.001)\textsuperscript{302}
• No significant difference in serious adverse events reported or deaths between rivastigmine and placebo groups\textsuperscript{302}
• Parkinsonian symptoms were reported as adverse events more frequently in rivastigmine than placebo (27.3\% versus 15.6\%, p=0.002)\textsuperscript{302}
• These were most commonly manifested as tremor (10.2\% versus 3.9\%, p=0.01)
• Nausea and vomiting were also reported more frequently (p<0.001) in rivastigmine group
• Level 1++
• Non-significant difference between donepezil and placebo groups for incidence of adverse events (5 people versus 4, respectively)\textsuperscript{303}
• Adverse events leading to withdrawal in the donepezil group included: acute diplopia, lightheadedness, constipation, nausea and vomiting, hypersalivation, rhinorrhea, urinary frequency and worsening of motor symptoms (gait impairment, increased number of falls, increased tremor).\textsuperscript{303} Level 1+

9.67 With respect to withdrawals:

\textsuperscript{7} Because executive function tests were not performed at all sites, these tests included only people who actually took these tests (74\% and 18\% of patient population respectively)
• No difference between the rivastigmine and placebo groups\textsuperscript{302,304} \textbf{Level 1++}

• Donepezil treated people remained in the trial for a mean duration of 13.1 weeks and placebo group for 17.3 weeks (p<0.05)\textsuperscript{303}

• 4/7 (57%) donepezil people withdrew versus 1/9 (11%) of the placebo-treated people because of adverse events\textsuperscript{303} \textbf{Level 1+}

\textit{Evidence to recommendations}

9.68 There is evidence from randomised placebo-controlled trials of the effectiveness and safety of cholinesterase inhibitors in the treatment of PD with dementia. They are effective in treating both cognitive decline and psychosis in this context. However, not all patients respond, so regular review of the need for these agents is required.

9.69 At present, none of the cholinesterase inhibitors has a Product Licence for use in PD with dementia in the UK. However, the GDG considers that these are useful agents which are commonly used in clinical practice and that they should be available.

9.70 NICE has commissioned the guideline titled ‘Dementia: management of dementia, including use of antipsychotic medication in older people’. NICE is developing this guideline in collaboration with the Social Care Institute for Excellence (SCIE). This guideline will cover all the major forms of dementia, including Alzheimer’s disease, vascular dementia, Lewy body dementia, subcortical dementia, frontotemporal dementias, and mixed cortical and subcortical dementia. Dementia encountered in the course of Parkinson’s disease will be addressed. The guidelines will, where appropriate, address the differences in treatment and care for people with mild, moderate and severe dementia.

\textit{Conclusion}

9.71 The guideline development group consider on the basis of the preceding analysis, that the cholinesterase inhibitors are clinically effective for the treatment of cognitive impairment and/or psychotic symptoms arising from dementia in people with PD. \textbf{Grade A}. A recommendation on their use will be made in the second consultation draft of this guideline following an analysis of their cost effectiveness. This additional work is being undertaken at the request of the National Institute for Health and Clinical Excellence.
Sleep Disturbance

“He has lots and lots of nightmares when he goes to sleep, and he comes to and doesn’t know where he is…” – carer

9.72 Sleep problems are common in PD and comprise of:
- Daytime hypersomnolence
- Nocturnal akinesia
- Restless legs syndrome (RLS or Ekbom’s syndrome)
- Periodic leg movements of sleep (PLMS)
- REM sleep behaviour disorder (RBD)
- Sudden onset of sleep
- Vivid dreams and/or hallucinations

9.73 They are particularly taxing to people with PD and their bed-partners because of their mixed nature comprising motor, sensory and sleep issues. In addition, if inadequate rest is gained by night, there is a high prevalence of excessive daytime somnolence that may have serious consequences on social functioning and safety.

9.74 Assessment should include a thorough sleep history including:
- Enquiry about the three phases of sleep: initiation, maintenance and awakening
- Enquiry about leg movements – periodic leg movements in sleep; restless legs syndrome
- Hallucinations and vivid dreams
- Questioning whether dreams are acted out sometimes violently indicative of REM sleep behavioural disorder which occurs in up to 15% of PD people and may precede the diagnosis of PD.

9.75 Drug induced hallucinations and/or vivid dreams may occur, and should be distinguished from RBD. Many centrally acting drugs may disturb sleep patterns, mainly by inducing sedation, but some may cause nocturnal alertness (e.g. selegiline).

9.76 One of the most common sleep disorders seen in PD is RLS. The International RLS Study Group criteria for the diagnosis of RLS are:
- Desire to move the extremities usually associated with discomfort or disagreeable sensations in the extremities
- Motor restlessness - people move to relieve the discomfort (e.g. walking or providing a counter-stimulus to relieve the discomfort such as rubbing the legs)
- Symptoms are worse at rest with at least temporary relief by activity
- Symptoms are worse later in the day or at night.
9.77 Vivid dreams and nightmares may be provoked by many of the commonly used drugs in PD. A review of medication and reduction/avoidance of suspected causes is usually effective. However, REM behavioural disorder may also occur in which dreams are so vivid that they are acted out. When pharmacotherapy is required, a response may be seen to low doses of clonazepam.306

9.78 ‘Sudden onset of sleep’ (SOOS) without warning has recently been described in PD people with the potential to cause road traffic accidents.308 Whilst certain dopamine agonists were initially incriminated, current opinion is that all PD medications can cause daytime hypersomnolence and that all people with PD are liable to hypersomnolence and should be warned of the possibility of falling asleep at the wheel. This may be more likely in people with late PD on multiple medications and also during upward dose titration, particularly with dopaminergic agonists. Any people so affected should not drive.

*Daytime hypersomnolence*

9.79 It has been recognised in recent years that daytime hypersomnolence is a major issue for people with PD. This may even lead to the sudden onset of sleep which can be dangerous.

9.80 How effective is modafinil in treating daytime hypersomnolence in PD?

*Methodology*

9.81 Two placebo-controlled, double-blind RCTs309,310 were found which investigated the effectiveness of modafinil treatment (200mg/d) for sleep disorders in people with PD.

9.82 One of the studies309 had a small sample size of n=21, but the trial reported the sample size met the power calculations provided to detect differences between groups. The other study was a crossover trial310 with a sample size of n=15 but did not provide power calculations. The trial durations were 6 and 8 weeks respectively. The mean age of the people included in these studies was 65 years with mean disease duration of seven years.

9.83 No randomised controlled trials were found on the specific treatment of REM sleep behaviour disorder, daytime hypersomnolence and restless legs syndrome in PD.

*Evidence Statements*

9.84 With respect to the Epworth Sleepiness Scale (ESS):

- One study309 demonstrated the change in ESS was statistically significant in favour of modafinil treatment (95%CI −8.6 to −0.2, \(p=0.039\)). Level 1++

9.85 With respect to patient-rated scales:
The patient-rated Clinical Global Impression of Change (CGI-C) scale improved significantly on modafinil (p=0.07) \textsuperscript{309} Level 1++

9.86 With respect to other outcome measures:
  - There was no significant differences between modafinil and placebo for the following:
    - Maintenance of Wakefulness Test (MWT) \textsuperscript{310}
    - Mean changes in sleep latency \textsuperscript{310}
    - Sleep logs (similar amounts of sleep) \textsuperscript{310}
    - Beck depression scores \textsuperscript{310}
    - Physician-rated CGI-C \textsuperscript{309}
    - Worsening/improvement of PD signs \textsuperscript{309}
    - UPDRS scores, Hoehn and Yahr scores, timed tapping tests, or patient diaries \textsuperscript{309}
    - Percentage ‘on’ time \textsuperscript{309}
    - Adverse events \textsuperscript{309,310}
    - Withdrawal rates \textsuperscript{309,310} Level 1++

Evidence to recommendations

9.87 Whilst there is little evidence from randomised controlled trials of the efficacy and safety of modafanil in the treatment of daytime hypersomnolence in PD, it has a Product License for use in hypersomnolence in chronic diseases. Members of the GDG have little experience in its use but acknowledged that modafanil can be useful in this clinical context.

Recommendations

9.88 Modafinil can be used to treat daytime hypersomnolence in people with PD. Grade B

Nocturnal Akinesia

9.89 Turning over in bed (nocturnal akinesia) may become difficult in PD due to truncal rigidity. This can have a major impact on people with PD and can interfere with sleep and thus lead to daytime hypersomnolence.

9.90 Treatment has traditionally been with either small doses of immediate-release levodopa or controlled-release levodopa last thing at night. There is insufficient experience with dopamine agonists and COMTI in this area.

9.91 General measures in the treatment of sleep disorders in PD include improvements in sleep hygiene such as:
  - Avoidance of stimulants (e.g. coffee, tea, caffeine) in the evening
  - Establish a regular pattern of sleep
  - Comfortable bedding (including silk sheets to aid turning) and temperature
• Provision of assistive devices, such as a bed lever or rails to aid with moving and turning allowing the person to get more comfortable
• Restriction of daytime siestas
• Review of all medication and avoidance of any drugs that might affect sleep or alertness, or may interact with other medication (e.g. selegiline, ant-histamines, H2 antagonists, antipsychotics and sedatives.

9.92 Are controlled-release levodopa preparations effective in the management of nocturnal akinesia in PD?

Methodology

9.93 A double-blind RCT\textsuperscript{311} was found which, compared controlled-release (CR) levodopa and immediate-release (IR) levodopa in the treatment of nocturnal and early-morning disability.

9.94 The RCT was a multi-centre trial including 103 people from eleven centres in the UK. The mean age of people included in the study was 68 years with average disease duration of 8 years. Controlled-release co-beneldopa or immediate-release co-beneldopa was given at a dose of 125mg/day immediately before going to bed.

9.95 Methodological limitations included: lack of randomisation and allocation concealment methods, no washout period or first-arm results, and intention-to-treat analysis was not stated. However, carry-over effects and differences between centres were statistically analysed and produced no significant differences.

Evidence statements

9.96 With respect to controlled-release (CR) levodopa versus immediate-release (IR) levodopa, one study\textsuperscript{311} reported the following outcomes:
• There were no significant differences in nocturnal and early morning disability. \textbf{Level 1+}

Evidence to recommendation

9.97 There is insufficient evidence from RCTs to support the use of controlled-release levodopa preparations in the treatment of nocturnal akinesia in PD. However, the GDG had considerable experience of their use in this context and were able to support their value.

Recommendation

9.98 \textbf{R48} Controlled-release levodopa preparations can be used for nocturnal akinesia. \textbf{Grade D (GPP)}
**Falls**

9.99 Falls are common in PD: two thirds of people with PD fall each year with most eventually becoming fallers\(^{12,312,313}\).

9.100 Early onset of falls may indicate an alternative diagnosis to idiopathic Parkinson’s disease such as PSP\(^{314}\).

9.101 Predictors of falls specific to PD include: \(^{12,312,313,315}\)
- Longer disease duration
- More advanced disease
- Dyskinesia
- Motor fluctuations
- Atypical Parkinsonism
- Postural instability
- Small steps
- Freezing
- Stride-to-stride variability
- Altered step and stance width
- Loss of arm swing.

9.102 Predictors of falls in PD similar to the general population include: \(^{12,316}\)
- Old age
- Previous falls
- Use of sedative drugs
- Depression
- Dementia.

9.103 The clinical impact of falls is considerable, often leading to injury requiring health care services, an incapacitating fear of renewed falls, anxiety and depression\(^{317}\). The associated costs for society are substantial both in terms of finances as well as stress on the patient and their support network.

**Assessment and prevention of falls**

9.104 People with PD require a multi-disciplinary assessment of the specific and non-specific predictors of falls together with the intrinsic and extrinsic factors which contribute to falls. In common with other people with repeated falls the assessment and prevention of falls in PD requires multifactorial assessment and intervention. The NICE Clinical Guideline 21 ‘Falls - the assessment and prevention of falls in older people’ published by NICE in November 2004 provides a framework for this process summarised in the “Quick reference guide” (Appendix C).

**Recommendation**

9.105 **R49** For guidance on the management of falls in PD refer to the NICE Guideline “Falls: assessment and prevention in older people”. (NICE)
Autonomic Disturbance

9.106 Autonomic dysfunction is common in PD due to the underlying pathophysiology of the condition affecting the catecholaminergic neurones of the autonomic nervous system.

9.107 While symptoms due to autonomic disturbance are common, and whilst this area has not undergone a systematic search for treatment trials, several crucial issues specific to PD were identified by the GDG as Good Practice Points.

Gastrointestinal Dysfunction

Weight loss

9.108 Unintended weight loss is common in PD, occurring in over 50% of individuals, with 20% losing over 12 kg in one study. A larger proportion of women than men with PD may experience weight loss. Moderate or severe dyskinesia is the strongest correlate of undernutrition in PD, although the reasons for weight loss are likely to be more complex than simply “burning off” more calories. Similarly, the weight gain commonly observed after bilateral deep brain stimulation has not yet been adequately explained.

9.109 When significant weight loss occurs, the following general points should be considered:

- Other medical causes for weight loss (e.g. malignancy, endocrine causes)
- Investigation of swallow
- Review of anti-parkinsonian medications if dyskinesias are problematic
- Dietary supplements
- Referral to a person with expertise in dietetics.

Dysphagia

9.110 Dysphagia is an impairment of swallowing. It is a complex process with risks of: asphyxiation, aspiration pneumonia, malnutrition, dehydration and drooling. Swallowing difficulties in PD usually relate to disease severity and may affect all phases of the swallow process (oral, pharyngeal and oesophageal). One group studied 75 people at different stages of PD and showed that up to 94% had problems with swallowing. In Hoehn and Yahr stages I-III the problems were often not noticed by the person with PD. However, abnormalities are often detected on modified barium swallow testing. In advanced PD swallowing difficulties can be severe and are usually obvious to the patient and their carers. There is a high incidence of silent aspiration in PD, putting the person at risk of developing recurrent chest infections.
if not properly investigated. Infected oral secretions are a prime cause of pneumonia and this may be caused by poor oral hygiene due to reduced motor movement in the mouth. Pneumonia is a leading cause of death in later stages of PD. 323

9.111 Dysphagia in PD results from catecholaminergic degeneration and Lewy body formation in the brainstem and within the pharyngeal muscles themselves. It does not respond fully to optimisation of dopaminergic medication324.  

9.112 Dysphagia poses a major problem to the taking of medications which are critical in the successful management of PD. Reduced tongue control leads to difficulty manipulating and clearing tablets from the mouth. Pharyngeal pooling and dysmotility may lead to retention of pills in the valleculae and pyriform fossae consequently delivery of medications may be erratic.

9.113 The management of dysphagia in PD may involve the following generic issues:

- Referral to person with expertise in speech and swallowing disorders for assessment, swallowing advice, and, where necessary, further investigation (e.g. videofluoroscopy or fibreoptic nasendoscopic examination of swallow safety)
- Enteral feeding options may need to be considered. This may involve short-term naso-gastric tube feeding to re-establish a suitable drug regimen or placement of a longer term feeding system such as a percutaneous endoscopic gastrostomy (PEG).
- Cricopharyngeal (CP) myotomy has been reported to be successful in some cases with specific CP deficits. However treatment must be based on physiology which is best revealed with video fluoroscopy. Cricopharyngeal myotomy may put people with PD at high risk of laryngeal penetration and pulmonary aspiration if oral and pharyngeal dysphagia is present. 325,326 CP myotomy also puts people at high risk of aspiration of reflux from the stomach.

### Constipation

9.114 Colonic dysmotility and anorectal dysfunction are common in PD, occurring up to 30% and 60% cases, respectively327. Lewy body degeneration occurs within the myenteric plexus of the colon in PD, leading to slow transit times and, occasionally, megacolon, intestinal pseudo-obstruction and volvulus. A combination of disordered contraction and relaxation of the muscles of defecation which may in part be dystonic leads to excessive straining, pain, and a sense of incomplete evacuation. Faecal incontinence, when it occurs in PD, is usually due to overflow around faecal impaction.

9.115 The management of constipation due to colonic dysmotility in PD should follow a staged, or stepladder, approach327.
Increasing dietary fibre and fluid intake (at least eight glasses of water per day), avoiding bananas and increasing exercise  
Fibre supplements such as psyllium\textsuperscript{328} or methylcellulose  
Stool softener (\textit{e.g.} docusate)  
Osmotic laxative (\textit{e.g.} lactulose)  
Polyethylene glycol electrolyte balanced solutions\textsuperscript{329}  
Enemas may be occasionally required.

\textbf{Genitourinary Dysfunction}

\textbf{Bladder}

9.116 Up to 75\% of people with PD develop urinary difficulties. Nocturia is the earliest and most common urinary problem, although daytime urgency and frequency may also be troublesome. Urinary incontinence is uncommon in PD. Detrusor hyperreflexia results from disinhibition of the ponto-mesencephalic micturition centre\textsuperscript{330}.

9.117 Where there is refractory or persistent urinary dysfunction, referral for urological evaluation should be considered.

9.118 Other management approaches include:
\begin{itemize}
\item Excluding urinary tract infection where there is an abrupt change in voiding pattern
\item Excluding diabetes mellitus where frequency and polyuria are prominent
\item Use of anticholinergic agents (tolterodine, oxybutynin, propantheline) although, since these drugs cross the blood-brain barrier, they must be used with caution as they may induce a toxic confusional state.
\end{itemize}

\textbf{Sexual Dysfunction}

9.119 Erectile dysfunction is more common in PD (60\%-70\%) than it is in age-matched controls (38\%)\textsuperscript{331,332}. Men with PD may also experience sexual dissatisfaction and premature ejaculation. In women, difficulties with arousal, low sexual desire and anorgasmia are common\textsuperscript{331}.

9.120 Dopaminergic therapy may also induce hypersexuality, even when there is erectile dysfunction.

9.121 In the management of erectile dysfunction the following should be considered:
\begin{itemize}
\item Co-morbid endocrine abnormalities (\textit{e.g.} hypothyroidism, hyperprolactinaemia)
\item “Latent” depression
\item Discontinuation of drugs associated with erectile dysfunction (\textit{e.g.} alpha-blockers) or anorgasmia (\textit{e.g.} selective serotonin reuptake inhibitors)
\item Type V cGMP-specific phosphodiesterase inhibitors (\textit{e.g.} sildenafil)\textsuperscript{332}
\end{itemize}
• Intracavernous injections or transurethral suppositories of alprostadil (a synthetic prostaglandin E₁)

**Orthostatic Hypotension**

9.122 Orthostatic hypotension (OH) occurs in 48% of people with PD in the community but is asymptomatic in up to 60%. It may be defined as a drop in systolic blood pressure after standing greater than or equal to 20 mmHg or to less than 90 mmHg. The aetiology of OH in PD is multifactorial and includes Lewy body degeneration in the hypothalamus, brainstem and peripheral nervous system. Symptoms of OH include fatigue, pre-syncope and syncope, while OH may also contribute to falling. Persisting or troublesome OH may warrant referral to a unit with expertise in falls and syncope.

9.123 The management of OH in PD should follow a “step-ladder” approach:
- Eliminate or reduce antihypertensive medications; reduce or change anti-parkinsonian drugs
- Increase dietary salt and fluid intake, avoid caffeine at night; eat frequent, small meals and avoid alcohol
- Elevate head of bed by 30-40°
- Salt-retaining steroid (e.g. fludrocortisone)
- Direct-acting sympathomimetic (e.g. midodrine, only available on named patient basis).

**Excessive Sweating**

9.124 Severe sweating may occur as an end of dose “off” phenomenon or while in the “on” motor state, usually associated with dyskinesias.

9.125 The management approach to excessive sweating may include general measures:
- Excluding a co-morbid medical problem (e.g. chronic infection, thyrotoxicosis), or the post-menopausal state

**Sialorrhoea**

9.126 Excessive saliva or drooling occurs in 70-80% of people with PD and may be more common in men. It may result from oropharyngeal dysfunction, including reduced swallow frequency. Apart from social embarrassment and soiling of clothing, sialorrhoea may also be associated with perioral infection.

9.127 General management measures may include:
- Referral to a Speech and language Therapist for full assessment of swallowing ability
- Advice and trial of behavioural management techniques to encourage regular saliva swallows
- Use of a portable metronomic brooch as a reminder for saliva swallows
Lip seal and swallow exercises
Sublingual 1% atropine ophthalmic solution twice daily\textsuperscript{339}
Injection of salivary glands with botulinum toxin A\textsuperscript{340}

**Recommendation**

9.128 **R50** People with PD should be treating accordingly for the following autonomic disturbances:

- Urinary dysfunction
- Dysphagia
- Constipation
- Erectile dysfunction
- Orthostatic hypotension
- Excessive sweating
- Sialorrhea. **Grade D (GPP)**

**Pain**

9.129 Pain is defined as an unpleasant or distressing sensory experience.\textsuperscript{341} Pain occurs in around 40% of people with PD but is rarely a major feature of the disorder.

9.130 Pain in PD has been classified\textsuperscript{341} as:

- Musculoskeletal – often secondary to parkinsonian rigidity and hypokinesia (e.g. frozen shoulder)
- Dystonic – associated with dystonic movements and postures which often occur in the off period in the feet
- Primary or central – burning or paraesthetic pain out with a dermatome or root territory which is not explained by a musculoskeletal or dystonic cause
- Neuropathic - pain in the distribution of a root or nerve with associated signs
- Akathisia-related – inner feeling of restlessness leading to inability to keep still.

