Draft for consultation

Parkinson's disease in adults

Parkinson's disease in adults: diagnosis and management

Update 2017

NICE guideline

Methods, evidence and recommendations

Draft for Consultation

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Disclaimer
Healthcare professionals are expected to take NICE clinical guidelines fully into account when exercising their clinical judgement. However, the guidance does not override the responsibility of healthcare professionals to make decisions appropriate to the circumstances of each patient, in consultation with the patient and/or their guardian or carer.

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1.3 Strength of recommendation

Some recommendations can be made with more certainty than others. The GDG makes a recommendation based on the trade-off between the benefits and harms of an intervention, taking into account the quality of the underpinning evidence. For some interventions, the GDG is confident that, given the information it has looked at, most patients would choose the intervention. The wording used in the recommendations in this guideline denotes the certainty with which the recommendation is made (the strength of the recommendation).

For all recommendations, NICE expects that there is discussion with the patient about the risks and benefits of the interventions, and their values and preferences. This discussion aims to help them to reach a fully informed decision (see also 'Patient-centred care').

Interventions that must (or must not) be used

We usually use 'must' or 'must not' only if there is a legal duty to apply the recommendation. Occasionally we use 'must' (or 'must not') if the consequences of not following the recommendation could be extremely serious or potentially life threatening.

Interventions that should (or should not) be used – a 'strong' recommendation

We use 'offer' (and similar words such as 'refer' or 'advise') when we are confident that, for the vast majority of patients, an intervention will do more good than harm, and be cost effective. We use similar forms of words (for example, 'Do not offer…') when we are confident that an intervention will not be of benefit for most patients.

Interventions that could be used

We use 'consider' when we are confident that an intervention will do more good than harm for most patients, and be cost effective, but other options may be similarly cost effective. The choice of intervention, and whether or not to have the intervention at all, is more likely to depend on the patient's values and preferences than for a strong recommendation, and so the healthcare professional should spend more time considering and discussing the options with the patient.

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2 Methods

This guideline was developed in accordance with the process set out in 'The guidelines manual (2012)'. There is more information about how NICE clinical guidelines are developed on the NICE website. A booklet, 'How NICE clinical guidelines are developed: an overview for stakeholders, the public and the NHS' is available. In instances where the guidelines manual does not provide advice, additional methods are used and are described below.

2.1 Additional methods used in this guideline

2.1.1 Evidence synthesis and meta-analyses

Where possible, meta-analyses were conducted to combine the results of studies for each outcome. For continuous outcomes, where change from baseline data were reported in the trials and were accompanied by a measure of spread (for example standard deviation), these were extracted and used in the meta-analysis. Where measures of spread for change from baseline values were not reported, the corresponding values at study end were used and were combined with change from baseline values to produce summary estimates of effect. These studies were assessed to ensure that baseline values were balanced across the treatment groups; if there were significant differences at baseline these studies were not included in any meta-analysis and were reported separately.

2.1.2 Interventional evidence

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2.1.2.1 Quality assessment

GRADE was used to assess the quality of evidence for the selected outcomes as specified in 'The guidelines manual (2012)'. Where RCTs are available, these are initially rated as high quality and the quality of the evidence for each outcome was downgraded or not from this initial point. If non-RCT evidence was included for intervention-type systematic reviews then these are initially rated a low quality and the quality of the evidence for each outcome was downgraded or not from this point.

2.1.2.2 Methods for combining intervention evidence

Meta-analysis of interventional data was conducted with reference to the Cochrane Handbook for Systematic Reviews of Interventions (Higgins et al. 2011).

Dichotomous outcomes were pooled on the relative risk scale (using the Mantel–Haenszel method).

Fixed- and random-effects models (der Simonian and Laird) were fitted for all syntheses, with the presented analysis dependent on the degree of heterogeneity in the assembled evidence. Fixed-effects models were the preferred choice to report, but in situations where the assumption of a shared mean for fixed-effects model were clearly not met (defined as I^2 ≥50%, and thus the presence of significant heterogeneity), random-effects results are presented.

Pairwise meta-analyses were performed in Cochrane Review Manager v5.3 or R v3.2.2, using identical methods across the two programs.