9.131 Little research has been done in this area and the management of many of these types of pain is generic rather than being specific to PD. Therefore, the GDG elected not to undertake a literature search in this area. The GDG did recognise though that dystonic pain, which is often responsive to the dopaminergic medications, as discussed elsewhere in the guideline (see chapter 7).
10. Other key interventions

"The biggest benefit of complementary therapies is the sense of empowerment they give
"—patient ²

“…never has anybody said to us ‘do you think you need a physiotherapist, a speech
therapist, or an occupational therapist- do you need these services?’ That’s something we
have gone out to find ourselves and I think too late.” --carer ³

Introduction

10.1 In previous chapters, consideration has been given to the evidence for
pharmacological treatments and surgical interventions. However, people with PD may also benefit from interventions provided by a range
of health disciplines. This chapter addresses the effectiveness of
specific interventions that are part of:
• Specialist nursing
• Physiotherapy
• Occupational therapy
• Speech and language therapy.

10.2 Because service issues lie outside the scope of this guideline, evidence
has been sought for the effectiveness of the interventions that are part
of a discipline and recommendations made accordingly. It should be
noted that some interventions, particularly those related to maintaining
independence, may in practice be carried out by professionals from a
number of disciplines.

Methodological limitations

10.3 When reviewing the evidence of the interventions delivered by health
professional the following methodological limitations should be
considered:
• Location of therapy varied (home, out-patient clinic, in-hospital)
• Lack of reporting the intensity of therapy given
• Therapy regimen varied between trials
• The qualifications and experience of person delivering the
intervention were unclear
• Short trial duration and lack of long-term follow-up
• Small sample sizes without power calculations provided
• Lack of reporting methods of randomisation or allocation
concealment
• Lack of reporting drop-outs from trials
• Lack of intention-to-treat analysis

Parkinson’s Disease Nurse Specialist Interventions
10.4 Parkinson’s Disease Nurse Specialist (PDNS) care has been pioneered in the United Kingdom over the last ten years supported by the UK Parkinson’s Disease Society. A PDNS role is defined as a specialist practitioner with essential skills in:

- Communication
- Patient and carer assessment
- Symptom management
- Medicines management
- Providing ongoing support and advice
- Referral to other therapists
- Education.

10.5 A recent report from the UK Parkinson’s Disease Society (2004) identified the key roles and responsibilities of the PDNS in the UK as:

- Making and receiving referrals directly to create an integrated and responsive service for people with PD
- Admitting and discharging people for specified conditions and within agreed protocols
- Managing caseloads
- Providing information, education and support to people in their homes, in clinics and in hospitals
- Prescribing medicines and treatment and to monitor the effectiveness of changes in medication and treatment
- To use the latest IT to triage people with PD to the most appropriate health professional
- Using IT to identify people at risk and speed up responses to crises.

10.6 What is the effectiveness of PDNS care versus standard medical care in the management of people with PD?

Methodology

10.7 Three RCTs were found which addressed the effectiveness of PDNS or other non-consultant care. The specific intervention of ‘nursing care’, the comparator and the sample size varied between the studies limiting the ability to draw general conclusions. The three studies and their variables are listed below:

- The effects of community-based PDNS care versus GP care in 1869 people with PD
- The effects of nurse practitioner care versus ‘standard care’ in a population of 40 people with PD recruited from a specialist neurology unit
- The effects of substituted consultant care versus PDNS care in a population of 185 people with PD attending hospital clinics.
10.8 Only one study provided data on statistical power. Another study involved only 58% of the 185 enrolled participants who completed the trial and in a third study the sample size was small (n=40).

10.9 The study environment varied considerably between trials. In one study, 438 GP practices were involved from nine randomly selected English health authorities. The practices recruited people who represented the PD population of England and Wales. In another study, clinics in London and Hull with established PDNS services were selected to participate. Finally, a third study considered only people recruited from the National Hospital for Neurology and Neurosurgery in London. The lack of random patient and centre selection methods in the latter studies limits their generalisability to care provided elsewhere in the UK.

Health economic methodology

10.10 Three economic studies of PDNS care were critically appraised and one met quality criteria. One study did not meet quality criteria in the health economic analysis, but was included in the clinical efficacy analysis. The reason for the exclusion here is due to 42% loss of people during follow-up, which may have led to bias in the economic results. The third other study was also excluded as the trial did not consider all costs relevant to the provision of PDNS care to reflect true cost-saving estimates.

10.11 The one study that met quality criteria evaluated community-based PDNS care with general practitioner care versus standard general practitioner care in a randomised controlled trial in the UK.

10.12 As part of the guideline development process, we have evaluated the cost-effectiveness of PDNS care in comparison to standard care over a one-year period from the NHS perspective. Full details of this analysis are shown in Appendix H.

Evidence statements

10.13 The PDNS versus GP care study evaluated the results of the Global Health Questionnaire at the end of a two year period and found only one significant outcome measure (out of approximately 20 measures) which favoured PDNS care (treatment difference -0.23, 95% CI, -0.4 to –0.06, p = 0.008). Level 1++

10.14 This study also reported non-significant results for the following outcome measures: two and four year mortality, stand-up tests, bone fracture, mean best hand score, Euroqol tariff, dot-in-square score,
PDQ-39 measures, physical functioning (SF-36) and general health (SF-36). **Level 1++**

10.15 The trial also found that PDNS care enabled more rapid implementation of what was then thought to be good-prescribing practice:

- The proportion of people with PD taking controlled-release levodopa increased significantly more in the nurse group (p=0.016).
- People in the nurse group had a greater tendency after two years to discontinue their use of selegiline (p<0.001)\(^{344}\). **Level 1++**

10.16 After one year, another trial\(^{346}\) found that substituted consultant care produced the following outcomes (out of 22 measures):

- One significant outcome in favour of PDNS care: the communication score on the PDQ-39 questionnaire (p=0.05).
- Two significant outcomes favouring the consultant care group: physical functioning on SF-36 (p=0.02) and general health on SF-36 (p=0.02). **Level 1+**

10.17 The nurse practitioner versus standard care RCT\(^{345}\) assessed people with PD and dystonia over six months. For the psychosocial outcome measures, no significant differences were found between the intervention and control groups. **Level 1+**

10.18 In addition, the results from an independent assessment\(^ {345}\) of patient satisfaction, in just the intervention group arm, showed that:

- The most common information provided by the nursing intervention concerned practical issues such as income support and mobility allowance.
- The mean rating for the nursing intervention was 8.5 on a scale of 1-10 (half rated the contact as 10, i.e. ‘very useful’).
- The aspect of the intervention most highly ranked in terms of usefulness was ‘the opportunity to talk to someone about the illness and the problems caused by it’.
- 89% considered the home visits the most useful aspect of the intervention.
- 81% thought that the duration of contact with the PDNS needed to be prolonged.
- 58% thought that the PDNS intervention would be useful to other people with PD (mean 9.0 on scale of 1 to 10). **Level 3**

*Health economic evidence statements*

10.19 The randomised control trial\(^ {344}\) found no significant difference in mean increase in annual costs between groups (p=0.47) from the year before the study to the second year of the study. This mean annual cost estimated the provision of nurse specialist care to cost \£200 per person
per year and excluded the cost of apomorphine. The mean annual cost in the specialist nurse group increased from £4050 to £5860 (UK£, 1996) and from £3480 to £5630 in the control group based on 1859 people from 438 general practices in nine randomly selected health authority areas of England.

10.20 Net cost-savings of approximately £640 per year were found for one PDNS based on completely substituted activities, such as monitoring on-going treatment and average nurse activity for one year of PDNS care. However, this result should be interpreted with caution given changes in three of four key parameters by 10% result in PDNS care costing more than standard care. Full details of these analyses are shown in Appendix H.

Evidence to recommendation

10.21 Most of the benefits derived from PDNS interventions have been shown to relate to the overall patient care experience and the delivery of services such as the monitoring of medication and provision of information. The communication issues for people with PD and their carers are further addressed in Chapter 4.

10.22 There has only been limited evidence showing improvements in direct measures of outcome, although, in the community PDNS study, the group with PDNS interventions had an improved global health score.

10.23 The evidence indicates the cost-effectiveness of PDNS care is inconclusive.

Recommendation

10.24 **R51** People with PD should have regular access to the following which can be part of specialist PD nursing:

- Monitor and alter medication appropriately. **Grade A**
- Provide a continuing point of contact for support, including home visits. **Grade C**
- Be a reliable source of information about clinical and social matters of concern to people with PD and their carers. **Grade C**

Physiotherapy

10.25 Physiotherapy or physical therapy can be defined as: ‘A health care profession which emphasises the use of physical approaches in the promotion, maintenance and restoration of an individual’s physical, psychological and social well-being, encompassing variations in health status’ 348
10.26 Physiotherapy primarily addresses the physical components of rehabilitation, essentially to maximise the functional capacity of a person and their role within society.

10.27 Where people receiving physiotherapy have a longer-term condition, such as PD, physiotherapy is generally regarded as an active, ongoing process and one that should be client-focussed in its approach and regularly reviewed.

10.28 Physiotherapy might incorporate only education and advice ensuring maintenance of a current level of fitness and ability, or involve exercises specific to the needs of the person with PD to regain movement, prevent falls, maximise respiratory function or reduce pain. It also has a role alongside medical and surgical intervention to enhance the person’s potential with these interventions.

10.29 Physical therapy may include approaches such as the Alexander Technique, yoga, Conductive Education or Pilates – techniques which not only promote movement, but also are linked with social well-being.

10.30 The principles of physiotherapy are:

- Early implementation of exercise programme to prevent deconditioning and other preventable complications
- Utilisation of a meaningful and practical assessment procedure to allow monitoring and identification of rehabilitation priorities
- The identification of deterioration and timely, appropriate intervention
- The opportunity for targeted therapy for restoration or compensation of function
- The involvement of patients and carers in decision-making and management strategies.

10.31 What is the effectiveness of physiotherapy interventions versus standard therapy in the care of people with PD?

Methodology

10.32 A Cochrane systematic review and an RCT were found which addressed the effectiveness of physiotherapy versus standard therapy or placebo in the treatment of Parkinson’s disease. Another study was found which addressed the effectiveness of the Alexander Technique (AT) versus no therapy or massage therapy.

10.33 The physiotherapy RCT (n=8) investigated the effect of a 16-week aerobic exercise program on aerobic capacity and movement initiation (MI) time for Parkinson’s disease (PD).

10.34 The Alexander Technique RCT (n=88) randomised participants to three groups: controls (n=30) or Alexander Technique (n=29) or massage group (n=29) (2 massage sessions per week for 12 weeks
(the massage group as to control for touch and attention)). The Alexander Technique consisted of two 40min lessons per week for 12 weeks, then five weeks after completion the participants received a short-audio tape that lead them through a 20min lying down exercise. The massage group received two massage sessions per week for 12 weeks (the massage group as to control for touch and attention).

10.35 The Cochrane review\textsuperscript{350} included eleven randomised trials with a total of 280 people. The participants in these trials received physiotherapy directed to trunk and limb functions and were treated for 8-30 hours over 3-52 weeks. The method of physiotherapy was usually described in a very broad manner; even the time spent by therapist with the patient was not specified in half of these trials.

10.36

\textit{Evidence statements}

10.37 For a summary of the effectiveness of physiotherapy techniques see Exhibit 10A below.
### Exhibit 10A: Effectiveness of physiotherapy techniques (Level 1+)

#### Conventional Physiotherapy techniques

<table>
<thead>
<tr>
<th>Outcomes</th>
<th>(N=)</th>
<th>Follow-up</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Activities of daily living</strong>&lt;sup&gt;353&lt;/sup&gt;</td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Barthel Index</td>
<td>20</td>
<td>Post-intervention</td>
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</tr>
<tr>
<td></td>
<td></td>
<td>5 months</td>
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<tr>
<td>NUDS</td>
<td></td>
<td>Post-intervention</td>
<td>NS</td>
</tr>
<tr>
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<td></td>
<td>5 months</td>
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<td>Functional Index Measure (FIM)</td>
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<tr>
<td></td>
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<td><strong>Clinical rating Scales</strong></td>
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<td>Post-intervention</td>
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<td></td>
<td></td>
<td>5 months</td>
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<td>Webster rating scale&lt;sup&gt;353&lt;/sup&gt;</td>
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<td>Parkinson’s Home Visiting Assessment Tool (5/53 items)&lt;sup&gt;354&lt;/sup&gt;</td>
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<td><strong>Motor impairments</strong></td>
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<td>Walking velocity&lt;sup&gt;353,355&lt;/sup&gt;</td>
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<td>Post-intervention</td>
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<td>Post-intervention</td>
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<td><strong>Exercise outcomes</strong>&lt;sup&gt;351&lt;/sup&gt;</td>
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<td>Aerobic capacity</td>
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<td>Post-intervention vs. controls</td>
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<td>Movement initiation</td>
<td></td>
<td>Post-intervention vs. controls</td>
<td>0.003</td>
</tr>
<tr>
<td><strong>Alexander technique (AT)</strong>&lt;sup&gt;352&lt;/sup&gt;</td>
<td></td>
<td></td>
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<tr>
<td>SPDDS ‘at best’</td>
<td>88</td>
<td>Post-intervention vs. controls</td>
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<td>SPDDS ‘at worst’</td>
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<td>6 months vs. controls</td>
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<td>6 months vs. controls</td>
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<td>6 months vs. controls</td>
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<td>Attitudes to Self Scale</td>
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<td>Post-intervention vs. controls</td>
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</tr>
<tr>
<td></td>
<td></td>
<td>6 months vs. controls</td>
<td>0.04</td>
</tr>
</tbody>
</table>

10.38 With respect to medication changes:<sup>352</sup>:
- The rate of medication change was statistically in favour of AT treatment compared to control (p=0.001)
- Fewer participants in the AT group changed their medication and yet were not experiencing worsening symptoms (p=0.047). Level 1++

**From evidence to recommendation**

10.39 There is encouraging RCT evidence of the effectiveness of some of the physiotherapy interventions for people with PD. However, further definitive trials are required to confirm these findings. Additional work is
necessary to define what physical therapy interventions are effective in the different stages of the disease.

10.40 In addition to this evidence, the experience of the GDG members supports the use of physiotherapy interventions in people with PD.

Recommendation

10.41 R52 Physical therapy should be available for people with PD and particular consideration should be given to the following:

- Gait re-education, balance and flexibility
- Enhancement of aerobic capacity
- Improvement of movement initiation
- Improvement of functional independence, including mobility and activities of daily living
- Provision of advice regarding safety in the home environment

Grade B

10.42 R53 The Alexander Technique can be used to benefit people with PD by helping to make lifestyle adjustments that affect both the physical nature of the condition and the person’s attitudes to having PD. Grade B

Occupational therapy

10.43 Occupational therapy (OT) is a profession concerned with promoting health and well being through occupation. The primary goal of occupational therapy is to enable people to participate in the activities of everyday life. Occupational therapists achieve this outcome by enabling people to do things that will enhance their ability to participate or by modifying their environment to better support participation.\(^\text{357}\)

10.44 Occupational therapists have expertise in assisting people who have disabilities to manage the practical aspects of everyday life. Referral to an OT can enable people with PD to maximise their current abilities, retain independence for as long as possible and develop their own coping strategies to deal with future problems.\(^\text{358}\)

10.45 The principles of occupational therapy are:

- Early intervention to establish rapport, prevent activities and roles being restricted or lost and where needed to develop appropriate coping strategies
- Client-centred assessment and intervention
- Development of goals in collaboration with the individual and carer with regular review
- Employment of a wide range of interventions to address physical and psychosocial problems to enhance participation in everyday activities such as self care, mobility, domestic and family roles, work and leisure.
10.46 Current UK practice emphasises functional goals centred around independence, safety and confidence including activities such as transfers, mobility and self-care.\(^{359}\)

10.47 A wide variety of interventions are used in PD. Owing to the individualised nature of the therapeutic process, this may include practising skills, cognitive and sensory cueing strategies, problem solving, advice, education, provision of equipment and environmental adaptations.\(^{360}\)

10.48 What is the effectiveness of occupational therapy versus standard medical therapy in the management of PD?

**Methodology**

10.49 A Cochrane review\(^ {361}\) was found on the effectiveness of OT versus placebo (or no interventions) in people with PD. The review included two randomised, parallel group trials, with a total of 84 people (n=64\(^ {362}\) and n=20\(^ {363}\)).

10.50 There were significant differences between the methodologies of the two studies. One trial\(^ {362}\) conducted 20 hours of treatment over five weeks with one-year follow-up while the other trial\(^ {363}\) conducted 12 hours of treatment over one month with no follow-up. The methodological limitations of these studies is covered in section 10.3.

10.51 Due to the lack of RCT evidence, papers with lower level study designs (e.g. non-randomised and/or uncontrolled trials) were also included in the search, but no further papers were found which addressed the effectiveness of OT in the treatment of people with PD.

**Evidence statements**

10.52 With respect to clinical outcome measures\(^ {362}\):

- Barthel Index score, an assessment of ADL, was maintained over one year in those treated with occupational therapy.
- The group without the OT intervention lost an average of 4.6 points (out of a total score of 100) (p values not available).

10.53 The other study\(^ {363}\) reported small differences in mean changes between groups on all outcome measures (motor impairment, activities of daily living, and quality of life measures) (p values not available).

**Evidence to recommendation**
10.54 In view of the methodological flaws in the trials and the small numbers of randomised participants, and only one outcome measure reported from one trial, there is insufficient evidence to support the efficacy of occupational therapy interventions in PD. However, the GDG support the value of many of the aspects of this therapy, particularly with respect to the provision of aids and adaptations to maintain functional independence in people with PD. There is evidence to support this from one trial where there was maintenance of ADL scores in the treated group but a decline in those not treated. Further trials are required to evaluate the role of different aspects of occupational therapy.

10.55 In spite of this lack of evidence, the experience of the GDG members supports the use of occupational therapy interventions in people with PD. It is recognised that, in practice, some of these interventions may be carried out by health professionals other than occupational therapists.

**Recommendation**

10.56 Occupational therapy should be available for people with PD and particular consideration should be given to the following:

- Maintenance of employment, home-care and leisure activities
- Improvement and maintenance of transfers and mobility
- Improvement of personal self-care activities such as eating, drinking, washing and dressing
- Environmental issues to improve safety and function
- Cognitive assessment and appropriate intervention. **Grade D**

**Speech and language therapy**

10.57 Deterioration in speech is a common manifestation of PD that increases in frequency and intensity with the progress of the disease.

10.58 The specific dysarthria resulting from PD is known as hypokinetic dysarthria and it is characterised by:

- Monotony with reduced loudness and pitch range
- Variable rate
- Short rushes of speech
- Imprecise consonant
- Breathy or harsh voice.

10.59 Treatment programmes have focused on specific components of the dysarthria such as respiratory exercise and prosodic exercises. These treatments can be used with individuals or in groups.

10.60 Lee Silverman Voice Treatment (LSVT) is a speech therapy programme developed specifically for individuals with PD. It focuses on
improving voice loudness with immediate carry over into daily communication. The intensive nature of the programme helps individuals with PD to recognise that their voice is too soft, convince them that a louder voice is within normal limits and makes them comfortable using the new louder voice. It is now provided by certified clinicians in England.

10.61 Some people with PD may benefit from use of augmentative and alternative communication devices (AAC), which can include the use of:

- Alphabet boards
- Pacing boards
- Voice amplifiers
- Digitised speech output systems
- Recorded voice messages.
- Delayed auditory feedback
- Micro computer-based wearable biofeedback device.

10.62 What is the effectiveness of speech and language therapy versus standard medical therapy or control in the treatment of speech disturbance in Parkinson’s disease?

Methodology

10.63 A systematic review was found which addressed the efficacy of speech and language therapy versus standard medical therapy in people with PD.

10.64 The review included three randomised controlled trials, with a total sample size of 63. One of these trials used the LSVT technique, whereas the rest used the more conventional SLT techniques. No raw numerical data was available from one of these studies, so data on only 41 participants was available from the review’s analysis. Another included study showed the intervention groups differed significantly from one another at baseline on a number of outcome measures, but no further analysis was provided.

10.65 There were significant differences in the intensity of the SLT intervention between studies. One trial treated participants for 10 hours over four weeks, another trial provided treatment for 16 hours over four weeks and a third trial treated people for 35-40 hours over two weeks.

Evidence statements

10.66 With respect to the assessment of speech impairment:

- One study found total impairment with the Frenchay Dysarthria Assessment improved in the intervention group compared to the placebo (p < 0.05) showing an overall improvement in the dysarthria
score, while all participants in the untreated group showed lower scores with a significant deterioration (p<0.05).

- Another study reported the scores of the Dysarthria Profile were comparable at baseline, but immediately after therapy the scores were significantly higher in the treatment group (p<0.05).

10.67 With respect to vocal loudness:

- Objective loudness improved by 11 dB and by 5.4 dB (p<0.005) immediately after therapy but reduced to 3.5 dB after six months although this was still significantly better (p<0.05)

- Mean objective loudness of speech when the participants were asked to describe a picture improved by 5.2 dB (p<0.025) and this improvement was maintained over six months (4.2 dB, p<0.02)

- The reading loudness of participants receiving LSVT was more than the placebo group immediately after therapy (p<0.001) and improvement was mostly maintained (p<0.005) at six months

- Mean objective loudness improved when people were asked to give a prolonged ‘a’ (12.1 dB, p<0.001) and this was mostly maintained (9.4 dB, p<0.001) at six months.

- Maximum vocal loudness increased after therapy by 16dB

10.68 Mean pitch range increased in the therapy group by 66Hz (162.7 to 228.3) and remained virtually static in the placebo group.

**Evidence to recommendations**

10.69 Although there is good preliminary evidence of the efficacy of speech and language therapy for speech disorders in PD, this is based on data from only 41 people with maximum follow-up of only 12 weeks. Much of the positive data concerns the unique North American therapy called Lee Silverman Voice Treatment. Whilst some therapists in England and Wales have attended the mandatory training programme for this intervention, it is not widely available at present. The GDG was also concerned about the practicalities of 16 one-hour treatment sessions in the context of the NHS financial climate.

10.70 In spite of this lack of evidence, the experience of the GDG members supports the use of speech and language therapy interventions in people with PD.

10.71 In the section on dysphagia (Chapter 9; 9.109) the potential contribution that could be made by speech and language therapist interventions is discussed.

**Recommendations**
10.72 **R54** Speech and language therapy should be available for people with PD and particular consideration should be given to the following:

- Improvement of vocal loudness and pitch, including speech therapy programmes such as LSVT  
  **Grade B**
- Teaching strategies to optimise speech intelligibility
- Ensuring an effective means of communication is maintained throughout the course of the disease, including use of assistive technologies
- Review of swallow safety and efficiency.  
  **Grade D (GPP)**
11. Palliative care in Parkinson’s disease

Introduction

11.1 In the absence of any curative treatment, the management of PD remains largely palliative despite the huge advances that have been made in medical knowledge. The principles of palliative care should be applied throughout the course of the disease and not limited to the terminal end of life period.

11.2 Palliative care can be defined as: “The active total care of patients whose disease is not responsive to curative treatment. Control of pain and other symptoms and of psychological, social & spiritual problems is paramount. The goal of palliative care is achievement of the best quality of life for patients and their families” (World Health Organisation 2002).

11.3 Palliative care is an approach that improves the quality of life of patients and their families facing the problems associated with life threatening illness. It does not necessarily mean the use of specialist care services but should focus on prevention and relief of suffering with early identification, impeccable assessment and treatment of pain and other physical, psychological and spiritual problems.

Figure 11.1: Palliative care time course (MacMahon, 2005)
11.4 The issues common to malignant and non-malignant conditions, that are the focus of palliative care, can be categorised\(^{372}\) as:

- **Physical:** pain, breathlessness, anorexia, immobility, and constipation
- **Social:** loss of employment, role change, fear for dependants
- **Psychological:** depression, fear and anxiety, uncertainty, guilt
- **Existential:** religious, non-religious, meaning of life, why?

### The palliative phase of PD

11.5 The needs of patients in the palliative care stage of PD are not always identified or satisfied\(^{373}\). Over time progression of the underlying disease process makes interventions less effective and they may be associated with intercurrent illnesses. As a result, patients become increasingly disabled and dependent. This physical disability is often combined with cognitive dysfunction and depression.

11.6 The ‘Palliative Phase’ in PD (Exhibit 11.1) has been defined by\(^{374}\):

- Inability to tolerate adequate dopaminergic therapy
- Unsuitability for surgery
- The presence of advanced co-morbidity.

11.7 The duration of time spent in each of the stages of PD is variable. From an audit of 73 patients undertaken in Cornwall\(^{375}\) the mean duration of disease was 14.6 years. The time spent in the four stages was: diagnosis 1.5 years; maintenance 6 years; complex 5 years, and palliative care 2.2 years. This reinforces that ‘palliative care’ in PD does not equate with imminent end of life but the emphasis of care will shift from a ‘therapeutic’ pharmacological approach to one that places greater emphasis on quality of life issues. This is in recognition of the shortened remaining life span of the patient and the inadequacy of current medications to meet the increase in needs.

11.8 The care of people with PD is best undertaken in a multidisciplinary way throughout each stage of the disease. In the later stages the palliative care team should also be incorporated with the main aims of care to provide symptom relief, prevent complications, minimise distress, maintain patient dignity and provide counselling. Dopaminergic drugs may need to be reduced or withdrawn or the patient may be unable to swallow oral therapy due to swallowing difficulties.

11.9 The National Service Framework for Long Term Medical Conditions (2005)\(^{376}\), focuses on the palliative care needs of patients will chronic disabling conditions such as PD in Quality Requirement 9: Palliative care.

### Palliative care and carers
11.10 Management of the palliative stage must always be in the context of the patient and the family/carer. Recognising the needs of carers of people with PD at an early stage will help enable patients to be maintained at home for as long as possible. Many will have been in the role of carer for a significant number of years and have become ‘experts’ in PD themselves. Realistic goals need to be agreed jointly by the patient/family and the multidisciplinary team caring for the patient. Respite periods, both for short and longer periods and to meet planned and emergency needs, are particularly important. It may be useful to refer to a carer care pathway to recognise some of the problems carers may experience. When looking at specific information and support for carers the Parkinson’s disease Society provides useful information sheets for Carers.\(^{377,378}\)

**Care homes**

11.11 Whilst the majority of people with PD will cope at home for many years, increasing dependency in the palliative stage when the care needs exceed the ability of their family or community to cope, will frequently lead to admission into care home settings. This may be due to increased disability or the result of a combination of disability and social factors when the burden of caring becomes too great. In particular PD studies suggest\(^ {379,380}\) that care home admission is often provoked by hallucinations. Admission of patients into care homes carries with it a greater mortality.\(^ {379,380}\) These trials found that all PD patients admitted into care homes died within 2 years of admission. PD may affect 5-10% of nursing home residents.\(^ {381}\)

**Social costs**

11.12 Social services will play an increasingly greater role in palliative care stages; in particular to address issues that may arise from increased disability and dependency. Results from a study\(^ {10}\) looking into the economic impact of PD showed that:

- Total Social Services costs accounted for 34% of total costs and tended to increase with increasing age
- Total NHS costs accounted for 38% of total costs and tended to fall with increasing age
- Total annual direct costs were £4,189 for patients living at home; £15,355 for patients whose time was divided between home and an institution; and £19,338 for patients in full-time institutional care
11.13 Wherever the patient resides their condition should be monitored to ensure comfort and quality of life is maintained. However it may be difficult to assess their needs in a hospital outpatient environment. Day hospital attendance may be easier or a Parkinson’s disease nurse specialist or other key worker visiting at home. Visiting in the home environment is less stressful for the patient, carer and care staff and allows time for more detailed discussion, advice, education and counselling.

**Withdrawal of drugs**

11.14 In later stages of PD there may be the need to withdraw dopaminergic drugs due to lack of drug efficacy and increasing sensitivity to unwanted effects such as hallucinations. As a general guide, medication withdrawal should be managed with help from the specialist clinician and PD nurse specialist. Where possible drug withdrawal should be gradual in order to achieve the best balance between relief of symptoms and minimal side effects. Patients and carers at this stage will often agree to reduce medications, exchanging greater levels of physical disability for increased mental clarity. This situation should however be reviewed on an ongoing basis as frequent adjustments may be required to maintain this balance.

**Pressure ulcers**

11.15 Immobility in the palliative care phase of PD places individuals at risk of pressure ulcer development and an assessment of risk for pressure ulcers should be a priority. Most pressure ulcers occur over a bony prominence but if contractures of the limbs have developed with immobility and the altered body shape of PD this may result in pressure sores appearing in more unusual locations.

11.16 Carers will require support and education in understanding how to move and handle patients safely.

- NICE documents:
  - Pressure Reliving Devices Guidelines\textsuperscript{382}
  - Pressure ulcer risk assessment and prevention Guidelines\textsuperscript{383}
- Royal College of Nursing (RCN) documents:
  - Clinical practice guidelines on Pressure ulcer risk assessment and prevention: implementation guide and audit protocol. \textsuperscript{384}

**End of Life Issues**
11.17 In July 2004 the Department of Health (England) started an initiative so that all adult patients, nearing the end of life, but irrespective of diagnosis, will have access to high quality specialist palliative care. The focus was to train and equip health care professional with the knowledge and skills to support patients to live and die in the place of their choice. Three key documents make up the basis of this “End of Life Initiative”:

- Preferred Place of Care Plan
- Gold Standards Framework
- Liverpool Care of the Dying Pathway

Increasingly, initiatives such as these have resulted in District General Hospitals, Primary Care and Care Homes achieving:

- Greater choice for patients in where they wish to live and die
- Decreased emergency admissions of patients who wish to die at home
- Decreased number of older people transferred from a care home to a DGH in the last week of life.

11.18 What are the end-of-life palliative care needs of PD patients and what treatments are available?

Methodology

11.19 No trials were found which addressed end-of-life palliative care needs of PD patients and what treatments are available.

Evidence to recommendation

11.20 The needs of patients in the palliative care stage of PD are often under recognised and considered too late in their care. Better understanding of the complexity of the manifestations of the disease, its innate variability, the roles of the extended team members, which may or may not include the palliative care team, can help to improve care and reduce distress. Care needs to be supported by good care planning since many problems can be predicted or avoided with appropriate strategies.

Recommendations

11.21 **R55** Palliative care requirements of people with PD must to be considered in all phases of the disease. **Grade D (GPP)**

11.22 **R56** People with PD and carers should be given the opportunity to discuss end of life issues with appropriate health professionals. **Grade D (GPP)**
Ethical issues

11.23 Patients and their families need to be allowed to have time to come to terms with the fact that the disease has reached a stage where no more can be done. Decisions may need to be made about management and treatment in the future and end of life decisions i.e. do not resuscitate policies (DNR) and Advanced Directives (Living Wills). These are never easy issues to discuss but they can provide an opportunity for the person with PD to state treatment preferences should they lose their capacity for decision making in the future. They derive their authority from the principle of informed consent and the promotion of personal autonomy and should be considered before mental or physical disability precludes its completion.

11.24 Additional information that may be of help includes: The British Geriatrics Society Compendium Advanced Directives section www.bgs.org.uk, or the BMA www.bma.org.uk

Figure 11.2 Three Essential Components of Palliative. Adapted from388
12. Research recommendations

Future research Recommendations

The Clinical Importance of Dementia in PD

12.1 The GDG recognise the clinical importance of dementia research in the field of Parkinson's disease and other patient groups suffering from dementia. The GDG have compiled a list below of 5 key future research questions but would like to highlight here the importance of dementia research in neurological disorders such as PD.

12.2 Cross-sectional studies report a prevalence of dementia in PD of 30-40%\textsuperscript{389}, although recent longitudinal data suggest a cumulative incidence as high as 80%\textsuperscript{300}. The guideline development group consider that the cholinesterase inhibitors are clinically effective for the treatment of cognitive impairment and/or psychotic symptoms arising from dementia in people with PD. A recommendation on their use will be made in the second consultation draft of this guideline following an analysis of their cost effectiveness. This additional work is being undertaken at the request of the National Institute for Health and Clinical Excellence. The role of cholinesterase inhibitors, memantine, and other putative cognition-enhancing compounds in the management of Parkinson's Disease Dementia (PDD) would benefit from further studies. Research to develop appropriate measurement scales, identify appropriate starting and stopping rules for treatment and responsive patient subgroups, for example, is of high priority. The newly established UK Clinical Research Network for Dementias and Neurodegenerative Disease, through an admixture of expertise in Local Research Networks, would be ideally placed to fulfil these and other research objectives for PDD.

Selected Top Five Research Recommendations

12.3 Question 1: Development of neuroprotective (disease-modifying) therapies for Parkinson's disease
Exhibit 6D

At present there is no agent which will slow down the progression of Parkinson's disease. Patients want such a 'cure' for their condition. The NHS requires neuroprotectants to reduce the burden of disability caused by Parkinson's disease, thereby reducing the direct and indirect costs of caring for an increasing number of people with the condition.

Whilst the pharmaceutical industry is trying to develop new putative neuroprotectants, 12 existing agents have been identified which may slow Parkinson's disease progression (Exhibit 6D). A systematic trial programme examining these agents is ongoing in North America (NetPD) funded by the NIH and the Michael J Fox Foundation. They are screening agents in small ‘futility studies’ using historical control data for decline in total UPDRS scores. Agents which delay progression by more than a 30% will go through to larger definitive studies.

The first futility study showed that both minocycline and GPI 1485 significantly delay decline in total UPDRS by more than 30% (K Kieburztz, personal communication). However, a small placebo comparator group also showed a similar effect raising doubts about the use of historical controls.
Future NetPD trials may use patients already established on symptomatic therapies. There are many more such patients than those who are untreated thereby allowing future neuroprotection trials to be much larger.

The recent rasagiline delayed start design trial versus placebo (Chapter 6, 6.44) raised the possibility that this may be a useful trial design to examine neuroprotection. Further pharmaceutical industry trials using this design are planned. This would be another option for UK neuroprotection trials.

UK investigators have recently carried out neurorestoration trials with intraputaminal infusion of GDNF, although these have now been stopped. Support for further surgical approaches to neuroprotection in Parkinson's disease should be considered.

12.4 Question 2: Is treating mild to moderate depression in Parkinson's disease with an antidepressant cost effective?

<table>
<thead>
<tr>
<th>Population</th>
<th>People with any stage of Parkinson's disease with mild to moderate depression according to a depression rating scale. Patients with severe depression will be excluded as treatment is mandatory. Any sex, age, ethnic group. Trials performed in secondary care.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Intervention</td>
<td>Any SSRI class of antidepressant.</td>
</tr>
<tr>
<td>Outcomes</td>
<td>Quality of life rated by disease specific (PDQ39) and generic (SF36; EuroQol) measures. Health economics. Depression scores on accepted depression rating scale.</td>
</tr>
</tbody>
</table>

Explanatory paragraph

Cross sectional studies have shown that depression affects around 40% of patients with Parkinson's disease and has a major impact on quality of life. In most cases depression is mild to moderate in severity and is often missed by the clinician caring for the patient.

This study will screen secondary care Parkinson's disease clinic populations for mild to moderate depression. This will then be treated with any SSRI class antidepressant or no such treatment in an open label fashion. This will be a large scale pragmatic trial.

If screening for and treating mild to moderate depression is cost effective, this will add to the evidence base for the management of depression in Parkinson's disease and will significantly change the next update of this guideline.

12.5 Question 3: Are physiotherapy and occupational therapy in Parkinson's disease cost effective?
The evidence to support the use of physiotherapy and occupational therapy in Parkinson's disease is poor and yet patients feel they are effective. Many patients are referred for such therapies in the NHS with little idea of their value and whether they have any long term benefits. In contrast, many other patients cannot access such therapy due to poor provision of service. This pragmatic trial will be performed in units which already have access to physiotherapy and occupational therapy services. This is likely to be in the elderly care setting since neurologists have poor access to such treatments. An NHS subvention will be required to ensure adequate therapy resources are available for the trial.

Many prevalent cases of Parkinson's disease will have already received such therapies, so the trial will recruit incident cases with new balance problems. This will require a long recruitment period, a large number of centres or both. If one or both therapies are cost effective then the provision of service needs to be increased. If one or other therapies is not cost effective, then services can be diverted to other conditions. Future trials will then need to examine what components of each therapy are effective and whether they are effective in the earlier stages of the disease.

12.6 Question 4: Is NHS speech and language therapy in Parkinson's disease cost effective?
The evidence to support the use of speech and language therapy in Parkinson's disease is poor and yet patients feel that it is effective. The provision of this service in the NHS is patchy with some patients not receiving speech and language therapy when it may be appropriate.

The trial must be preceded by survey work to identify current and best practice speech and language therapy for Parkinson's disease in the UK. Similar work has already been performed for physiotherapy and occupational therapy to prepare for analogous trials.

In this pragmatic trial, standard NHS speech and language therapy will be compared with no treatment. Whilst most Parkinson's disease units will have access to some speech and language therapy service, this may be insufficient for trial purposes so an NHS subvention will be required.

If therapies are cost effective then the provision of service needs to be increased. If speech and language therapy is cost effective, then the provision of service needs to be increased. If it is not cost effective, then services can be diverted to other conditions.

12.7 Question 5: Development of diagnostic investigations for Parkinson's disease and biomarkers to measure its progression.
Explanatory paragraph

The diagnosis of Parkinson's disease remains clinical, $^{123}$I-FP-CIT SPECT may be of additional help in a small proportion of clinically uncertain cases. The diagnostic error rate on presentation may be as high as 10% in expert hands which may lead to inappropriate therapy and distress following revision of the diagnosis.

A systematic approach led by university researchers and funded by Government would expedite the evaluation of existing and new diagnostic techniques.

The considerable debate surrounding biomarkers to measure the progression of Parkinson's disease has highlighted the need for further studies in this area. More work on existing techniques (e.g. SPECT and PET) is required and new potential markers (e.g. onset of falls) are an urgent requirement.

General research recommendations

12.8 The GDG recognises that there are many areas of ongoing research activity in the diagnosis, treatment and management of PD. The following were agreed as broad areas for future research development.

Methodology

12.9 There were methodological limitations in many of the studies reviewed in the guideline. The GDG agreed that there was a need to make some general recommendations on the design of future research trials in PD.
12.10 The following issues should be considered in future trial design:
- Performing sample size calculations before the study to ensure large enough numbers of patients are included to prevent false negative conclusions
- Using UK Brain Bank Diagnostic Criteria to ensure all trial participants have idiopathic PD
- Trials should attempt to include a more representative spectrum of patients with PD, particularly the elderly and those with co-morbidity
- Outcome measures should include patient-rated quality of life instruments and health economics evaluations
- Following patients for prolonged periods
- Performing an intention-to-treat analysis of the data from all randomised participants
- Reporting of the results to CONSORT standards

Diagnosis

12.11 In the development of diagnostic tests for PD in the future, study designs must be improved to include:
- Blinding of investigators
- Assessment of established cases then assessment of newly diagnosed cases with prospective follow-up
- Reporting of appropriate statistics (including sensitivity, specificity, positive and negative predictive values)

12.12 More research is needed in the use of MRI, magnetic resonance volumetry, MRS, PET, MIBZ-SPECT, IBZM-SPECT, transcranial ultrasound and smell testing as diagnostic tools to accurately differentiate PD from controls, those with essential tremor and those with other parkinsonian conditions before further conclusions can be reached regarding their value.

12.13 Many of these investigations are expensive with limited availability. It would be particularly useful to develop inexpensive tests for PD based on serum or CSF biomarkers or more sophisticated bedside tests e.g. olfaction, eye movements, neuropsychological testing and detailed movement analysis.

12.14 Studies should be done to examine the possibility of combining two or more diagnostic tests to improve accuracy. This is particularly applicable to less expensive investigations. In addition, studies should also compare promising diagnostic tests directly (e.g. SPECT scanning with objective smell identification).

Neuroprotection
12.15 Careful consideration must be given to the design of neuroprotection trials in PD in the future to avoid the mistakes of the past.

12.16 A systematic approach to the development of neuroprotection trials in PD should be adopted in England and Wales along the lines of, and possibly in collaboration with, the National Institute of Neurologic Disorders and Stroke (NINDS) in the United States. From a societal perspective, it would be more cost effective to slow or halt the progression of PD than to continue to treat it symptomatically.

12.17 The UK has recently led neurorestoration trials using intra-putaminal GDNF infusions in PD. Support for similar trials in the future will be imperative.

12.18 Methods to improve neuroprotection trial design include:
- Prolonged washout of drug at the end of the trial or do trial in patients not requiring symptomatic medication (i.e. very early disease)
- Future longitudinal clinico-pathological studies are required to evaluate the ultimate diagnosis and prognosis of patients bearing an initial clinical diagnosis of PD who are found to have normal SPECT and/or PET images
- Misdiagnosis must be taken into account when sample size calculations are performed
- Larger and longer studies may be able to show more clinically meaningful effects
- Better standardisation of imaging methodology with blind evaluation of results
- Repeated imaging after dose titration and after drug withdrawal at end of trial
- If the predicted therapeutic effect is mild or slight- trials need to be much larger (i.e. 1000s of patients)
- Roll on large explanatory trials in early disease into pragmatic long-term trials reflecting real-life practice with quality of life and health economics outcomes.

**Symptomatic therapy**

12.19 Future clinical trials examining the effectiveness of symptomatic therapies in PD should be longer and larger than those in the past to provide more reliable evidence of the long-term effects of treatments. Such trials should use robust clinical criteria for the diagnosis of PD. Results should be reported on an intention-to-treat basis using CONSORT reporting guidelines. Cross over trials should report the results of the first half of the study separately from the overall results and should have a sufficiently long wash out period to prevent carry over effects.
12.20 More data on the comparative efficacy and safety of the most commonly used symptomatic therapies for early PD is required. In particular, we need more information on the relative merits of levodopa, dopamine agonists, amantadine, anticholinergic and MAO-B inhibitors in terms of quality of life and health economics outcomes.