2.1.2.3 GRADE for pairwise meta-analyses for interventional evidence

The quality of the evidence for each outcome was downgraded where appropriate for the reasons outlined in Table 1

Table 1: Rationale for downgrading quality of evidence for intervention studies

GRADE criteria	Example reasons for downgrading quality
Risk of bias	The quality of the evidence was downgraded if there were concerns about the design or execution of the study, including concealment of allocation, blinding, loss to follow up using intervention checklists in the NICE guidelines manual (2012)
Inconsistency	The quality of the evidence was downgraded if there were concerns about inconsistency of effects across studies: occurring when there is variability in the treatment effect demonstrated across studies (heterogeneity). This was assessed using the statistic, I^2 where ; $I^2 < 40\%$ was categorised as no inconsistency, and $I^2 \geq 40\%$ was categorised as serious inconsistency
Indirectness	The quality of the evidence was downgraded if there were concerns about the population, intervention and outcome in the included studies and how directly these variables could address the specific review question.
Imprecision	The quality of the evidence was downgraded if uncertainty around the effect estimate encompassed a range of values that could lead to different clinical decisions – that is, when 95% confidence intervals crossed the lines of minimally important effect (see 2.1.3), or the line of no effect in cases where no minimally important difference was defined . Very serious imprecision – when the data were consistent with appreciable benefit, appreciable harm and no difference at the 95% confidence level – led to the outcome being downgraded twice.

2.1.2.4 Methods for combining direct and indirect evidence (network meta-analysis)

Conventional pairwise meta-analysis involves the statistical combination of direct evidence about pairs of interventions that originate from 2 or more separate studies (for example, where there are two or more studies comparing A vs B).

In situations where there are more than 2 interventions, pairwise meta-analysis of the direct evidence alone is of limited use. This is because multiple pairwise comparisons need to be performed to analyse each pair of interventions in the evidence, and these results can be difficult to interpret. Furthermore, direct evidence about interventions of interest may not be available. For example studies may compare A vs B and B vs C, but there may be no direct evidence comparing A vs C. Network meta-analysis (NMA) overcomes these problems by combining all evidence into a single, internally consistent model, synthesising data from direct and indirect comparisons, and providing estimates of relative effectiveness for all comparators and the ranking of different interventions.

Synthesis

Two methods of network meta-analysis were used in this guideline.

- For section 7.5, hierarchical Bayesian NMA was performed using WinBUGS version 1.4.3. The models used reflected the recommendations of the NICE Decision Support Unit's Technical Support Documents (TSDs) on evidence synthesis, particularly TSD 2 ('A generalised linear modelling framework for pairwise and network meta-analysis of randomised controlled trials'; see http://www.nicedsu.org.uk). The WinBUGS code provided in the appendices of TSD 2 was used without substantive alteration to specify synthesis models.

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Results were reported summarising 10,000 samples from the posterior distribution of each model, having first run and discarded 50,000 'burn-in' iterations. Three separate chains with different initial values were used.

Non-informative prior distributions were used in all models. Trial-specific baselines and treatment effects were assigned N(0, 1000) priors, and the between-trial standard deviations used in random-effects models were given U(0, 5) priors. These are consistent with the recommendations in TSD 2 for dichotomous outcomes.

Fixed- and random-effects models were explored for each outcome, with the final choice of model based on deviance information criterion (DIC): if DIC was at least 3 points lower for the random-effects model, it was preferred; otherwise, the fixed effects model was considered to provide an equivalent fit to the data in a more parsimonious analysis, and was preferred.

- For sections 6.1, 6.2 and 8, NMAs were undertaken using the `netmeta` package in R3.2.2. This uses a graph-theoretical method which is mathematically equivalent to frequentist network meta-analysis (Rücker 2012). Inconsistency was assessed using the overall I^2 value for the whole network, which is a weighted average of the I^2 value for all comparisons where there are multiple trials (both direct and indirect), and random-effects models were used if the I^2 value was above 50% (as for pairwise meta-analyses, this was interpreted as showing the assumption of a shared underlying mean was not met, and therefore a fixed-effects model was inappropriate).

Because different approaches and software had been applied, sensitivity analysis was undertaken to establish whether this might have led to any substantive difference in output. Specimen dichotomous and continuous NMAs from section 7.5 were rerun in the frequentist framework, and generated results that were materially indistinguishable from the Bayesian version.