12.21 Clinicians require more data on the comparative efficacy and safety of adjuvant therapies for later PD once levodopa has been commenced and motor complications have developed. There is insufficient information on which to base a decision whether to add a dopamine agonist, a COMT inhibitor or an MAO-B inhibitor.

Non-motor complications

12.22 Depression is common in PD but further work is required to:
- Develop suitable ways to screen for mild depression in clinic populations
- Obtain information on the value of cognitive behavioural therapy
- Obtain more trial data on the efficacy and safety of SSRI and other modern classes of antidepressant in PD
- Further work is needed to evaluate the role of electroconvulsive therapy in drug and CBT refractory depression.

12.23 Further research is required to evaluate treatments for daytime hypersomnolence, constipation, bladder disturbance, autonomic dysfunction, and REM sleep behaviour disorder associated with PD.

12.24 Additional trials should be performed with memory enhancing agents in PD dementia. Trials are needed to compare the effects of atypical antipsychotics with those of memory enhancing agents in PD dementia.

Other key interventions

12.25 Further research is required into the impact of speech and language therapy intervention for people with PD including large well designed trials to investigate:
- Different therapy programmes and their impact on features such as vocal loudness and overall communication competency/ intelligibility
- Trials of different intensities of treatments and their impact on communication over time
- The optimal timing for intervention
- The benefit of using assistive augmentative communication devices for people with PD
- The benefit of speech and language therapy intervention on quality of life such as feelings of social isolation
- The impact of communication difficulties on family and carers and whether this can be reduced with intervention.
12.26 In the development of evidence to support physiotherapy intervention, future research should include large, well-designed trials to investigate:

- The optimal stage in the condition for referral to a physiotherapy practitioner
- The benefit of exercise for people in the different stages of the condition in relation to maintenance of their movement capability and function
- The role of optimising physical to delay the onset and manifestation of disability
- The benefit of physiotherapy in preventing falls in people with PD
- The benefit of physiotherapy in maintaining confidence to move in people with PD
- The benefit of multi- and interdisciplinary intervention (including physiotherapy) in enabling a good quality of life in people with PD and their family and carers.
- Physiotherapy as an adjunct to change in medical and surgical intervention

12.27 Further large well designed trials are required to assess whether occupational therapy can reduce functional difficulties with daily tasks and improve quality of life for people with PD?
Appendix A. National Institute for Clinical Excellence- Scope

Guideline title

Parkinson’s disease: diagnosis, management and treatment of Parkinson’s disease in primary and secondary care.

Background

The National Institute for Clinical Excellence (‘NICE’ or ‘the Institute’) has commissioned the National Collaborating Centre for Chronic Conditions to develop a clinical guideline on Parkinson’s disease (PD) for use in the NHS in England and Wales. This follows referral of the topic by the Department of Health and Welsh Assembly Government (see Appendix). The guideline will provide recommendations for good practice that are based on the best available evidence of clinical and cost effectiveness.

The Institute’s clinical guidelines will support the implementation of National Service Frameworks (NSFs) in those aspects of care where a Framework has been published. The statements in each NSF reflect the evidence that was used at the time the Framework was prepared. The clinical guidelines and technology appraisals published by the Institute after an NSF has been issued will have the effect of updating the Framework.

Clinical need for the guideline

Parkinson’s disease is a progressive neurodegenerative condition leading to death of the dopamine containing cells of the substantia nigra. The “cardinal signs” of the disease are rest tremor, rigidity, and bradykinesia. Postural instability and falls occur later during the course of the condition. Additional common findings are asymmetric onset of symptoms and symptomatic response to L-dopa (levodopa). Although predominantly a movement disorder, cognitive impairments including dementia do occur. All of these problems lead to significant disability and handicap with impaired quality of life for both patients and their carers and increased health care costs.

Parkinson’s disease is one of the commonest neurological conditions. It is estimated to affect up to 160 per 100,000 of the general population with an annual incidence of 15-20 per 100,000. Many population studies have shown the rising prevalence with age (up to 2% of the population aged 80 and over). Around 1 in 7 cases are diagnosed below the age of 60 years.

The costs of treatment have been estimated at between £560,000 and £1.6 million per 100,000 population. Significant cost drivers include the onset of motor fluctuations, psychiatric symptoms, and institutional care. Parkinson’s
disease is a frequent cause of falls, fractures, and hospital admission and is therefore a costly disease, especially in the later stages 10,344,392.

The guideline

The guideline development process is described in detail in three booklets that are available from the NICE website (see ‘Further information’). The Guideline Development Process – Information for Stakeholders describes how organisations can become involved in the development of a guideline.

This document is the scope. It defines exactly what this guideline will (and will not) examine, and what the guideline developers will consider. The scope is based on the referral from the Department of Health and Welsh Assembly Government (see Appendix).

The areas that will be addressed by the guideline are described in the following sections.

Population

Groups that will be covered

- Both sexes over 20yrs of age;
- Diagnoses: Parkinson’s disease and Parkinsonism;
- Treatment: Idiopathic Parkinson’s disease only.

Groups that will not be covered

- Juvenile onset Parkinson’s disease (<20 yrs);
- Pregnant females;
- Treatment: Parkinsonism (a neurological disorder that manifests with bradykinesia, tremor, or muscular rigidity) and other tremulous disorders (e.g. essential tremor) – except for accurate differential diagnosis.

Healthcare setting

Primary, secondary and tertiary NHS care settings.

Areas to be covered

Diagnosis and Monitoring

- Clinical expert diagnosis (using UK brain bank criteria):
- Versus non-expert diagnosis
- Versus post-mortem gold standard
- Other diagnostic tests (e.g. acute levodopa and apomorphine tests, radionuclide imaging: PET and SPECT, magnetic resonance
imaging, magnetic resonance volumetry, magnetic resonance spectroscopy, growth hormone stimulation test)

Communication and Education
- Communication of the diagnosis and patient understanding.
- Patient education (self-help) both specific and generic issues, including falls prevention

Pharmacotherapy
- Prevention of progression - the use of neuro-protective therapy, (e.g. dopamine agonists, monoamine oxidase B inhibitors, amantadine, co-enzyme Q10, vitamins).

Functional disability - treatment of early disease with:
- immediate-release levodopa
- Modified-release levodopa
- Dopamine agonists
- Monoamine oxidase B inhibitors
- Amantadine
- Anticholinergics
- Beta-blockers

Adjuvant pharmacotherapy
- Dopamine agonists
- COMT inhibitors
- Monoamine oxidase B inhibitors
- Amantadine,
- Intermittent apomorphine injections and continuous infusion.
- Treatment of non-motor symptoms (e.g. sleep disturbance)

Non-pharmacological management
- Current surgical options (e.g. deep brain stimulation)
- Physiotherapy
- Speech and language therapy
- Occupational therapy.
- Parkinson’s disease nurse specialists

Neuropsychiatric Conditions
- Psychosis management specific to Parkinson’s disease.
- Depression management specific to Parkinson’s disease
- Dementia management specific to Parkinson’s disease

Palliative Care
- End of life issues specific to Parkinson’s disease

Interventions / management that will not be included.
• Radical therapies that do not form common clinical management will not be addressed: Fetal Cell Transplantation; Stem Cells; Genes that code protein responsible for producing dopamine; Drugs that block the action of glutamate; GDNF; viral transfection.
• Co-morbidities in Parkinson’s disease (except where treatment will differ from treatment of these co-morbidities in patients without Parkinson’s disease).
• Generic health problems where the care for people with Parkinson’s disease does not differ to that of the general population (e.g. constipation)

Audit support within guideline

The guideline will include Level 1 clinical audit criteria.

Further information

• Information on the guideline development process is provided in:
  • The Guideline Development Process – Information for the Public and the NHS
  • The Guideline Development Process – Information for Stakeholders
  • The Guideline Development Process – Information for National Collaborating Centres and Guideline Development Groups
  • These booklets are available as PDF files from the NICE website (www.nice.org.uk). Information on the progress of the guideline will also be available from the website.

Referral from the Department of Health and Welsh Assembly Government

The Department of Health and the Welsh Assembly Government asked the Institute:

(May 2002)

“To prepare clinical guidelines for the NHS in England and Wales for the diagnosis, management and treatment of Parkinson’s Disease in both primary and secondary care settings, including examination of the evidence for the effectiveness of management of the condition by physiotherapy, speech, language and occupational therapies, self-help, drug therapies and surgery”
### Appendix B. Details of questions and literature searches

<table>
<thead>
<tr>
<th>Question ID</th>
<th>Question wording</th>
<th>Study Type</th>
<th>Database and Years</th>
</tr>
</thead>
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<td>** Redone to include differential diagnosis of PD and other.</td>
<td></td>
<td></td>
</tr>
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<td>DIAG8</td>
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<td>Cinahl 1982 – 2005</td>
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<td>MON1</td>
<td>What is the most appropriate frequency of follow-up after the initial diagnosis of Parkinson's disease?</td>
<td>All study types</td>
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<td></td>
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<td>Cinahl 1982 – 2005</td>
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<tr>
<td>COMM1</td>
<td>What approach to patient engagement best aids patient understanding on diagnosis of Parkinson’s disease?</td>
<td>All study types incl. qualitative</td>
<td>Medline 1966 – 2005</td>
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<td></td>
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<td>Is MAO-B vs. placebo or levodopa effective in reducing the rate of progression of early Parkinson’s disease?</td>
<td>Systematic Reviews and RCTs and comparative studies</td>
<td>Medline 1966 – 2005</td>
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<td>Embase 1980 – 2005</td>
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<td>Cinahl 1982 – 2005</td>
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<td>TxNP2</td>
<td>Are dopamine agonists vs. placebo or levodopa effective in reducing the rate of progression of early Parkinson’s disease?</td>
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<td>Embase 1980 – 2005</td>
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<td></td>
<td>Cinahl 1982 – 2005</td>
</tr>
<tr>
<td>TxNP3</td>
<td>Is Co-enzyme Q10 vs. placebo or levodopa effective in reducing the rate of progression of early Parkinson’s disease?</td>
<td>Systematic Reviews and RCTs and comparative studies</td>
<td>Medline 1966 – 2005</td>
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<td>AMED 1985 - 2005</td>
</tr>
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<td>TxNP4</td>
<td>Are specific vitamins vs. placebo or levodopa effective in reducing the rate of progression of early Parkinson’s disease?</td>
<td>Systematic Reviews and RCTs and comparative studies</td>
<td>Medline 1966 – 2005</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Embase 1980 – 2005</td>
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<td></td>
<td>AMED 1985 - 2005</td>
</tr>
<tr>
<td>TxMN1</td>
<td>What is the effectiveness of MAO-B vs. placebo or levodopa in the treatment of early Parkinson’s disease?</td>
<td>Systematic Reviews and RCTs and comparative studies</td>
<td>Medline 1966 – 2005</td>
</tr>
<tr>
<td></td>
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<td></td>
<td>Embase 1980 – 2005</td>
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</tbody>
</table>

NOTE: The final cut-off date for all searches was 28\textsuperscript{th} Feb 2005.
Appendix C. PDS Communication Table

Figure C1: “Communicating with People with Parkinson’s and their Carers’ (2005). (Adapted from Parkinson's Disease Society report26)

<table>
<thead>
<tr>
<th>Principle</th>
<th>Comment</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>General</strong></td>
<td></td>
</tr>
<tr>
<td>Maintain a good knowledge of Parkinson’s disease including the symptoms, co-morbidities, care and treatment</td>
<td>All staff who come into contact with people with Parkinson’s need to have training and updating on the core symptoms, pharmacology and care</td>
</tr>
<tr>
<td>Use clear language and avoid medical jargon when communicating with people with Parkinson’s</td>
<td>Essential</td>
</tr>
<tr>
<td>Check if the person has understood information provided</td>
<td>Essential</td>
</tr>
<tr>
<td>Give the person extra time to respond to questions</td>
<td>Essential</td>
</tr>
<tr>
<td>Ensure information is appropriate, accessible and available in a range of formats</td>
<td>Essential</td>
</tr>
<tr>
<td>Provide an appropriate setting to communicate, e.g. a quiet room without interruptions or distractions</td>
<td>Essential</td>
</tr>
<tr>
<td><strong>Diagnosis</strong></td>
<td></td>
</tr>
<tr>
<td>Communicate the diagnosis in a manner that is sensitive to the needs of the individual, i.e. if the person wants more information, make this available; if they demonstrate shock or bewilderment offer a follow up appointment for further discussion of the symptoms and treatment</td>
<td>Essential</td>
</tr>
<tr>
<td>Allow extensive opportunities for questions and discussion</td>
<td>The consultation time should be sufficient to allow for this.</td>
</tr>
<tr>
<td>Offer a follow up discussion</td>
<td>Essential</td>
</tr>
<tr>
<td>If the consultation reveals a demand for additional specialist information, the person should be referred promptly to the relevant professional, e.g. Parkinson’s nurse, psychiatrist, speech and language therapist, counsellor</td>
<td>Essential</td>
</tr>
<tr>
<td>Offer written information to supplement the diagnosis.</td>
<td>Essential</td>
</tr>
<tr>
<td>This should include details of specialist organisations such as the Parkinson's Disease Society</td>
<td></td>
</tr>
<tr>
<td>Put the person in contact with specialist support e.g. Parkinson's nurse, PDS community support worker. This should encompass multi-disciplinary support (speech and language therapy, neurologist, Parkinson’s Nurse specialist, social workers)</td>
<td>Essential</td>
</tr>
<tr>
<td>---</td>
<td>---</td>
</tr>
<tr>
<td>Provide information for carers</td>
<td>Important but not in all circumstances – the needs of the patient should come first.</td>
</tr>
<tr>
<td>Maintenance</td>
<td>The PDS recommends that all people with Parkinson’s should have access to a PDNS</td>
</tr>
<tr>
<td>Provide the person with a point of contact for further information.</td>
<td></td>
</tr>
<tr>
<td>Ensure the person has relevant and current information about the condition and treatment specific to their needs and stage of the condition. Provide them with information about all their options, e.g. medications, home care, therapy</td>
<td>Essential. Frequency of reviews varies according to the individual but is optimally 6 months. Consultation can take place additionally and in the interim via telephone and email contact.</td>
</tr>
<tr>
<td>Consult the person regularly about their physical and emotional needs and financial needs.</td>
<td>Essential</td>
</tr>
<tr>
<td>Consult the carer about the physical and emotional needs of the person they are caring for, and their own support needs.</td>
<td>Essential</td>
</tr>
<tr>
<td>If/when the person goes into hospital, ask them whether they are self medicating, and if so, facilitate this with access to their drugs at the times prescribed for them</td>
<td>Essential</td>
</tr>
<tr>
<td>Offer the person access to self-management resources e.g. the Expert Patient Programme if appropriate.</td>
<td>Essential</td>
</tr>
<tr>
<td>Advanced Stage Care</td>
<td>These should be available in a variety of formats, such as print, audio and/or video</td>
</tr>
<tr>
<td>Ensure that people and carers receive regular information about the condition, the medications, the financial support and the support networks.</td>
<td></td>
</tr>
<tr>
<td>Ensure that staff are aware of the complexities of this stage of the disease and care for their holistic needs and those of their carers including emotional, spiritual and psychological needs.</td>
<td>Essential</td>
</tr>
</tbody>
</table>
Appendix D: NICE Falls Quick Reference Guide

NICE Quick Reference Guide on: the assessment and prevention of falls in older people

Key Priorities for Implementation

Case/risk identification

- Older people in contact with healthcare professionals should be asked routinely whether they have fallen in the past year and asked about the frequency, context and characteristics of the fall.
- Older people reporting a fall or considered at risk of falling should be observed for balance and gait deficits and considered for their ability to benefit from interventions to improve strength and balance. (Tests of balance and gait commonly used in the UK are detailed in the full guideline.)

Multifactorial falls risk assessment

- Older people who present for medical attention because of a fall, or report recurrent falls in the past year, or demonstrate abnormalities of gait and/or balance should be offered a multifactorial falls risk assessment. This assessment should be performed by healthcare professionals with appropriate skills and experience, normally in the setting of a specialist falls service. This assessment should be part of an individualized, multifactorial intervention.

Multifactorial assessment may include the following:

- Identification of falls history
- Assessment of gait, balance and mobility, and muscle weakness
- Assessment of osteoporosis risk
- Assessment of the older person’s perceived functional ability and fear relating to falling
- Assessment of visual impairment
- Assessment of cognitive impairment and neurological examination
- Assessment of urinary incontinence
- Assessment of home hazards
- Cardiovascular examination and medication review.

Multifactorial interventions

- All older people with recurrent falls or assessed as being at increased risk of falling should be considered for an individualised multifactorial intervention.
- In successful multifactorial intervention programmes the following specific components are common (against a background of the general diagnosis and management of causes and recognised risk factors):
  - Strength and balance training
  - Home hazard assessment and intervention
  - Vision assessment and referral
  - Medication review with modification/withdrawal.
- Following treatment for an injurious fall, older people should be offered a multidisciplinary assessment to identify and address future risk, and individualised intervention aimed at promoting independence and improving physical and psychological function.
- Encouraging the participation of older people in falls prevention programmes including education and information giving
- Individuals at risk of falling, and their carers, should be offered information orally and in writing about what measures they can take to prevent further falls.

Professional education

- All healthcare professionals dealing with patients known to be at risk of falling should develop and maintain basic professional competence in falls assessment and prevention.
Appendix E. Economic Modelling- SPECT

Background

13.1 The GDG considered the evidence for the diagnostic accuracy of clinical examination and concluded that the diagnosis of Parkinson’s disease (PD) can be wrong in up to 10% of cases even in the best hands. Differentiating essential tremor (ET) from idiopathic Parkinson’s disease (IPD) can be particularly difficult, especially in the elderly.

13.2 In the past when ET could not be differentiated from IPD clinically, the patient was followed for several years in clinic, on or off levodopa therapy. In time, the diagnosis became clear from the nature of the patients evolving clinical signs. However, some patients were not adequately treated during this period and may have suffered as a result. Now, many clinicians in PD clinics have SPECT available and are using this to accurately diagnose such cases sooner, allowing patients to go on appropriate treatment much earlier. The benefit would be seen in improvements in patient’s quality of life from more effective early treatment and the removal of the stress of diagnostic uncertainty. Recent work has suggested that quality of life falls rapidly in early PD before treatment is initiated [PD LIFE study, unpublished but presented].

13.3 Those with experience of SPECT estimate that they are scanning 20% of their new cases. However, this will include the backlog of prevalent cases in which a clear diagnosis could not be reached in the past. The number of incident cases may be much smaller, probably less than 10% [GDG].

13.4 A literature search was performed and only one study met quality criteria that addressed the economic evaluation of Single Photon Emission computed Tomography (SPECT) using the $^{123}$I-FP-CIT tracer licensed for use in the UK. The economic results are presented along with the clinical evidence of SPECT. However, due to the subjectivity of the effectiveness measurement in the study, the GDG decided the economic study does not support nor is against the clinical recommendations. The GDG considered the topic valuable for further consideration in this guideline.

Aim

13.5 The aim was to compare the costs and effectiveness of using SPECT to differentiate suspected parkinsonism (i.e. PD, MSA or PSP) from essential tremor in a specialised centre at initial examination. The cost per true positive case diagnosed and cost per true negative case diagnosed in the UK context was calculated.

Methods
13.6 A cost effectiveness analysis was performed from the perspective of the NHS. The effectiveness outcome measures used were i) the difference in true positives diagnosed in SPECT compared to clinical examination and ii) the difference in true negatives diagnosed in SPECT compared to clinical examination. One-way sensitivity analyses were run to assess the impact of variables on the incremental cost-effectiveness ratio (ICER).

13.7 Incremental cost per effectiveness = \( \frac{(C_1 - C_2)}{(E_1 - E_2)} \)

**WHERE**
- \( C_1 = \) ESTIMATED COST OF SPECT
- \( C_2 = \) ESTIMATED COST OF CLINICAL EXAMINATION
- \( E_1 = \) ESTIMATED TRUE POSITIVE CASES DIAGNOSED (TRUE NEGATIVE CASES DIAGNOSED) WITH SPECT
- \( E_2 = \) Estimated true positive cases diagnosed (true negative cases diagnosed) with clinical examination

**Data sources and assumptions**

13.8 Tables 1-4 list the base-line cost and effectiveness values used to compute the incremental cost-effectiveness ratios.

**Table 1. Costs**

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<thead>
<tr>
<th>Item</th>
<th>Cost (£)</th>
<th>Source</th>
</tr>
</thead>
<tbody>
<tr>
<td>Clinical examination by medical consultant lasting 30 minutes</td>
<td>57</td>
<td>[Unit costs of Health and Social Care 2004]</td>
</tr>
<tr>
<td>SPECT</td>
<td>909 (57 + 852)</td>
<td>[NHS Reference Costs 2003 and National Tariff 2004]</td>
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</table>

13.9 It was estimated that a standard clinical examination for new movement disorder patients would take approximately 30 minutes [GDG]. Estimate was based on the unit cost (£114) per patient-related hour for a medical consultant with qualifications (A to F). This analysis does not include additional clinical examinations.

13.10 The inter-quartile range of unit costs of Band L-Radionuclide [Isotope] tests in the NHS Reference Costs 2003 is £295.97 to £980.25. The national average unit cost was £852 and used as the estimate of cost of SPECT. The cost of clinical examination is included in the total cost of SPECT as the examination would need to take place in order to decide diagnosis by clinical examination is unclear and therefore would not be saved by the SPECT strategy.

**Table 2. Clinical parameters**

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Value</th>
<th>Source</th>
<th>Comment</th>
</tr>
</thead>
</table>

Parkinson’s disease: full guideline DRAFT (August 2005)
Frequency of PD in clinic population 70%\[19818\] Estimated from 37 patients with suspected Parkinsonian Syndrome referred to study, 2 excluded due to scan artefact and loss to follow-up, 25 positive cases and 10 negative cases found via Gold Standard diagnosis

| Sensitivity of Exam | 93% \[19898\] Diagnosis by blinded movement disorder expert |
| Specificity of Exam | 70% \[19898\] Diagnosis by blinded movement disorder expert |
| Sensitivity of SPECT | 92% \[19898\] ($^{123}$I) β-CIT and SPECT imaging |
| Specificity of SPECT | 100% \[19898\] ($^{123}$I) β-CIT and SPECT imaging |

Table 3. Accuracy of Clinical Diagnosis based on N=1,000

<table>
<thead>
<tr>
<th>Clinical Exam</th>
<th>True</th>
<th>False</th>
</tr>
</thead>
<tbody>
<tr>
<td>Positive</td>
<td>616</td>
<td>90</td>
</tr>
<tr>
<td>Negative</td>
<td>210</td>
<td>84</td>
</tr>
</tbody>
</table>

Table 4. Accuracy of SPECT based on N=1,000

<table>
<thead>
<tr>
<th>SPECT</th>
<th>True</th>
<th>False</th>
</tr>
</thead>
<tbody>
<tr>
<td>Positive</td>
<td>644</td>
<td>0</td>
</tr>
<tr>
<td>Negative</td>
<td>300</td>
<td>56</td>
</tr>
</tbody>
</table>

Results

13.11 The results using the base-line estimates are displayed in Table 5-6.

Table 5. Incremental Analysis of True Positives

<table>
<thead>
<tr>
<th>Effect (true positives)</th>
<th>Cost (£)</th>
<th>ICER (£ per true positive)</th>
<th>TRUE</th>
</tr>
</thead>
<tbody>
<tr>
<td>Clinical exam</td>
<td>616</td>
<td>57,000</td>
<td></td>
</tr>
<tr>
<td>SPECT</td>
<td>644</td>
<td>909,000</td>
<td></td>
</tr>
<tr>
<td>Difference</td>
<td>28</td>
<td>852,000</td>
<td>30,429</td>
</tr>
</tbody>
</table>

Table 6. Incremental Analysis of True Negatives

<table>
<thead>
<tr>
<th>Effect (true negatives)</th>
<th>Cost (£)</th>
<th>ICER (£ per true negative)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Clinical</td>
<td>210</td>
<td>57,000</td>
</tr>
<tr>
<td>SPECT</td>
<td>300</td>
<td>909,000</td>
</tr>
<tr>
<td>Difference</td>
<td>90</td>
<td>852,000</td>
</tr>
</tbody>
</table>
Sensitivity analysis

13.12 The estimates used in the model are subject to uncertainty. Therefore, a one-way sensitivity analysis was carried out to assess the impact of each of the three key variables used the model. A one-way sensitivity analysis varies one parameter while maintaining the other parameters at base-line values. The seven variables varied were i) frequency of PD in clinic population ii) cost of SPECT iii) cost of clinical exam iv) sensitivity of SPECT v) specificity of SPECT vi) sensitivity of clinical exam and vii) specificity of clinical exam. Results for the upper and lower estimates are given in Table 7. The ranges evaluated for the frequency of PD in clinic population are based on reasonable estimates in movement disorder centres. The range of the cost of SPECT was the higher (£296) and lower (£980) inter-quartile range of unit costs of Band L-Radionuclide [Isotope] tests in the NHS Reference Costs 2003 plus the cost of clinical examination (£57). The lower range of cost of clinical examination was based on a 20 minute examination and the upper range was based on a 40 minute examination. The sensitivity and specificity ranges were estimated at ± 5%.

Table 7. One-way sensitivity analysis

<table>
<thead>
<tr>
<th>Variable</th>
<th>Base-line value</th>
<th>Lower Range</th>
<th>Higher Range</th>
<th>ICER lower range estimate</th>
<th>ICER higher range estimate</th>
</tr>
</thead>
<tbody>
<tr>
<td>Frequency of PD in clinic population</td>
<td>.70</td>
<td>.40</td>
<td>.90</td>
<td>53,250</td>
<td>23,667</td>
</tr>
<tr>
<td>Cost of SPECT</td>
<td>909</td>
<td>£353</td>
<td>£1,037</td>
<td>10,571</td>
<td>35,000</td>
</tr>
<tr>
<td>Cost of clinical exam</td>
<td>57</td>
<td>£38</td>
<td>£76</td>
<td>30,429</td>
<td>30,429</td>
</tr>
<tr>
<td>Sensitivity of SPECT</td>
<td>92%</td>
<td>87%</td>
<td>97%</td>
<td>Dominated by clinical exam</td>
<td>13,524</td>
</tr>
<tr>
<td>Specificity of SPECT</td>
<td>100%</td>
<td>95%</td>
<td>-</td>
<td>30,429</td>
<td>-</td>
</tr>
<tr>
<td>Sensitivity of clinical exam</td>
<td>93%</td>
<td>83%</td>
<td>93%</td>
<td>13,524</td>
<td>Dominated by clinical exam</td>
</tr>
<tr>
<td>Specificity of clinical exam</td>
<td>70%</td>
<td>65%</td>
<td>75%</td>
<td>30,429</td>
<td>30,429</td>
</tr>
</tbody>
</table>

Parkinson's disease: full guideline DRAFT (August 2005)
13.13 The unclear cases in initial diagnosis may have a greater difference in specificity and sensitivity in comparison to SPECT. Therefore relative differences of 10% to 50% were additionally assessed (Table 8.). There is a clear decrease in cost per outcome as the difference in sensitivity and specificity in favour of SPECT increases.

**Table 8. Difference in Specificity and Sensitivity in Unclear Cases**

<table>
<thead>
<tr>
<th>Difference in Sensitivity/Specificity</th>
<th>Cost per true positive case diagnosed</th>
<th>Cost per true negative case diagnosed</th>
</tr>
</thead>
<tbody>
<tr>
<td>10%</td>
<td>£12,171</td>
<td>£28,400</td>
</tr>
<tr>
<td>20%</td>
<td>£6,086</td>
<td>£14,200</td>
</tr>
<tr>
<td>30%</td>
<td>£4,057</td>
<td>£9,467</td>
</tr>
<tr>
<td>40%</td>
<td>£3,043</td>
<td>£7,100</td>
</tr>
<tr>
<td>50%</td>
<td>£2,434</td>
<td>£5,680</td>
</tr>
</tbody>
</table>

**Discussion**

13.14 Using base-line estimates, it costs approximately £30,429 per true positive case diagnosed by SPECT in comparison to initial clinical examination. Alternatively, using true negatives as the outcome, it costs £9,467 per true negative case diagnosed. The sensitivity and specificity of clinical examination in unclear cases may vary. When the difference in sensitivity ranges from 10-50%, the cost per true positive case ranges from £12,171 to £2,434. When the difference in specificity ranges from 10-50%, the cost per true negative case ranges from £28,400 to £5,680.

13.15 Identifying additional true negatives has the benefit of avoiding the costs of treating individuals who do not suffer from PD and avoiding reduced quality of life of the individual over the uncertain diagnostic period. The cost per true positive case is higher than the cost per true negative case due to the closer relative sensitivities than specificities. However, identifying a true positive case at initial diagnosis means the individual can receive treatment and diagnosis earlier and is avoided a length of time of uncertainty in clinical diagnosis. From clinical experience, the GDG felt the length of uncertainty may range between 6-24 months with an average of just less than 12 months between the onset of PD symptoms and final diagnosis.

13.16 The higher the frequency of PD in the clinic population, the lower the cost per true positive case diagnosed but the higher the cost per true negative cost diagnosed. This may be attributed to the increased number of true positives at the same costs and reduced number of true negative cases in the population. Therefore, the ICERs will differ between centres with different frequencies of PD.
13.17 When the cost of SPECT is varied, the results ranged from £10,571 to £35,000 for the cost per true positive and £3,289 to £10,889 for the cost per true negative (vs. 30,429 and 9,467 base-line). This suggests the cost base-line estimate is at the higher end of potential outcomes.

13.18 Varying the cost of clinical exam does not have an effect on the ICERs. This is due to the inclusion of the cost of the clinical exam with SPECT. The incremental cost of SPECT is derived from the cost of clinical exam plus the unit cost of SPECT minus the cost of clinical exam. This will always equal the unit cost of SPECT for any cost of the clinical exam.

13.19 Varying the sensitivity will only impact the cost per true positive case diagnosed. The model is sensitive to a decrease in sensitivity of SPECT of 5% (same as an increase in sensitivity of clinical exam of 5%). When the sensitivity of SPECT is equal to or less than the sensitivity of clinical examination (the same as when the sensitivity of clinical examination is equal to or greater), SPECT does not gain additional benefits for a higher cost and would therefore not be a practical strategy. Similarly, varying the specificity will only impact the cost per true negative case diagnosed. When the specificity of clinical examination is varied to 65% (70%, £9,467 base-line) the cost per true negative case diagnosed is £8,114 and varied to 75% (same as reducing the specificity of SPECT by 5%) it is £11,360. This again suggests the strength of the SPECT strategy is its relative greater specificity to clinical examination and the ability to diagnose more true negatives initially. Furthermore, as the relative sensitivity of SPECT to clinical examination increases, the cost per true positive case diagnosed decreases. This is also true of the relative specificity of SPECT and cost per true negative case diagnosed. However, in the number of unclear cases in clinical examination, the relative sensitivity and specificity of SPECT is likely to be high.

13.20 While the costs and consequences of false positives and false negatives are not included in the cost per outcomes measures of this analysis, the base-line amounts are lower by SPECT than by clinical examination (Table 3, 4).

13.21 In the UK, the number of new patients with suspected PD presenting to clinicians is not known, but there are around 8,000 new cases of PD each year in the UK [GDG]. Essential tremor is approximately 10 times more common than PD [GDG]. Therefore, there may also be unclear cases of essential tremor that would increase, possibly double, the number of cases presenting with unclear PD or ET. Those with experience of SPECT estimate that they are scanning 20% of their new cases [GDG]. However, this will include the backlog of prevalent cases in which a clear diagnosis could not be reached in the past. The number of incident cases may be much smaller, probably less than 10%. Therefore, assuming a range of 10-20%, approximately 16,000 to 3,200 scans would be required per year. However, the cost per true case diagnosed would not change with the number of scans.
Conclusion

13.22 Using base-line estimates, it costs approximately £30,429 per true positive case diagnosed by SPECT in comparison to initial clinical examination. Alternatively, using true negatives as the outcome, it costs £9,467 per true negative case diagnosed. SPECT produces the benefit of avoiding the costs of treating individuals who do not suffer from PD, allowing earlier diagnosis and preventing treatment delays in those with PD and avoiding reduced quality of life of the individual over the uncertain diagnostic period. The outcome of the analysis is not in terms of cost per QALY and the cost-effectiveness is open to interpretation.

13.23 A variety of assumptions, such as restricting the costs and benefits of SPECT to true positive and true negative cases only, have been used in the base-line analysis and therefore the results should be interpreted correspondingly. Further investigation of the cost-effectiveness of SPECT is needed to quantify all the costs and benefits of this technology, including considerations of follow-up during uncertainty in clinical examinations and quality of life outcomes.
Appendix F. Economic Modelling- Dopamine Agonists

Background

13.24 Levodopa remains the mainstay of treatment for PD but with long-term use it causes abnormal involuntary movements (dyskinesias) and fluctuations in motor performance (end-of-dose deterioration and unpredictable ‘on’/’off’ fluctuations). To avoid these motor complications, oral dopamine agonists have been used to treat early PD on their own (i.e. monotherapy).

13.25 However, dopamine agonists cost in the region of three times as much as levodopa per year [GDG]. The incremental cost-effectiveness of this approach has not been considered in the UK. The large pragmatic PD MED trial will examine the cost effectiveness of these two approaches in the management of early PD but will not report for several years.

Aim

13.26 The aim of the model was to perform a cost-minimisation analysis based on the assumption of equivalent effectiveness of dopamine agonist vs. levodopa therapy in early PD over a 1-year time horizon.

Methods

13.27 A cost-minimisation model was constructed from the perspective of the NHS. The effectiveness outcome measure used quality of life. The data sources of the costs and benefits are described in further detail in Tables 1-2. No discount rate was used over a 1-year time horizon in accordance with standard practice. A one-way sensitivity analysis was run to assess the impact of variables on the incremental cost of dopamine agonists.

13.28 Incremental cost = (C₁ – C₂)

WHERE:

C₁ = ESTIMATED COST OF DOPAMINE AGONIST TREATMENT
C₂ = ESTIMATED COST OF LEVODOPA TREATMENT

Data Sources and Assumptions

13.29 Tables 1-2 list the baseline cost parameters along with the sources of data. Assumptions and methods of calculating estimates are described in further detail below.

Costs

13.30 One study suggests medication costs over a two-year period is the only cost category in which there was a statistically significant difference by treatment group (mean difference = $1,870, P<0.0001)\textsuperscript{157}. The other cost categories assessed included acute hospitalizations, outpatient
provider visits, diagnostic procedures, test and surgeries, emergency department visits, nursing home care, rehabilitation hospital care, durable medical devices, lost wages and home health aid service. Therefore, it was assumed all other cost factors were similar between the alternatives and only the cost of medications were used to compute the incremental costs of dopamine agonist over the levodopa strategy.

Table 1. Mean Total Daily Dosage

<table>
<thead>
<tr>
<th>Source</th>
<th>Levodopa group (n=150)</th>
<th>Dopamine Agonist group (n=151)</th>
<th>Source</th>
</tr>
</thead>
<tbody>
<tr>
<td>Experimental dosage</td>
<td>427 ±112 mg (LD)</td>
<td>2.78 ± 1.1 mg/d (Salt)</td>
<td>[19842]</td>
</tr>
<tr>
<td>Supplemental LD dosage</td>
<td>274 ± 442 mg</td>
<td>434 ± 498 mg/d</td>
<td>[19842]</td>
</tr>
</tbody>
</table>

13.31 The mean total daily dosage in each alternative was derived from a 4-year RCT comparing Pramipexole vs. Levodopa in initial treatment for PD\textsuperscript{150}. In this study, Carbidopa/Levodopa was taken as 12.5/50-mg or 25/100-mg capsules or matching placebo capsules and Pramipexole was taken 3 times per day as 0.25-mg, 0.5-mg or 1-mg salt tablets or matching placebo tablets. Therefore, these tablet sizes were used to derive the unit costs of the medications. The choice of Pramipexole as the dopamine agonist was based solely on the availability of RCT evidence in the literature.

13.32 The daily cost of the experimental drug therapy and supplemental levodopa was estimated by multiplying the daily dosages in mg with the cost per mg. Total daily cost was the sum of the experimental drug cost and supplemental levodopa cost. Total cost of therapy over one year was calculated as total daily cost multiplied by 365 days.

Additional Cost of Dopamine Agonist Treatment

13.33 The additional cost of dopamine agonist treatment over a 1-year period was calculated by subtracting the cost of levodopa treatment from the cost of dopamine agonist treatment.
**Table 2. Unit Costs of Medications**

<table>
<thead>
<tr>
<th>Medication</th>
<th>Cost per mg (£2004)</th>
<th>Source</th>
<th>Type</th>
<th>Pack Size</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pramipexole</td>
<td>2.467</td>
<td>BNF</td>
<td>180 MICROGRAMS BASE = 250 MICROGRAMS SALT (0.25-MG)</td>
<td>30-TAB PACK = £18.50, 100-TAB PACK = £61.67;</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>1.963 700 micrograms = 1 mg salt (1-mg)</td>
</tr>
<tr>
<td>Levodopa</td>
<td>0.002</td>
<td>BNF</td>
<td>carbidopa 12.5 mg (as monohydrate), levodopa 50 mg</td>
<td>90-tab pack = £7.03</td>
</tr>
<tr>
<td></td>
<td>0.001</td>
<td></td>
<td>carbidopa 25 mg (as monohydrate), levodopa 100 mg</td>
<td>90-tab pack = £10.05</td>
</tr>
</tbody>
</table>

**Effectiveness**

13.34 The mean change of quality of life scores on both the PDQUALIF and the EuroQoL VAS were not significantly different between the dopamine agonist group and levodopa group and there were no significant treatment differences in the 7 subscales of the PDQUALIF in the four-year randomised control trial [19842]. The GDG agreed there was no clear clinically important difference between the two treatment strategies as many dyskinesias are mild and non-disabling and therefore well tolerated by patients. After 4 years of treatment, there is only one additional moderately disabling dyskinesia (0.1%), 2 mildly disabling dyskinesias (2.0%) and 17 non-disabling dyskinesias (16.8%) in 101 individuals in the levodopa group versus the pramipexole group, whereas, the mean improvements in total, motor and activities of daily living UPDRS scores were greater in the levodopa group versus the pramipexole group[150].

**Results**

**TABLE 4. MEAN TOTAL DAILY COST**

<table>
<thead>
<tr>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Experimental dosage</td>
<td>0.7839 (LD)</td>
<td>6.8573</td>
</tr>
<tr>
<td>Supplemental LD dosage</td>
<td>0.3060</td>
<td>0.4846</td>
</tr>
</tbody>
</table>
### TABLE 5. MEAN TOTAL COST OVER 1-YEAR PERIOD

<table>
<thead>
<tr>
<th>ALTERNATIVE</th>
<th>Cost (£ 2004)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pramipexole</td>
<td>2,680</td>
</tr>
<tr>
<td>Levodopa</td>
<td>286</td>
</tr>
<tr>
<td>Incremental Cost</td>
<td>2,394</td>
</tr>
</tbody>
</table>

13.35 Under the base-case analysis, the additional cost of dopamine agonist treatment versus levodopa over one year is £2,394.

**Sensitivity Analysis**

13.36 The estimates used in the model are subject to uncertainty. Therefore, a one-way sensitivity analysis was carried out to assess the impact of key variables used the model. A one-way sensitivity analysis varies one parameter while maintaining the other parameters at base-line values. The variables included are i) unit cost of levodopa ii) unit cost of pramipexole iii) mean total daily dosage of experimental levodopa in levodopa treatment iv) mean total daily dosage of supplemental levodopa in levodopa treatment v) mean total daily dosage of experimental pramipexole in pramipexole treatment and vi) mean total daily dosage of supplemental levodopa in pramipexole treatment. Results for the upper and lower estimates are given in Table 8. The higher range of the unit cost of levodopa was derived from the higher unit cost of alternative pack size and the lower range was estimated as minus 10%. The lower range of the unit cost of pramipexole was derived from the lower unit cost of alternative pack size and the higher range was estimated as plus 10%. The ranges of the mean total daily dosages were estimated as ± two standard errors derived from the standard deviations and population size in the study.

#### Table 8. One-way sensitivity analysis

<table>
<thead>
<tr>
<th>Variable</th>
<th>Base-line value</th>
<th>Range evaluated</th>
<th>Incr cost with lower range estimate (£ per year)</th>
<th>Incr cost with higher range estimate (£ per year)</th>
</tr>
</thead>
<tbody>
<tr>
<td>unit cost of levodopa</td>
<td>0.0011</td>
<td>0.0010-0.0016</td>
<td>2,405</td>
<td>2,351</td>
</tr>
<tr>
<td>unit cost of pramipexole</td>
<td>2.4667</td>
<td>1.963-2.713</td>
<td>1,883</td>
<td>2,644</td>
</tr>
<tr>
<td>mean daily dosage of exp levodopa (LD)</td>
<td>427</td>
<td>409-445</td>
<td>2,402</td>
<td>2,387</td>
</tr>
<tr>
<td>mean daily dosage of suppl levodopa (LD)</td>
<td>274</td>
<td>202-346</td>
<td>2,424</td>
<td>2,365</td>
</tr>
<tr>
<td>mean daily</td>
<td>2.78</td>
<td>2.60-2.96</td>
<td>2,233</td>
<td>2,555</td>
</tr>
</tbody>
</table>
13.37 The unit cost of pramipexole had the most impact on the ICER and resulted in the widest range of all the incremental cost estimates (£1,883 to £2,644). The mean daily dosage of experimental levodopa (LD) had the least impact on incremental cost.

**Discussion**

13.38 The base-line estimates result in an incremental cost (IC) of £2,394 for pramipexole treatment over a one-year period.

13.39 All base-line values were assessed within ranges of uncertainty. The unit cost of pramipexole had the most impact on the IC and resulted in the widest range of all the IC estimates (£1,883 to £2,644). All other variables resulted in a range of incremental costs with approximately a difference of £322 or less between the upper and lower estimates.