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Applying GRADE to network meta-analysis

The use of GRADE to assess the quality of studies addressing a particular review question for pairwise comparisons of interventions is relatively established. However, the use of GRADE to assess the quality of evidence across a network meta-analysis is still a developing methodology. While most criteria for pairwise meta-analyses still apply, it is important to adapt some of the criteria to take into consideration additional factors, such as how each 'link' or pairwise comparison within the network applies to the others. As a result, the following was used when modifying the GRADE framework to a network meta-analysis.

Risk of bias

In addition to the usual criteria to assess the risk of bias or 'limitations' of studies for each pairwise analysis within a network, the risk of bias was assessed for each direct comparison and assessed to see how it would affect the indirect comparisons. In addition, there was an assessment of treatment effect modifiers to see if they differed between links in the network.

For network meta-analyses with a large proportion of studies that were judged to be susceptible to bias, some downgrading decision rules were applied.

- If 50% or more studies in the network were inadequate or unclear for a particular parameter of quality, the outcome was downgraded by 1 level.
- As with pairwise meta-analyses, studies with differences in concomitant treatment between groups, or which did not report concomitant treatment between groups (where permitted), were treated with caution. Additionally, if there were differences in concomitant treatment among the studies included in different links across the network, the overall outcome was downgraded.

Inconsistency

Inconsistency was assessed for the heterogeneity of individual pairwise comparisons in the network, and also between direct and indirect comparisons where both were available (that is, where there were 'loops' in the network).

Heterogeneity across studies for each direct pairwise meta-analysis was assessed using I^2. This allowed for the assessment of heterogeneity within the included studies using the following decision rules:

- If there was considerable heterogeneity for 1 link or more in a network, the outcome was downgraded 1 level.
- If there was more than 1 link in the network with considerable, substantial or moderate heterogeneity, consideration was given to downgrading 2 levels.

To assess for consistency in each pairwise comparison where both direct and indirect evidence are available, the values of the direct and indirect estimates were compared to see if they were similar.

The overall values of I^2 (which combines heterogeneity between multiple studies of the same comparison and inconsistency between direct and indirect comparisons) and tau were also assessed to compare heterogeneity across the network.

Indirectness

As with pairwise meta-analyses, studies included in a network were assessed for how well they fit the PICO (population, intervention, comparator, outcome) specified in the review protocol.

Imprecision

Imprecision was assessed for a number of variables:

- Sufficient head-to-head trials in the network.
- Sufficient number of studies to form the network (if there was a high proportion of 'links' formed with only 1 trial, the outcome was downgraded).
- Overall certainty/uncertainty of the effect estimates (size of confidence/credible intervals, including for each drug compared with the reference option, and size of confidence/credible intervals for the overall rankings within the network).
- For networks, imprecision was considered around both the direct and indirect effect estimates.

When assessing imprecision for pairwise comparisons, or for networks with only 1 trial for all 'links' in the network, the confidence interval around the direct estimate was used.

2.1.3 Minimally important differences

The following published MIDs for Parkinson's outcomes in the research literature were adopted for this guideline:

- PDQ39 single index: 1.6 points (Peto et al., 2001)
- UPDRS-II (activities of daily living): 3 points (Schrag et al., 2006)
- UPDRS-III (motor): between 3.25 (Horváth et al., 2015) and 5 points (Schrag et al., 2006)

For some outcomes (EQ-5D, Zarit carer burden interview, on time and off time), the committee agreed that any statistically significant differences in changes from baseline would also be clinically meaningful.

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The committee also agreed that it was not sensible to attempt to define a population-level MID for changes in HY stage: individuals can only move by whole or half-points on the scale (and any such changes are reflective of obviously meaningful deterioration/improvement), but a population-level mean change of a fraction of a point is more difficult to interpret. Therefore, the committee decided it was reasonable to conclude that any treatments that result in measurable, statistically significant differences in mean Hoehn and Yahr score must have affected a nontrivial proportion of people by a nontrivial amount.

2.1.4 Qualitative evidence

Modified GRADE was used to assess the quality of evidence for the selected outcomes as specified in 'The guidelines manual (2012)'. All qualitative design studies (surveys and interviews) were initially graded as high-quality evidence if well conducted, and then downgraded according to the standard GRADE criteria (risk of bias, inconsistency and indirectness) as detailed in Table 2 below. Imprecision was not applicable here as qualitative data do not provide a measure of variation (standard deviation).