13.40 This study assumed all other costs, such as acute hospitalizations etc. (see Costs under Data Sources and Assumptions), were similar between the pramipexole and levodopa groups based on the results of an American 2-year study. Evidence of this in the UK setting awaits further research. The study also assumed the quality of life measures are sufficiently sensitive to reflect benefit differences between the alternatives. This study compared initial dopamine agonist therapy with levodopa therapy, however, combination therapy was not included as an alternative.

13.41 The model was developed from one RCT based on pramipexole on the basis of available evidence. Other dopamine agonists are currently available and may or may not have similar incremental costs. This is an important consideration as the unit cost of pramipexole had the most impact on the incremental cost.

**Conclusion**

13.42 The base-line estimates result in an incremental cost of £2,394 for pramipexole treatment over a one-year period. The unit cost of pramipexole had the most impact on the IC and resulted in the widest range of all the IC estimates (£1,883 to £2,644). On the basis of equivalent quality of life between the treatments, the levodopa strategy is the less costly option. The analysis is specific to pramipexole and does not consider the broader range of dopamine agonists available. The model is a simplified version of the costs and benefits of DBS-STN therapy versus standard care and variety of assumptions have been
used in the base-line analysis. Therefore, the results should be interpreted correspondingly.

Appendix G. Economic Modelling- Surgery

Background

13.43 Bilateral subthalamic stimulation has become established for the management of moderate to severe motor complications in the later stages of PD that are unresponsive to changes in medical therapy.

13.44 A literature was performed and four economic studies met quality criteria\textsuperscript{254-257}. The economic results are presented along with the clinical evidence of deep brain stimulation.

13.45 Whilst conclusive evidence on the cost effectiveness of this procedure awaits the results of ongoing large pragmatic trials in the UK (PD SURG) and US, the GDG considered the topic valuable for further consideration in this guideline.

Aim

13.46 The aim of the model was to compare the additional cost of bilateral deep brain stimulation of the subthalamic nucleus (DBS-STN) therapy to the benefits in quality of life gained by this procedure. Treatment option 1 is the intervention: DBS-STN and post-operative care over a 5-year period. Treatment option 2 is standard therapy over a 5-year period. The cost per quality-adjusted life year (QALY) gained was calculated.

Methods

13.47 A cost-effectiveness model was constructed from the perspective of the NHS. The effectiveness outcome measure used was quality-adjusted life years (QALYs) and the cost per QALY was calculated. The data sources of the costs and benefits are described in further detail in Tables 1-4. Costs and benefits were discounted at 3.5% in accordance with current NICE recommendations. A one-way sensitivity analysis was run to assess the impact of variables on the incremental cost-effectiveness ratio (ICER).

Incremental cost per QALY = \( \frac{(C_1 - C_2)}{(Q_1 - Q_2)} \)
WHERE:

\[ C_1 = \text{ESTIMATED COST OF DBS-STN PROCEDURE AND POST-OPERATIVE CARE} \]
\[ C_2 = \text{ESTIMATED COST OF STANDARD CARE} \]
\[ Q_1 = \text{ESTIMATED QUALITY-ADJUSTED LIFE YEARS AFTER DBS-STN} \]
\[ Q_2 = \text{ESTIMATED QUALITY-ADJUSTED LIFE YEARS WITH NO DBS-STN} \]

Data Sources and Assumptions

13.48 Tables 1-4 list the baseline cost and effectiveness outcomes along with the sources of data. Assumptions and methods of calculating estimates are described in further detail below.

Table 1. Costs of Standard Care of PD

<table>
<thead>
<tr>
<th>Cost</th>
<th>Value (£1998)</th>
<th>SOURCE</th>
</tr>
</thead>
<tbody>
<tr>
<td>Annual cost of care per patient in Hoehn and Yahr stage III-IV</td>
<td>6,216</td>
<td>[40]</td>
</tr>
<tr>
<td>Total costs for 5-Year period with 3.5% discount</td>
<td>28,066</td>
<td>[Estimate]</td>
</tr>
</tbody>
</table>

TABLE 2. COSTS OF DBS-STN PROCEDURE

<table>
<thead>
<tr>
<th>Item</th>
<th>Minimum</th>
<th>Maximum</th>
<th>Baseline</th>
<th>Quantity</th>
</tr>
</thead>
<tbody>
<tr>
<td>DBS-STN (including device)</td>
<td>12,740</td>
<td>14,450</td>
<td>13,595</td>
<td>1</td>
</tr>
<tr>
<td>Follow-up appointment</td>
<td>70</td>
<td>376</td>
<td>223</td>
<td>4</td>
</tr>
<tr>
<td>Annual follow-up appointment*</td>
<td>582</td>
<td>582</td>
<td>582</td>
<td>5</td>
</tr>
<tr>
<td>In-patient follow-up for adjustment of stimulator including batteries*</td>
<td>3,000</td>
<td>6,000</td>
<td>4,500</td>
<td>5</td>
</tr>
<tr>
<td>Total procedure costs with 3.5% discount*</td>
<td>29,193</td>
<td>45,672</td>
<td>37,432</td>
<td></td>
</tr>
</tbody>
</table>

SOURCE: [43]

TABLE 3. COSTS OF POST-OPERATIVE MEDICATION

<table>
<thead>
<tr>
<th>Item</th>
<th>Value</th>
<th>Source</th>
</tr>
</thead>
<tbody>
<tr>
<td>Annual post-operative drug costs per patient</td>
<td>1,414</td>
<td>[40]</td>
</tr>
<tr>
<td>% of patients with no medication after DBS-STN</td>
<td>26.19%</td>
<td>[19699]</td>
</tr>
<tr>
<td>Total costs for 5-Year period assuming 26.19% with no medication after DBS-STN and 3.5% discount</td>
<td>4,712</td>
<td>[Estimate]</td>
</tr>
</tbody>
</table>

Table 4. Benefits after DBS-STN with annual 3.5% discount rate

<table>
<thead>
<tr>
<th>Year after DBS-STN</th>
<th>Percent increase in quality of life from initial.</th>
<th>Quality of Life</th>
<th>SOURCE</th>
</tr>
</thead>
</table>

Parkinson's disease: full guideline DRAFT (August 2005)
Explanation of assumptions and data used

Costs

STANDARD CARE

13.49 The annual cost of care per patient with Parkinson’s disease in the UK without undergoing DBS-STN was derived from one UK study that estimated the annual cost of care in 1998. The study indicated Hoehn and Yahr stage significantly influenced cost by stage (p<0.001). Therefore the annual NHS costs in Hoehn and Yahr stages III-IV were averaged to derive the annual standard cost of care of patients with moderate to severe motor complications in the later stages of PD.

13.50 To calculate the total cost of care per patient over a 5-year period, the annual cost of care per patient per year is considered stable for the 5-year period and was adjusted by a 3.5% discount rate.

DBS-STN Procedure

13.51 The cost of the DBS-STN procedure per patient was estimated from cost data obtained from 7 of the 17 centres in the UK offering DBS-STN at the time of the study993. Costs of annual follow-up appointment and in-patient follow-up for adjustment of stimulator including batteries after year 1 were discounted at an annual rate of 3.5%. This resulted in a figure similar but conservatively higher figure (£37,432 (1998) vs. £32,526 (2002)) to the estimate in a study assessing the total health service costs of deep brain stimulation of the subthalamic nucleus, including preoperative assessment, surgery and post-operative management over a 5-year period based on one centre in the UK [404].

Post-operative Medication

13.52 The annual post-operative drug costs were derived from the same study used to estimate the cost of standard care10. In the study, drug costs were lower in older age groups. The highest drug cost per patient per year in the under 65-year old age group was used as a conservative estimate in favour of standard care.
13.53 The study that estimated the 5-year follow-up of DBS-STN found 11 of the 42 patients no longer required levodopa. Therefore 26.19% (11/42) was used as the base-line value for the percentage of patients no longer requiring medication.

13.54 To calculate the cost of post-operative medication per patient over a 5-year period, the annual cost of care per patient per year is considered stable for the 5-year period and was adjusted by a 3.5% discount rate. 26.19% of this cost was subtracted from the result to give the total cost of post-operative medication over the 5-year period.

**Total DBS-STN Costs**

13.55 The total cost of the DBS-STN was the sum of the DBS-STN procedure and post-operative medication costs over the 5-year period.

**Additional costs of DBS-STN**

13.56 The additional cost of DBS-STN therapy over a 5-year period was calculated by subtracting the cost of standard care from the cost of DBS-STN therapy.

**QALYs**

**DBS-STN therapy**

13.57 The initial quality of life and the quality of life 12 months after DBS-STN was derived from one study assessing the quality of life of 60 patients before DBS-STN surgery and 12 months after using a disease specific quality of life instrument, the PD Quality of Life scale (PDQL).

13.58 There is limited data on the quality of life after DBS-STN beyond the first 12 months and very limited data for converting quality of life outcomes of Parkinson’s disease health states, such as UPDRS, into quality adjusted life years. Therefore, as UPDRS III has been found to correlate with improvements in QOL, for years 2 through 5, it was assumed that percent changes in UPDRS III scores correspond with improvements in quality of life. The QoL study found UPDRSIII (motor functions) improved by 55% and UPDRS II (activities of daily living) improved by 45% after 12 months. A second study found UPDRS III improved by 54% and UPDRS II improved by 49% after 5 years. Therefore, it was assumed the quality of life improvements found after 12 months would also remain improved at its 43% increase from baseline after 5 years.

13.59 In the UPDRS study over a 5-year follow-up, there was a 7% (3, n=42) rate of mortality, 5% rate of dementia (2, n=42), 19% with eye-lid opening apraxia (8, n=42) and other side effects. To include the 7% mortality, only 93% of the total possible QALY gain was included. The
other side effects were assumed to be captured in the quality of life assessment. Total QALY gain in each year was added with a 3.5% annual discount rate.

**Standard care**

13.60 As a conservative estimate in favour of standard care, the study assumed there is no change in quality of life from the initial value over the 5-year period. QALYs were discounted at 3.5%.

**Results**

**Table 5.** DBS-STN Therapy

<p>| | |</p>
<table>
<thead>
<tr>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Cost</td>
<td>£42,144</td>
</tr>
<tr>
<td>QALY</td>
<td>3.147</td>
</tr>
<tr>
<td>QALY including 7% mortality</td>
<td>2.927</td>
</tr>
</tbody>
</table>

**Table 6.** Standard therapy

<p>| | |</p>
<table>
<thead>
<tr>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Cost</td>
<td>£28,066</td>
</tr>
<tr>
<td>QALY</td>
<td>2.203</td>
</tr>
</tbody>
</table>

**Table 7.** Incremental results of base-line values

<p>| | |</p>
<table>
<thead>
<tr>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Incremental cost</td>
<td>£14,079</td>
</tr>
<tr>
<td>Incremental QALY</td>
<td>0.944</td>
</tr>
<tr>
<td><strong>INCREMENTAL QALY INCLUDING 7% MORTALITY</strong></td>
<td>0.723</td>
</tr>
<tr>
<td>Incremental cost-effectiveness ratio (ICER)</td>
<td>£14,900 per QALY</td>
</tr>
<tr>
<td>ICER including 7% mortality</td>
<td>£19,500 per QALY</td>
</tr>
</tbody>
</table>

Differences due to rounding

13.61 Under the base-case analysis including 7% mortality, the additional cost per additional quality-adjusted life year gained is £19,500 per QALY gained.

**Sensitivity Analysis**

13.62 The estimates used in the model are subject to uncertainty. Therefore, a one-way sensitivity analysis was carried out to assess the impact of key variables used the model. A one-way sensitivity analysis varies one parameter while maintaining the other parameters at base-line values. The variables included are i) cost of DBS-STN (including device) ii) cost of follow-up appointment, iii) cost of in-patient follow-up for adjustment of stimulator including batteries iv) total costs of DBS-STN procedure with 3.5% discount v) drug costs after DBS-STN vi) total costs of standard care vii) total QALY gains in standard care and viii) total QALY gains in DBS-STN therapy. Results for the upper and lower estimates
are given in Table 8. The ranges of DBS-STN procedure component costs were derived from the minimum and maximum values given in the cost data literature. The range of the total costs of standard care were estimated from ± two standard errors (867) from the standard deviation (6,235) and sample size of 207 of the annual cost of care. The range of the total DBS-STN procedure cost was estimated as half (X 0.5) and twice (X 2.0) the value. The range of the QALY gains were estimated as ± two standard errors (0.04), from a standard deviation of 0.16 of the percent increase in quality of life and sample size of 60.
**Table 8. One-way sensitivity analysis**

<table>
<thead>
<tr>
<th>Variable</th>
<th>Base-line value</th>
<th>Range evaluated</th>
<th>ICER lower range estimate</th>
<th>ICER higher range estimate</th>
<th>ICER LOWER RANGE ESTIMATE</th>
<th>ICER UPPER RANGE ESTIMATE</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cost of DBS-STN (including device)</td>
<td>13,595</td>
<td>12,740-14,450</td>
<td>14,014</td>
<td>15,826</td>
<td>18,282</td>
<td>20,646</td>
</tr>
<tr>
<td>Cost of Follow-up appointment</td>
<td>223</td>
<td>70-376</td>
<td>14,271</td>
<td>15,568</td>
<td>18,618</td>
<td>20,310</td>
</tr>
<tr>
<td>Cost of In-patient follow-up for adjustment of stimulator including batteries</td>
<td>4,500</td>
<td>3,000-6,000</td>
<td>7,743</td>
<td>22,097</td>
<td>10,101</td>
<td>28,826</td>
</tr>
<tr>
<td>Total DBS-STN procedure costs with 3.5% discount</td>
<td>37,432</td>
<td>18,716-74,865</td>
<td>6,188</td>
<td>23,652</td>
<td>8,073</td>
<td>30,854</td>
</tr>
<tr>
<td>Drug costs after DBS-STN % of patients after DBS-STN with no medication</td>
<td>4,712</td>
<td>3,192-6,384</td>
<td>13,309</td>
<td>16,692</td>
<td>17,362</td>
<td>21,775</td>
</tr>
<tr>
<td>Total costs of standard care</td>
<td>28,066</td>
<td>24,152-31,979</td>
<td>19,067</td>
<td>24,874</td>
<td>14,054</td>
<td></td>
</tr>
<tr>
<td>Annual cost of standard care</td>
<td>6,216</td>
<td>5,349-7,083</td>
<td>10,773</td>
<td>15,796</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total QALY gains in standard care</td>
<td>2.203</td>
<td>2.023-2.384</td>
<td>12,523</td>
<td>18,451</td>
<td>15,575</td>
<td>25,940</td>
</tr>
<tr>
<td>Total QALY gains in DBS-STN therapy</td>
<td>3.147</td>
<td>2.966-3.328</td>
<td>18,451</td>
<td>12,523</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total QALY gains in DBS-STN</td>
<td>2.927</td>
<td>2.759-3.095</td>
<td>25,350</td>
<td>15,796</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
13.63 The total DBS-STN procedure costs with 3.5% discount had the most impact on the ICER and resulted in the widest range of all the ICER estimates (£8,073 to £30,854 per QALY). The cost of DBS-STN (including device) and cost-of follow-up appointment had the least impact on the ICER.

**Discussion**

13.64 When possible, the model used conservative estimates that favoured standard care. With these estimates, the ICER value of £19,500 per QALY falls within an accepted range of cost-effectiveness. This result is lower than the cost per QALY estimated in the American study, $49,194 (US$, 2000) per QALY\(^{255}\) attributable to methodological and pricing differences between the countries.

13.65 Due to the assumptions of UPDRS III and quality of life and the exclusion of side-effects and mortality, the estimate of the QALY gains are associated with the most uncertainty. Nevertheless, the high and low estimates in the sensitivity impact on the ICER resulted in a range of £15,575 to £25,940 per QALY varying QALYs in standard care and £15,796 to £25,350 per QALY varying QALYs after DBS-STN, still falling within a normally accepted range. Even if the improvement in QALY is less than the observed improvement in UPDRS III used to estimate the QALY gain, with the base-line incremental cost of approximately £14,079, only an increase in 0.4693 (achieved by year 3 in base-line analysis) or greater from DBS-STN over a 5-year period would be required to achieve a cost per QALY of £30,000 or less. Doubling the incremental cost of DBS-STN (£28,158) would require an increase in only 0.9386 (achieved by year 5 in base-line analysis) in quality of life or greater to achieve a cost per QALY of £30,000 or less. Therefore, unless the actual total net QALY gain over a 5-year period is less than 0.4693, DBS-STN is still arguably likely to be cost-effective.

13.66 The benefits in this model are assessed only for a 5-year period. This means that any benefits from DBS-STN accrued after 5 years is not accounted for in the model. This makes each benefit in the 5-year period cost more than it would over time, assuming further benefits after 5 years. Therefore, cost-effectiveness may improve over greater lengths of time, however, with only small improvements in the ICER. Additionally, the benefits over time are limited by increases in costs of care after DBS-STN as PD progresses and by mortality.

13.67 The sensitivity analysis indicates the higher the costs of care of standard therapy, the more favourable the ICER. This may indicate that using DBS-STN in patients with higher costs of care, potentially those with greater severity of PD, is more cost-effective, but only if the QALY gains remain the same. Since the higher cost patients may or may not
gain on average the same benefits, the sensitivity analysis results do not help to identify those patients better suited to DBS-STN therapy. The lower the cost of the DBS-STN procedure, the more favourable the ICER. This suggests that ICER values will improve if the technology becomes available at lower costs in the future.

**Conclusion**

13.68 Bilateral deep brain stimulation of the subthalamic nucleus is a clinical alternative to standard care for the management of moderate to severe motor complications in the later stages of PD that are unresponsive to changes in medical therapy. Costs and benefits of DBS-STN accrued over greater lengths of time (5-years) in comparison to standard care indicate the potential for cost-effective use of the technology in particular individuals with the clinical potential to benefit from the procedure. Estimate suggests DBS-STN therapy costs approximately £19,500 per QALY over a 5-year period in comparison to standard PD care in the UK (£1998). The results are relatively robust based on one-way sensitivity analysis. The model is a simplified version of the costs and benefits of DBS-STN therapy versus standard care and variety of assumptions have been used in the base-line analysis. Therefore, the results should be interpreted correspondingly.
Appendix H. Economic Modelling-PDNS care

Background

13.69 The Parkinson's Disease Society is encouraging the development of PDNS's across the UK. There are in the region of 180 nurses already in post with plans to increase this to 240 over the next few years [GDG].

13.70 A literature search was performed to identify economic evaluations of PDNS care. One study met quality criteria and is presented along with the clinical evidence of Parkinson's disease nurse specialist intervention.

13.71 In practice there may be interactions between PDNS care and standard care, which makes it difficult to separate the costs and benefits discretely between the interventions. The GDG considered monitoring medications, as opposed to diagnosing, an appropriate example where PDNS care may substitute standard care with equivalent outcomes. Therefore, the GDG felt it was of value to investigate in this guideline the cost implications of PDNS care based on equivalent effectiveness of completely substituted activities.

Aim

13.72 The aim was to estimate the costs and costs saved with equivalently effective and completely substituted PDNS care in comparison to standard care over a one-year period from the NHS perspective. The additional costs of PDNS care and the cost-savings per home visit, per clinic consultation and per hospital-based visit were calculated.

Methods

13.73 The annual cost per PDNS was estimated using the sum of the annual salary and training costs discounted at 3.5%. Additional costs of PDNS care were estimated using the unit costs of other professional’s time used in discussing patient care.

13.74 Cost-savings were estimated from the perspective of the NHS. Estimates were derived from unit costs and discounted at 3.5% (Table 1). Savings were calculated for PDNS care by i) home visit ii) clinic consultation and iii) hospital-based visit. To calculate savings per intervention, the unit costs of standard care were used to estimate the resources saved by PDNS care.

13.75 The net cost of PDNS care over one year was calculated as the sum of the annual salary, training costs and additional costs of PDNS care minus the cost-savings.

Data sources

Table 1. Unit costs derived from Unit Costs of Health & Social Care 2004.

<table>
<thead>
<tr>
<th>Intervention</th>
<th>Unit cost (£2004)</th>
</tr>
</thead>
</table>

GP home visit lasting 13.2 minutes (plus 12 minutes travel time) 65
District nurse home visit (A-F) 20
GP clinic consultation lasting 12.6 minutes 28
Nurse practitioner in primary care surgery consultation 14
Hospital-based consultant: per patient-related hour (A to F) 114
Hospital-based staff nurse, 24-hr ward per hour of patient contact 41
Expected annual cost of training at 3.5% discount rate (District nurse) 5,149
Salary per year of District nurse 25,362
Additional cost per visit to GP by PDNS to discuss patient care 28
Additional cost per visit to carer to discuss patient care 0
Additional cost per visit to consultant to discuss patient care 38

Table 2. Nurse Activity-Assessing Patients

<table>
<thead>
<tr>
<th>Source</th>
<th>Average N or % of patients assessed</th>
</tr>
</thead>
<tbody>
<tr>
<td>Per week</td>
<td>13.7 [223]</td>
</tr>
<tr>
<td>At home</td>
<td>75% [223]</td>
</tr>
<tr>
<td>At GP</td>
<td>14% [223]</td>
</tr>
<tr>
<td>At hospital consultant clinics</td>
<td>11% [223]</td>
</tr>
</tbody>
</table>

Table 3. Nurse Activity-Discussing Patients

<table>
<thead>
<tr>
<th>Source</th>
<th>Number of Visits per Week</th>
</tr>
</thead>
<tbody>
<tr>
<td>To GPs</td>
<td>5 [223]</td>
</tr>
<tr>
<td>To Carers</td>
<td>2 [223]</td>
</tr>
<tr>
<td>To Consultants</td>
<td>1 [223]</td>
</tr>
</tbody>
</table>

Assumptions

13.76 The main assumptions to this costing approach are as follows:
PDNS care substitutes for standard care for on-going monitoring of treatment at equivalent effectiveness
Nurse activity reflects substituted activities
PDNS care is provided at the unit costs and includes the costs for consultant time spent discussing patient care
Consultant time is costed per 20 minute visit
Healthcare resources for patients by PDNS, such as medication, are similar to standard care
Administration activities are included in salary
Cost of visit to GP to discuss patient care = Cost of nurse time included in salary + Cost of GP time = £28
Cost of visit to carer to discuss patient care = Cost of nurse time included in salary = £0
Cost of 20 minute visit to consultant to discuss patient care = Cost of nurse time included salary + Cost of consultant time = £38

13.77 The results from a randomised control trial suggest PDNS care maintains clinical effectiveness and improves patients’ sense of wellbeing\(^{344}\). This supports the assumption that PDNS care has at least equivalent effectiveness to consultant care.

13.78 It is not always clear whether PDNS care is substituting some or all of the consultant care or is serving as additional care\(^{346}\). Therefore, the cost-saving estimates pertain only to situations where care is a substitution, such as monitoring medications and not where the care may be additional to standard care or duplicating standard care.

Results

Table 4. Net Cost of PDNS over One-Year Period with 3.5% discount rate

<table>
<thead>
<tr>
<th>Item</th>
<th>Costs (£2004)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cost of training per year</td>
<td>+5,149</td>
</tr>
<tr>
<td>Cost of salary per year</td>
<td>+24,504</td>
</tr>
<tr>
<td>Additional costs of other health professional’s time discussing patients in one year</td>
<td>+8,974</td>
</tr>
<tr>
<td>Cost-savings of other health professional’s costs from assessing patients in one year</td>
<td>-39,264</td>
</tr>
<tr>
<td>Net cost of PDNS care over one year</td>
<td>-637</td>
</tr>
</tbody>
</table>

Table 5. Additional Costs of Nurse Activity-Discussing Patient Care

<table>
<thead>
<tr>
<th>Number of visits per year to discuss patient care(^{+})</th>
<th>Costs per Year (£2004)</th>
</tr>
</thead>
<tbody>
<tr>
<td>To GPs</td>
<td>261</td>
</tr>
<tr>
<td>To Carers</td>
<td>104</td>
</tr>
<tr>
<td>To Consultants</td>
<td>52</td>
</tr>
<tr>
<td>Total Costs</td>
<td></td>
</tr>
<tr>
<td>Total Costs at 3.5% discount rate</td>
<td></td>
</tr>
</tbody>
</table>

\(^{+}\)Estimated from Table 3. with 1 year = 52.177457 weeks 10.73
### Table 6. Cost-savings of PDNS Care when Substituting Standard Care

<table>
<thead>
<tr>
<th>Average number of patients assessed*</th>
<th>Costs per Year (£2004)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Per Year</td>
<td></td>
</tr>
<tr>
<td>At home</td>
<td>714</td>
</tr>
<tr>
<td>At GP</td>
<td>536</td>
</tr>
<tr>
<td>At hospital consultant clinics</td>
<td>100</td>
</tr>
<tr>
<td>Total</td>
<td>79</td>
</tr>
<tr>
<td>Total Costs at 3.5% discount rate</td>
<td>40,638</td>
</tr>
<tr>
<td>*Estimated from Table 2.</td>
<td></td>
</tr>
</tbody>
</table>

### Sensitivity Analysis

13.79 The estimates used in the model are subject to uncertainty. Therefore, a one-way sensitivity analysis was carried out to assess the impact of key variables used the model. A one-way sensitivity analysis varies one parameter while maintaining the other parameters at base-line values. The variables included are i) cost of training per year ii) cost of salary per year iii) additional costs of other health professional’s time discussing patients in one year and iv) cost-savings of other health professional’s costs from assessing patients in one year. Plus or minus 10% was used as an estimate of the variability of the parameters.

### Table 7. One-way Sensitivity Analysis

<table>
<thead>
<tr>
<th>Variable</th>
<th>Base-line value (£)</th>
<th>Range evaluated</th>
<th>ICER lower range estimate</th>
<th>ICER higher range estimate</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cost of training per year</td>
<td>5,149</td>
<td>4,634-5,664</td>
<td>-1,152</td>
<td>-123</td>
</tr>
<tr>
<td>Cost of salary per year</td>
<td>24,504</td>
<td>22,054-26,955</td>
<td>-3,087</td>
<td>+1,813</td>
</tr>
<tr>
<td>Additional costs of other health professional’s time discussing patients in one year</td>
<td>8,974</td>
<td>8,076-9,871</td>
<td>-1,535</td>
<td>+260</td>
</tr>
<tr>
<td>Cost-savings of other health professional’s costs from assessing patients in one year</td>
<td>39,264</td>
<td>35,338-43,190</td>
<td>+3,289</td>
<td>-4,564</td>
</tr>
</tbody>
</table>

- cost-savings
+ additional cost

13.80 The cost-savings of other health professional’s costs had the most impact on the ICER ranging from an additional cost of £3,289 to cost-savings of £4,564. Increasing and decreasing the cost of PDNS training by 10% resulted in cost-savings of PDNS. However, by altering the other three parameters, costs range from cost-savings to additional costs implying the model is not robust to changes in the assumptions.
Discussion

13.81 Based on the average nurse activity in the randomized controlled trial in the UK Table 2. and 3, approximately £640 is saved. Cost-savings appear when PDNS care is substituting for standard care. However, in practice there may be variability in the interactions between types of care. There may be substituted care, additional care, duplication of care or a combination of these. Nevertheless, the more PDNS care substitutes for standard care in a practice, the greater the potential for the outcomes to approach these average cost-savings. How much PDNS care substitutes, duplicates or increases benefit for the same cost in comparison to standard care is not known. As the sensitivity analysis indicates, the cost-savings from other health professional’s costs had the most impact on the ICER ranging from cost-savings of £4,564 to an additional cost of £3,289. The costing of other health professional’s reflects the average activity of PDNS. Therefore, how much PDNS care is substituting standard care at equivalent effectiveness needs to be assessed in further studies to improve cost estimates.

13.82 Only unit costs were used to assess the benefit of PDNS care vs. standard care in terms of cost-savings. However, unit costs may not fully represent all costs and benefits. This may have under-estimated the benefit of PDNS care. There may be increased patient benefits gained from a greater responsiveness of PDNS care to emerging scientific evidence, such as the earlier reduction in selegiline use found in nurses vs. doctors or improved access to care. There may be an improved sense of patient’s well-being while maintaining clinical effectiveness. There also may be interactions of care as an additional benefit to PDNS care working in standard care that has not been measured. Currently, however, there is insufficient evidence available to measure such benefits.

13.83 On the other hand, the unit costs may under-estimate the costs of PDNS care. The resources used in PDNS care are assumed to be equivalent to those used in standard care. However, PDNS care may use more or less or higher or lower cost resources resulting in higher or lower costs that are not reflected in the estimate. The RCT is the only study that gives an indication of the cost components in PDNS care vs. standard care and suggests that these are similar between the groups. However, apomorphine was excluded from the total cost of healthcare. Therefore, further evidence on the costs of resources used is needed to inform cost-effectiveness analyses.

13.84 The initial cost of establishing PDNS care will be incurred by the NHS. Therefore it would be helpful to evaluate whether initial costs can be recovered over time to warrant the initial investment. However, this is also contingent on the resource implications of the care. This cost-savings estimate is based on one PDNS with average nurse activity. While activity with less substitution of standard care or higher resources used would reasonably decrease the cost-savings and potentially result...
in a net cost, it has not been determined how having more than one PDNS would affect costs and cost-savings. The net estimate should not be interpreted as the complete indication of the benefit of PDNS care, nor do the estimates provide an indication of the appropriate amount of PDNS care that should be available. Instead, the net estimates suggest on average the cost-savings of one PDNS based on average nurse activity.

13.85 A sensitivity analysis was performed to investigate changes to the cost inputs used in this analysis on the net cost. Increasing and decreasing the cost of PDNS training by 10% was the only parameter that maintained cost-savings of PDNS. Increasing the cost of salary per year and the additional costs of other health professional's time discussing patients and reducing the cost-savings of other health professional's costs from assessing patients by 10% resulted in additional costs. This suggests further data is needed to assess the cost-effectiveness of PDNS. The base-line analysis pertains to average PDNS care across the UK, however, this does not limit the applicability of the methods to individual centres to assess differences in both costs and cost-savings estimates.

13.86 The incremental costs compared to the incremental benefits was not estimated due to the difficulty in separating PDNS care from standard care and the limited evidence on measurable benefits. One study estimated Parkinson’s disease nurse specialist care costs £200 per patient per year\textsuperscript{344}. However, it is likely this value depends on the total number of patients, PDNS’s and nurse activity. Furthermore, PDNS care versus standard care and nurse activity may not be consistent between services. Therefore, cost-effectiveness results may not be generalisable. Due to the difficulty in disentangling PDNS care and consultant care in different practices and the limited measurable benefits, a more general net cost approach, based on completely substituted care with equivalent effectiveness and average nurse activity was performed.

Conclusion

13.87 Approximately £640 pounds are saved with one PDNS per year based on base-line values of average activity of substituted care, such as monitoring medications, of equivalent effectiveness. In each practice there may be variability in the interactions between types of care and costs of care. Increasing the cost of salary per year and the additional costs of other health professional’s time discussing patients and reducing the cost-savings of other health professional’s costs from assessing patients by 10% resulted in additional costs. Therefore, the cost-effectiveness of PDNS care requires further evidence. This highlights the need for further studies to measure the benefits of PDNS care to adequately assess the cost-effectiveness. Due to the interactions of care and data limitations, benefits have been simplified in the form of cost-savings from standard unit costs. The cost-saving
estimates are subject to the assumptions and therefore the results should be interpreted correspondingly.
## Appendix J. Glossary

### Guide to assessment scales

<table>
<thead>
<tr>
<th>Measure</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>Activities of daily living (ADL)</td>
<td>Measures the impact of PD on 14 categories; each category is scored on a 0-4 scale, with higher scores reflecting greater disability and the need for assistance. The overall score ranges from 0 to 56.</td>
</tr>
<tr>
<td>Alzheimer’s disease assessment scale-cognitive subscore (ADAS-cog)</td>
<td>A test for measuring cognitive function in people suffering from dementia. The scale can range from 0 to 70, with higher scores indicating more severe impairment and lower scores indicating improvement.</td>
</tr>
<tr>
<td>Alzheimer’s disease cooperative study- Activities of Daily living (ADCS-ADL)</td>
<td>A test for measuring quality of life in people suffering from dementia. Scores range from 0-78, with higher scores indicating better function.</td>
</tr>
<tr>
<td>Alzheimer’s disease cooperative study-clinician's global impression of change (ADCS-CGIC)</td>
<td>A test for assessing a change in condition (i.e. improvement, worsening or no change) of a person suffering from dementia as judged by the clinician. Scores can range from 1-7, with a score of 1 indicating marked improvement to a score of 7 indicating marked worsening.</td>
</tr>
<tr>
<td>Attitudes to Self Scale</td>
<td>‘Feelings and attitudes towards our bodies/selves’. Consisted of 15 semantic paired opposite (e.g. tense/relaxed). Positive score was 0 and negative score was 6 (range of total scores 0-90)</td>
</tr>
<tr>
<td>Barthel index</td>
<td>Measures the impact of PD on 10 categories of ‘activities of daily living’. The range of scores is 0-100 with higher scores indicating better functionality.</td>
</tr>
<tr>
<td>Beck Depression Inventory (BDI)</td>
<td>A test used to measure manifestations and severity of depression. The BDI is a 21-item self-rating scale depression. Each item comprises 4 statements (rated 0-4) describing increasing severity of the abnormality concerned.</td>
</tr>
<tr>
<td>Brief Psychiatric Rating Scale (BPRS)</td>
<td>An 18-item scale measuring psychiatric symptoms. Some items can be rated simply on observation; other items involve an element of self-reporting. There are 24 symptom constructs; each rated on a 7-point scale of severity ranging from ‘not present’ (1) to ‘extremely severe’ (7).</td>
</tr>
<tr>
<td>Clinical Global Impression (CGI) Scale</td>
<td>A participant’s illness is compared to change over time, and rated on a scale of very much improved to very much worse. A three-item scale (severity of illness; global improvement; and efficacy index) used to assess treatment response in participants.</td>
</tr>
<tr>
<td>Core Assessment Program for Intracerebral Transplantations (CAPIT) dyskinesia Rating Scale</td>
<td>A preoperative neurological evaluation. People are evaluated in the 'on' and 'off' phases according to CAPIT protocol. The protocol incorporates UPDRS, a dyskinesia rating scale and timed motor tests to demonstrate efficacy of surgical interventions.</td>
</tr>
<tr>
<td>Delis-Kaplan Executive Function System (D-KEFS) Verbal Fluency Test</td>
<td>Assesses key areas of cognitive function (problem-solving, thinking flexibility, fluency, planning, deductive reasoning) in both spatial...</td>
</tr>
<tr>
<td>Test Name</td>
<td>Description</td>
</tr>
<tr>
<td>-----------------------------------------------</td>
<td>------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------</td>
</tr>
<tr>
<td>Dementia Rating Scale (DRS) total score</td>
<td>A test to assess cognitive function in older adults with neurological impairment. The test provides a measurement of attention, initiation, construction, conceptualization, and memory.</td>
</tr>
<tr>
<td>Epworth sleepiness scale (ESS)</td>
<td>The Epworth Sleepiness Scale (ESS) is a subjective scale in which participants rate the likelihood that they will fall asleep or doze in daily sedentary settings (e.g. watching TV, sitting in a care, etc). Each question receives a score of 0 to 3, making the maximum score 24.</td>
</tr>
<tr>
<td>EuroQol EQ-5D</td>
<td>A questionnaire that provides a simple descriptive profile and a single index value for health status. The questionnaire describes states of health in five dimensions: mobility, self care, usual activities, pain or discomfort, and anxiety or depression.</td>
</tr>
<tr>
<td>Frenchay Dysarthria assessment</td>
<td>A tool developed to diagnose dysarthria by quantitatively evaluating speech across a range of parameters including orofacial muscle movements and a measurement of intelligibility.</td>
</tr>
<tr>
<td>Hamilton Rating Scale for Depression (HRSD/HAM-D)</td>
<td>This is a 17-21 item observer-rated scale to assess the presence and severity of depressive states. A score of 11 is generally regarded as indicative of a diagnosis of depression.</td>
</tr>
</tbody>
</table>
| Hoehn and Yahr staging                        | To establish the severity of PD, stages of disease are classified from I to V where:  
- I indicates unilateral disease,  
- II indicates bilateral without postural instability,  
- III indicates postural instability,  
- IV indicates considerable disability but able to walk independently,  
- V indicates wheelchair-bound or walking only with assistance. |
<p>| Health related quality of life (HRQL)         | A combination of a person’s physical, mental and social well-being; not merely the absence of disease.                                                                                                      |
| Maintenance of wakefulness test (MWT)         | An evaluation of the person’s ability to maintain wakefulness for 20-minute periods in a quiet, darkened room with the participant in a reclined position. This test evaluates the person’s degree of alertness and his/her tendency to fall asleep at inappropriate times. |
| Mini-mental State Examination (MMSE)          | Assessment scale of global cognitive function, with scores ranging from 0-30. Higher scores indicate better mental function; &lt; 23 is usually indicative of cognitive impairment. |
| Modified Columbia Rating Scale (MCRS)        | 22-item scale (maximum possible score 240) which evaluates parkinsonian and dyskinesia severity, where global disability is rated as 0 (absent) to 4 (severe). |
| Modified Hoehn and Yahr scale                 | A modified eight-point version of the original scale.                                                                                                                                                      |
| Montgomery-Asberg Depression                  | A depression rating scale used to monitor a                                                                                                                                                                |</p>
<table>
<thead>
<tr>
<th>Rating Scale</th>
<th>participant’s depressive state over time. Scores range from 0 to 60, with higher scores indicating a greater degree of depression.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Neuropsychiatric Inventory 10-item (NPI-10)</td>
<td>A test that evaluates dementia related behaviours. Scores range from 1-120, with higher scores indicating more severe or more frequent behavioural problems.</td>
</tr>
<tr>
<td>New York University Parkinson’s Disease Scale (NYUPDS)</td>
<td>Determines clinical efficacy by rating participants on 5 symptoms using a 5-point scale ranging from 0 (normal functioning) to 4 (marked impairment).</td>
</tr>
<tr>
<td>Northwestern University Disability Scale (NUDS)</td>
<td>Assessed impairments in activities of daily living on 6 categories, with a scale ranging from 0 (normal functioning) to 10 (marked disability).</td>
</tr>
<tr>
<td>Nottingham Health Profile</td>
<td>Generic health-related quality of life measure. The instrument is used to evaluate perceived distress across various populations. There are 38 items with 6 domains. Scores range from 0-100 where higher scores indicate a greater health problem.</td>
</tr>
<tr>
<td>Parkinson’s disease Quality of life Questionnaire (PDQL)</td>
<td>To assess the quality-of-life in participants with Parkinson’s disease using standardized measures of disease severity, depressive symptomatology and cognitive function.</td>
</tr>
<tr>
<td>Parkinson’s Disease Questionnaire 39 (PDQ 39)</td>
<td>A self-administered questionnaire, which comprises 39 items addressing eight domains of health, which participants consider to be adversely affected by the disease. Scores range from 0 to 100, where lower scores indicate a better-perceived health status. The results are presented as eight discrete domain scores and not as a total score.</td>
</tr>
<tr>
<td>Patient’s Global Impression (PGI) Scale</td>
<td>A participant rates the change in their illness over time on a scale of ‘1’ very much improved to ‘7’ very much worse.</td>
</tr>
<tr>
<td>Positive and negative symptoms scale (PANSS)</td>
<td>A psychotic rating scale of 30 items, each assessed on a seven-point scale from absent to extreme. It is divided into sub-scales covering both positive (PANSS-P) and negative symptoms (N).</td>
</tr>
<tr>
<td>Scale for the assessment of positive symptoms (SAPS)</td>
<td>Assesses the severity of psychotic symptoms.</td>
</tr>
<tr>
<td>Schwab and England scale ADL (SEADL)</td>
<td>The Schwab and England Scale reflects the participant’s ability to perform daily activities in terms of speed and independence, and is comprised of 20 points.</td>
</tr>
<tr>
<td>Self-Assessment Parkinson’s disease Disability Scale (SPDDS)</td>
<td>Participants rate how easy or difficult it was to perform 25 separate actions at their best and at their worst times on a 5-point scale (range of total scores 25-125). Higher scores indicate increased difficulty.</td>
</tr>
<tr>
<td>Short Form 36 (SF 36)</td>
<td>The SF-36 assesses functioning and well-being in any participant group with chronic disease. Thirty-six items in eight domains are included, which cover functional status, well-being, and overall evaluation of health. Scored range from 0 to 100, where a higher score indicates a better-perceived health status.</td>
</tr>
<tr>
<td><strong>Sickness Impact Profile (SIP)</strong></td>
<td>SIP is a general quality of life scale. It consists of 136 items, which measure 12 distinct domains of quality of life. Participants identify those statements, which describe their experience. Higher scores represent greater dysfunction.</td>
</tr>
<tr>
<td><strong>Ten-point Clock Drawing Test</strong></td>
<td>A test in which the participant is asked to draw a clock face marking the hours and then draw the hands to indicate a particular time.</td>
</tr>
<tr>
<td><strong>Timed-tapping scores</strong></td>
<td>The number of times the participant hits with a finger two spots some 40 cm apart in a 20-second interval.</td>
</tr>
<tr>
<td><strong>Trail Making Test</strong></td>
<td>The test consists of two parts. In Part A participants connect, in order, numbers 1-25 in as little time as possible. Part B is requires the participant to connect numbers and letters in an alternating pattern (i.e. 1-A-2-B) in as little time as possible.</td>
</tr>
<tr>
<td><strong>Unified Parkinson's Disease Rating Scale (UPDRS)</strong></td>
<td>A scale used to measure severity of Parkinson's Disease. It has six parts, and a higher score denotes greater disability.</td>
</tr>
<tr>
<td><strong>UPDRS I</strong></td>
<td>Mentation, behaviour, and mood (4 items)</td>
</tr>
<tr>
<td><strong>UPDRS II</strong></td>
<td>Activities of daily living (13 items)</td>
</tr>
<tr>
<td><strong>UPDRS III</strong></td>
<td>Motor examination (14 items)</td>
</tr>
<tr>
<td><strong>UPDRS IV</strong></td>
<td>Complications of treatment (11 items)</td>
</tr>
<tr>
<td><strong>UPDRS Total score</strong></td>
<td>Sum total of subscores</td>
</tr>
<tr>
<td><strong>UPDRS V</strong></td>
<td>Modified Hoehn and Yahr staging (8 items)</td>
</tr>
<tr>
<td><strong>UPDRS VI</strong></td>
<td>Schwab and England Activities of daily living score (20 items)</td>
</tr>
<tr>
<td><strong>UPSIT</strong></td>
<td>University of Pennsylvania Smell Identification Test. There are 40 microencapsulated scented pads in a booklet. Each individual scented pad is scratched with a pencil and sniffed one at a time. From a list of 4 choices for each pad, a correct answer must be chosen or a guess made.</td>
</tr>
<tr>
<td><strong>Webster rating scale</strong></td>
<td>Changes in the scale over time can reflect changes due to disease progression or therapeutic interventions. The scores range from 0 to 30; higher scores indicate greater disease severity.</td>
</tr>
</tbody>
</table>