2.1.4.1 Methods for combining qualitative evidence

Due to the relatively few papers identified for qualitative evidence, it was deemed not appropriate to synthesise them. Instead, a narrative summary of the key themes or illustrative quotes of each paper were provided.

2.1.4.2 GRADE for qualitative evidence

GRADE has not been developed for use with qualitative studies; therefore a modified approach was applied using the GRADE framework.

Table 2: Rational for downgrading quality of evidence for qualitative studies

GRADE criteria	Example reasons for downgrading quality
Risk of bias	The quality of evidence was downgraded if there were concerns about the design or execution of the study, using relevant checklists in the NICE guidelines manual (2012) or CASP. For example, studies were downgraded if the study methodology was unclear and/or if survey/interview materials had not been standardised or validated.
Inconsistency	In situations where there are more than 1 study, the quality of evidence was downgraded if there is variability in the derived themes.
Indirectness	The quality of the evidence was downgraded if there were concerns about the population and outcome in the included studies and how directly these variables could address the specific review question.

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Evidence reviews and recommendations

3 Communication with people with Parkinson's disease and their carers

'I'd like them to remember to ask the patient how he feels and to listen to the patient. I'd like them to be more aware that each patient is an individual.' (patient)[2]

'I think what would have really helped was if someone had encouraged me to keep asking questions. The more you find out the easier it is to understand.' (patient)[4]

3.1.1 Introduction

Good communication is at the heart of every interaction between people with Parkinson's disease, their carers and health professionals. Issues that need to be considered include:

- style, manner and frequency of communication content and means of transmission
- ease of access for those receiving information, and consistency of content
- recognition that people with Parkinson's disease have particular clinical problems requiring carefully and sensitively tailored communication
- communication goals including self-management by people with Parkinson's disease and involvement of carers.

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 living with their own condition 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.

For people with Parkinson's disease the main objective should be collaborative care, although interventions such as the Expert Patient Programme,[25] which concentrates on self-management, will have a part to play for some individuals. In addition, the NSF for Long-term (Neurological) Conditions (2005),[14] especially Quality requirement 1, which relates to a person-centred service, should underpin the principles of communication with people with Parkinson's disease and their carers.

3.1.2 Methodology

Six studies [26–31] have addressed communication about the diagnosis of Parkinson's disease. Since there were few RCTs in this area, qualitative studies and cross-sectional studies using questionnaire data collection tools were included. The literature search included the area of self-help in relation to communication and education of people with Parkinson's disease. However, no studies were found which specifically addressed this topic.

Qualitative studies were assigned evidence level 3 in accordance with NICE guidance.[1]

A qualitative study[29,30] using an interpretive phenomenological method identified a number of themes, but did not include a clear audit trail demonstrating how these were derived from the original patient data collected.

A cross-sectional self-report questionnaire study [29,30] collected response data from physio-therapists and occupational therapists who observed video records of patients.

It should be noted that:

- the PROPATH program [26,27] was a pharmaceutically sponsored educational service only available in the USA
- the survey from the Parkinson's Disease Society (PDS)[31] was based on a questionnaire of members in the UK.

The PROPATH program consisted of a disease assessment questionnaire, which was completed by people with Parkinson's disease or their carer. The questionnaire was analysed and computer-generated reports were returned to physicians and individualised recommendation letters returned to people with Parkinson's disease. 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.

3.1.3 Evidence statements

Two RCTs [26,27] were found, which assessed the effectiveness of the PROPATH education program, as a novel approach to communication with people with Parkinson's disease.

A 6-month follow-up PROPATH study[26] (N=155) showed multiple benefits of the PROPATH intervention which are listed in Table 4.1. (1+)

Table 4.1 Effectiveness of PROPATH program versus standard care

Outcome measures (N=322)	p value
Rate of disease progression during the program*	0.03
Number of people with PD exercising	0.006
Medical utilisation (in terms of doctor visits)	0.06
Time 'off'	>0.01
Quality-of-life assessment: self-efficacy measure**	
6 months score	<0.05
Total score	<0.01

*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 to 100 horizontal analogue scale.