**Glossary of terms**

<p>| <strong>Adverse events</strong> | A harmful, and usually relatively rare, event arising from treatment. |
| <strong>Akinesia</strong> | Absence or reduced functionality of movements. |
| <strong>Algorithm (in guidelines)</strong> | A flow chart of the clinical decision pathway described in the guideline. |
| <strong>Allied health professional (AHP)</strong> | Allied Health professionals are involved in the delivery of health services pertaining to the identification, evaluation and prevention of diseases and disorders. |
| <strong>Allocation concealment</strong> | The process used to prevent advance knowledge of group assignment in an RCT, and potential bias that may result. |</p>
<table>
<thead>
<tr>
<th>Term</th>
<th>Definition</th>
</tr>
</thead>
<tbody>
<tr>
<td>Baseline</td>
<td>The initial set of measurements at the beginning of a study (after run-in period where applicable), with which subsequent results are compared.</td>
</tr>
<tr>
<td>Bias</td>
<td>The effect that the results of a study are not an accurate reflection of any trends in the wider population. This may result from flaws in the design of a study or in the analysis of results.</td>
</tr>
<tr>
<td>Blinding (masking)</td>
<td>A feature of study design to keep the participants, researchers and outcome assessors unaware of the interventions which have been allocated.</td>
</tr>
<tr>
<td>Bradykinesia</td>
<td>Bradykinesia refers to slowness of movement.</td>
</tr>
<tr>
<td>Carer (caregiver)</td>
<td>Someone other than a health professional who is involved in caring for a person with a medical condition, such as a relative or spouse.</td>
</tr>
<tr>
<td>Clinical Audit</td>
<td>A systematic process for setting and monitoring standards of clinical care.</td>
</tr>
<tr>
<td>Cochrane Review</td>
<td>A systematic review of the evidence from randomized controlled trials relating to a particular health problem or healthcare intervention, produced by the Cochrane Collaboration.</td>
</tr>
<tr>
<td>Cohort</td>
<td>A group of participants.</td>
</tr>
<tr>
<td>Confidence interval (CI)</td>
<td>A range of values, which contains the true value for the population with a stated “confidence” (conventionally 95%).</td>
</tr>
<tr>
<td>Control</td>
<td>A person in the comparison group who receives a placebo, no intervention, usual care or another form of care.</td>
</tr>
<tr>
<td>Cost-effectiveness analysis (CEA)</td>
<td>An analytic tool in which costs and effects of a programme and at least one alternative are calculated and presented in a ratio of incremental cost to incremental effect. Effects are health outcomes, such as cases of a disease prevented, years of life gained, or quality-adjusted life years, rather than monetary measures as in cost-benefit analysis.</td>
</tr>
<tr>
<td>Cost-minimisation analysis (CMA)</td>
<td>An analytic tool used to compare the net costs of programmes that achieve the same outcome.</td>
</tr>
<tr>
<td>Cross-over trials</td>
<td>Type of trial comparing two or more interventions in which participants, upon completion of the course of one treatment, are switched to another.</td>
</tr>
<tr>
<td>DBS</td>
<td>Deep Brain Stimulation</td>
</tr>
<tr>
<td>Diagnostic study</td>
<td>Any research study aimed at evaluating the utility of a diagnostic procedure.</td>
</tr>
<tr>
<td>Differential diagnosis</td>
<td>An attempt to determine which of two or more diseases with similar symptoms a patient is suffering from.</td>
</tr>
<tr>
<td>Direct costs</td>
<td>The value of all goods, services and other resources that are consumed in the provision of an intervention or in dealing with the side effects or other current and future consequences linked to it.</td>
</tr>
<tr>
<td>Discount rate</td>
<td>The interest rate used to compute present value or the interest rate used in discounting future values.</td>
</tr>
<tr>
<td>Discounting</td>
<td>The process of converting future values and future health outcomes to their present value.</td>
</tr>
<tr>
<td>Term</td>
<td>Definition</td>
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<td>-------------------------------------------</td>
<td>---------------------------------------------------------------------------</td>
</tr>
<tr>
<td>Disease modifying therapy</td>
<td>Disease modifying therapy is the term used to refer to any treatment that beneficially affects the underlying pathophysiology of PD. (also known as 'neuroprotection').</td>
</tr>
<tr>
<td>Dysarthria</td>
<td>Slurred or otherwise impaired speech.</td>
</tr>
<tr>
<td>Dysarthria profile</td>
<td>A description of the dysarthric person’s problems, to supply the speech therapist with indications of where to begin in treatment.</td>
</tr>
<tr>
<td>Dyskinesia</td>
<td>The impairment of the power of voluntary movement, resulting in fragmentary or incomplete movements.</td>
</tr>
<tr>
<td>Dysphagia</td>
<td>Difficulty in swallowing.</td>
</tr>
<tr>
<td>Dystonia</td>
<td>Disordered tonicity of muscle.</td>
</tr>
<tr>
<td>Evidence-based health care</td>
<td>The process of systematically finding, appraising, and using research findings as the basis for clinical decisions.</td>
</tr>
<tr>
<td>Expert</td>
<td>A qualified medical specialist (see specialist)</td>
</tr>
<tr>
<td>False positive</td>
<td>Positive diagnostic test results in a person who does not possess the attribute for which the test is conducted.</td>
</tr>
<tr>
<td>Follow up</td>
<td>An attempt to measure the outcomes of an intervention after the intervention has ended.</td>
</tr>
<tr>
<td>Generalisability</td>
<td>The degree to which the results of a study or systematic review can be extrapolated to other circumstances, particularly routine health care situations in the NHS in England and Wales.</td>
</tr>
<tr>
<td>Gold standard</td>
<td>See ‘Reference standard’</td>
</tr>
<tr>
<td>Good Practice Points</td>
<td>Recommended good practice based on the clinical experience of the Guideline Development Group.</td>
</tr>
<tr>
<td>Guideline development group (GDG)</td>
<td>An independent group set up by NICE to develop a guideline. They include healthcare professionals and person/carer representatives.</td>
</tr>
<tr>
<td>Hazard ratio (HR)</td>
<td>A statistic to describe the relative risk of complications due to treatment, based on a comparison of event rates.</td>
</tr>
<tr>
<td>Heterogeneity</td>
<td>In systematic reviews, heterogeneity refers to variability or differences between studies in estimates of effect.</td>
</tr>
<tr>
<td>Homogeneity</td>
<td>In a systematic review, homogeneity means there are no or minor variations in the results between individual studies included in a systematic review.</td>
</tr>
<tr>
<td>Hypersomnolence</td>
<td>Excessive sleepiness.</td>
</tr>
<tr>
<td>Hypokinesia</td>
<td>Decreased muscular activity.</td>
</tr>
<tr>
<td>Inclusion criteria</td>
<td>Explicit criteria used to decide which studies should be considered as potential sources of evidence.</td>
</tr>
<tr>
<td>Incremental cost</td>
<td>The cost of one alternative less the cost of another.</td>
</tr>
<tr>
<td>Incremental cost effectiveness ratio (ICER)</td>
<td>The ratio of the difference in costs between two alternatives to the difference in effectiveness between the same two alternatives.</td>
</tr>
</tbody>
</table>
| Intention-to-treat analysis (ITT analysis)| An analysis of the results of a clinical study in which the data are analysed for all study participants as if they had remained in the group to
which they were randomised, regardless of whether or not they remained in the study until the end, crossed over to another treatment or received an alternative intervention.

<table>
<thead>
<tr>
<th>Term</th>
<th>Definition</th>
</tr>
</thead>
<tbody>
<tr>
<td>LD</td>
<td>Levodopa</td>
</tr>
<tr>
<td>Lee Silverman Voice Treatment (LSVT)</td>
<td>A treatment for voice and speech disorders associated with Parkinson’s disease to improve loudness, voice quality, and articulation.</td>
</tr>
<tr>
<td>MAO-B</td>
<td>Monoamine oxidase- B</td>
</tr>
<tr>
<td>Meta-analysis</td>
<td>A statistical technique for combining (pooling) the results of a number of studies that address the same question and report on the same outcomes to produce a summary result.</td>
</tr>
<tr>
<td>Mortality</td>
<td>The number of deaths in a given population and during a given time.</td>
</tr>
<tr>
<td>Motor fluctuations</td>
<td>Periods of the day with poor or absent motor response to medication alternating with periods of improved motor function.</td>
</tr>
<tr>
<td>MSA</td>
<td>Multiple System Atrophy</td>
</tr>
<tr>
<td>National Collaborating Centres (NCC)</td>
<td>Professionally led groups established by NICE to harness the expertise of the Royal Medical Colleges, specialist societies and person/carer organisations when developing clinical guidelines.</td>
</tr>
<tr>
<td>NCC-CC</td>
<td>National Collaborating Centre for Chronic Conditions</td>
</tr>
<tr>
<td>Negative predictive value</td>
<td>The proportion of people with a negative test result who do not have the disease.</td>
</tr>
<tr>
<td>NICE</td>
<td>National Institute for Clinical Excellence</td>
</tr>
<tr>
<td>NSF</td>
<td>National Service Framework</td>
</tr>
<tr>
<td>Odds ratio (OR)</td>
<td>The odds of an event happening in the treatment group, divided by the odds of it happening in the control group.</td>
</tr>
<tr>
<td>Off time</td>
<td>The duration of time when anti-parkinsonian medication is not controlling the person’s symptoms or is &quot;wearing-off&quot;.</td>
</tr>
<tr>
<td>On time</td>
<td>The duration of time when anti-parkinsonian medication is controlling PD symptoms.</td>
</tr>
<tr>
<td>Open label trial design</td>
<td>A clinical trial in which the investigator and participant are aware which intervention is being used for which person. These trials may or may not be randomised.</td>
</tr>
<tr>
<td>P values</td>
<td>The probability that an observed difference could have occurred by chance. A P value of less than 0.05 is conventionally considered to be 'statistically significant'.</td>
</tr>
<tr>
<td>PD</td>
<td>Parkinson’s disease</td>
</tr>
<tr>
<td>PDNS</td>
<td>Parkinson’s disease Nursing Specialist</td>
</tr>
<tr>
<td>PDS</td>
<td>Parkinson’s disease Society</td>
</tr>
<tr>
<td>Phenomenological study</td>
<td>The goal of qualitative phenomenological research is to describe a &quot;lived experience&quot;.</td>
</tr>
<tr>
<td>Placebo</td>
<td>An inactive and physically indistinguishable substitute for a medication or procedure, used as a comparator in controlled clinical trials.</td>
</tr>
<tr>
<td>Term</td>
<td>Definition</td>
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</tr>
<tr>
<td>Positive predictive value (PPV)</td>
<td>The proportion of people with a positive test result who actually have the disease.</td>
</tr>
<tr>
<td>Present value</td>
<td>The value which health care professionals and people with PD would attribute at present to an outcome (or avoidance of an outcome) in the future.</td>
</tr>
<tr>
<td>PSP</td>
<td>Progressive Supranuclear Palsy</td>
</tr>
<tr>
<td>Quality of life</td>
<td>Refers to the level of comfort, enjoyment, and ability to pursue daily activities.</td>
</tr>
<tr>
<td>Quality-of-life adjusted year (QALY)</td>
<td>A measure of health outcome which assigns to each period of time a weight, ranging from 0 to 1, corresponding to the health-related quality of life during that period, where a weight of 1 corresponds to optimal health, and a weight of 0 corresponds to a health state judged equivalent to death; these are then aggregated across time periods.</td>
</tr>
<tr>
<td>Randomisation</td>
<td>Allocation of participants in a study to two or more alternative groups using a chance procedure, such as computer-generated random numbers. This approach is used in an attempt to reduce sources of bias.</td>
</tr>
<tr>
<td>Randomised controlled Trial (RCT)</td>
<td>A comparative study in which participants are randomly allocated to intervention and control groups and followed up to examine differences in outcomes between the groups.</td>
</tr>
<tr>
<td>Reference standard (or gold standard)</td>
<td>An agreed desirable standard, for example a diagnostic test or treatment, against which other interventions can be compared.</td>
</tr>
<tr>
<td>Relative risk (RR)</td>
<td>The number of times more likely or less likely an event is to happen in one group compared with another.</td>
</tr>
<tr>
<td>Rigidity</td>
<td>Abnormal stiffness or inflexibility.</td>
</tr>
<tr>
<td>Sample size</td>
<td>The number of participants included in a trial or intervention group.</td>
</tr>
<tr>
<td>Sensitivity (of a test)</td>
<td>The proportion of people classified as positive by the gold standard, who are correctly identified by the study test.</td>
</tr>
<tr>
<td>Sensitivity analysis</td>
<td>A measure of the extent to which small changes in parameters and variables affect a result calculated from them. In this guideline, sensitivity analysis is used in health economic modelling.</td>
</tr>
<tr>
<td>Sialorrhoea</td>
<td>Increased saliva or drooling</td>
</tr>
<tr>
<td>Single blind study</td>
<td>A study where the investigator is aware of the treatment or intervention the participant is being given, but the participant is unaware.</td>
</tr>
<tr>
<td>Somnolence</td>
<td>Sleepiness or unnatural drowsiness.</td>
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<tr>
<td>Specialist</td>
<td>A clinician whose practice is limited to a particular branch of medicine or surgery, especially one who is certified by a higher medical educational organisation.</td>
</tr>
<tr>
<td>Specificity (of a test)</td>
<td>The proportion of people classified as negative by the gold standard, who are correctly identified by</td>
</tr>
<tr>
<td><strong>Stakeholder</strong></td>
<td>Any national organisation, including patient and carers’ groups, healthcare professionals and commercial companies with an interest in the guideline under development.</td>
</tr>
<tr>
<td>-----------------</td>
<td>--------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------</td>
</tr>
<tr>
<td><strong>Statistical power</strong></td>
<td>In clinical trials, the probability of correctly detecting an effect due to the intervention or treatment under consideration. Power is determined by the study design, and in particular, the sample size. Larger sample sizes increase the chance of small effects being detected correctly.</td>
</tr>
<tr>
<td><strong>Statistical significance</strong></td>
<td>A result is deemed statistically significant if the probability of the result occurring by chance is less than 1 in 20 (p&lt;0.05).</td>
</tr>
<tr>
<td><strong>Stereotactic Surgery</strong></td>
<td>A precise method of locating deep brain structures by using three-dimensional co-ordinates. The surgical technique may either involve stimulation or lesioning of the located site.</td>
</tr>
<tr>
<td><strong>Systematic review</strong></td>
<td>Research that summarises the evidence on a clearly formulated question according to a pre-defined protocol using systematic and explicit methods to identify, select and appraise relevant studies, and to extract, collate and report their findings. It may or may not use statistical meta-analysis.</td>
</tr>
<tr>
<td><strong>Time horizon</strong></td>
<td>The period of time for which costs and effects are measured in a cost-effectiveness analysis.</td>
</tr>
<tr>
<td><strong>Uptake</strong></td>
<td>The absorption of a substance (often a radionucleotide such as Fluoro-dopa) into the brain tissue which can then be visualised through imaging techniques.</td>
</tr>
<tr>
<td><strong>Washout period</strong></td>
<td>The stage in a crossover trial when one treatment is withdrawn before the second treatment is given.</td>
</tr>
<tr>
<td><strong>Withdrawal</strong></td>
<td>When a trial participant discontinues the assigned intervention before completion of the study.</td>
</tr>
</tbody>
</table>
Appendix K. List of Registered Stakeholders
• Addenbrooke’s NHS Trust
• Age Concern Cymru
• Age Concern England
• Airedale General Hospital
• Alliance Pharmaceuticals Ltd
• Amersham Health
• Anglesey Local Health Board
• Ashfield and Mansfield District PCTs
• Association for Continence Advice (ACA)
• Association of British Health-Care Industries
• Association of British Neurologists
• Association of Professional Music Therapists
• Association of the British Pharmaceuticals Industry (ABPI)
• Barts and the London NHS Trust
• Bayer PLC
• Birmingham Clinical Trials Unit
• Birmingham Heartlands & Solihull NHS Trust
• Boehringer Ingelheim Ltd
• Bolton, Salford & Trafford Mental Health
• Bradford South & West Primary Care Trust
• Brain and Spine Foundation
• Bristol-Myers Squibb Pharmaceuticals Ltd
• Britannia Pharmaceuticals Ltd
• British Association for Counselling and Psychotherapy
• British Association for Psychopharmacology
• British Dietetic Association
• British Geriatrics Society
• British National Formulary (BNF)
• British Neuropsychiatry Association
• British Nuclear Medicine Society
• British Psychological Society, The
• British Society of Neuroradiologists
• British Society of Rehabilitation Medicine
• BUPA
• Cephalon UK Ltd
• Chartered Society of Physiotherapy
• Cheltenham & Tewkesbury PCT
• Cochrane Movement Disorders Group
• College of Occupational Therapists
• Community District Nurses Association
• Community Psychiatric Nurses’ Association
• Continence Foundation
• Co-operative Pharmacy Association
• Cyberonics S.A/N.V.
• Department of Health
• Derbyshire Mental Health Services NHS Trust
• Dudley Beacon & Castle Primary Care Trust
• Eisai Limited
• Elan Pharmaceuticals Ltd
• Eli Lilly and Company Ltd
• Faculty of Public Health
• Gateshead Health NHS Trust
• GE Health Care
• Gedling Primary Care Trust
• GlaxoSmithKline UK
• Greater Peterborough Primary Care Partnership-North PCT
• Guys & St Thomas NHS Trust
• Hammersmith Hospitals NHS Trust
Hampshire Partnership NHS Trust
Healthcare Commission
Help the Aged
Help the Hospices
Hereford Hospital NHS Trust
Herefordshire Primary Care Trust
Hertfordshire Partnership NHS Trust
Independent Healthcare Forum
Institute of Rehabilitation
Institute of Sport and Recreation Management
James Parkinson Centre
Kyowa Hakko UK Ltd
Long Term Medical Conditions Alliance
Lundbeck Limited
Mansfield District PCT
Medeus Pharma Limited
Medicines and Healthcare Products Regulatory Agency (MHRA)
Medtronic Limited
Merck Pharmaceuticals
Mid Staffordshire General Hospitals NHS Trust
National Council for Disabled People, Black, Minority and Ethnic Community (Equalities)
National Mental Health Partnership
National Patient Safety Agency
National Public Health Service - Wales
National Schizophrenia Fellowship (Rethink)
National Tremor Foundation
Neurological Alliance
Newcastle, North Tyneside and Northumberland MH Trust
NHS Direct
NHS Health and Social Care Information Centre
NHS Modernisation Agency, The
NHS Quality Improvement Scotland
North Essex Mental Health Partnership Trust
North Staffordshire Combined Healthcare NHS Trust
Novartis Pharmaceuticals UK Ltd
Orion Pharma (UK) Ltd
Orphan Europe UK Ltd
Parkinson's Disease Nurse Specialist Association (PDNSA)
Parkinson's Disease Society
Pfizer Limited
Plymouth Primary Care Trust
Primary Care Neurology Society
Princess Alexandra Hospital NHS Trust
PromoCon (Disabled Living)
Relatives and Residents Association
Roche Products Limited
Royal College of Anaesthetists
Royal College of General Practitioners
Royal College of General Practitioners Wales
Royal College of Nursing (RCN)
Royal College of Physicians of London
Royal College of Psychiatrists
Royal College of Speech and Language Therapists
Royal Pharmaceutical Society of Great Britain
Sanofi-Synthelabo
Schwarz Pharma
Scottish Intercollegiate Guidelines Network (SIGN)
Selby & York PCT
Sheffield Teaching Hospitals NHS Trust
Sherwood Forest Hospitals NHS Trust
• Social Care Institute for Excellence (SCIE)
• Society of British Neurological Surgeons
• Solvay Healthcare Limited
• South Birmingham Primary Care Trust
• Sue Ryder Care
• Teva Pharmaceuticals Ltd
• The Medway NHS Trust
• The Progressive Supranuclear Palsy [PSP Europe] Association
• The Royal Society of Medicine
• The Royal West Sussex Trust
• Trafford Primary Care Trusts
• UK Clinical Pharmacy Association
• University College Londons Hospital NHS Trust
• Valeant Pharmaceuticals
• Walton Centre for Neurology and Neurosurgery NHS Trust
• Welsh Assembly Government (formerly National Assembly for Wales)
• West Cornwall PCT
• West of Cornwall PCT
• Wirral Hospital NHS Trust
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