A separate 12-month follow-up PROPATH study (N=73)[27] 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). (1+)

A multinational Global Parkinson's Disease Survey[28] of people with Parkinson's disease (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 Parkinson's disease:

- depression as measured by the 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). (3)

An interpretative phenomenological study [29] in 16 people with Parkinson's disease identified the theme of 'gaining formal knowledge' and provided the following information on their perspectives:

- Once diagnosed, people with Parkinson's disease 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. (3)

In a questionnaire study, 30 physiotherapists and occupational therapists (N=91) were asked to compare the video-recorded conversations of people with Parkinson's disease (N=4) and people with cardiac conditions (N=4) without the soundtrack. The aim was for the therapists to gauge their initial impressions of the people seen. The therapists were told the people being interviewed suffered from a neurological disorder, but the clinical diagnosis was not revealed. 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 Parkinson's disease 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 ($p<0.001$). (3)

In addition to their observations, the therapists were asked how likeable the person with Parkinson's disease appeared to them. People with Parkinson's disease appeared less likeable ($p<0.001$). (3)

It is worth noting that the people with Parkinson's disease 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 Parkinson's disease, and this could influence the development of their relationship with their clinician.

Another study[32] (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). The findings are summarised as follows.

- The average patient education score indicated 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 Short Form 36 (SF-36), except for physical function and bodily pain.

- Patients were most satisfied with regard to 'role emotional' and least satisfied with regard 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 Table 4.2 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 aspects of daily living.
- Motor complications associated with therapy had a substantial effect on each subscale of SF-36. (3)

Table 4.2 Relationship of patient education with SF-36 (regression coefficients of patient education score)

	All patients	Excluding Hoehn and Yahr (stage 4 and 5)
Physical functioning	–0.76	–0.47
Role – physical	3.74*	5.23*
Bodily pain	2.01	0.06
General health	2.10*	1.99
Vitality	3.32*	3.66*
Social functioning	3.04*	4.40*
Role – emotional	4.18*	4.91*
Mental health	2.83*	4.10*

Adjusted for age, sex, number of comorbidities, 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

The UK PDS[31] 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 Table 4.3. (3)

Table 4.3 PDS survey (1999)[31]

Whether the person had PD explained to them on diagnosis (N=1,127)	(%)
Very clearly explained	20
Fairly clearly explained	24
Neither clearly nor unclearly explained	9
Not very clearly explained	17
Not at all clearly explained	9
No explanation given	15
Whether people were given an opportunity to ask questions on diagnosis	
Adequate opportunity	28
Fairly adequate opportunity	22
No opportunity at all	15
Did not want/feel able to ask questions at the time	22

How useful people find PD information resources (N=1,693)

	Very useful	Not very useful	Not used/ not available	Did not answer
Hospital doctor/consultant	56	19	14	12
PDS – local branch	40	7	36	17
GP	39	37	13	11
PDS – national office	36	9	36	19
People who have PD or care for someone with PD	36	7	36	21
Newspapers or magazines	32	24	26	19
Pharmacist	25	11	45	19
PDNS	24	3	56	17
Physiotherapist	23	9	50	18
Occupational therapist	19	7	56	19
Television/radio	19	29	32	20
Social services department	18	12	51	18
Speech therapist	16	7	58	19
PDS – field staff (eg area officer)	15	6	57	21

continued

Table 4.3 PDS survey (1999)[31] – *continued*

Subjects on which people need information (N=945)	(%)
New treatments that may be available in future	90
What drugs are available and/or their side effects	84
Specific health problems related to PD	81
How the disease is likely to affect me or the person I care for in the future	75
Aids and equipment and how to get them	49
How PD can affect personal relationships	44
How to get health or social services assistance	41
How to get welfare benefits and financial help	39
How to deal with difficulties in getting services for people with PD from insurance companies, banks, etc.	30
How to find a suitable holiday	29
How to find suitable respite care	26

3.1.4 From evidence to recommendation

People with Parkinson's disease 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. The choice of initial therapy should aim to optimise the quality of life over the whole expected lifespan of an individual. It is essential that these decisions are specific to an individual and agreed between the person with Parkinson's disease and the appropriate clinicians after a period of reflection including involvement of the family.

The evidence shows that the way in which the diagnosis of Parkinson's disease is communicated is important and often not well done. People with Parkinson's disease 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 PDNS (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 PDS.

Particular features that need to be taken into account when communicating with people with Parkinson's disease are:

- occurrence of cognitive impairment and depression
- occurrence of a communication impairment (which increases in severity with increasing severity of the disease process)
- negative impression that may be given by a person with Parkinson's disease need for emotional support
- involvement of carers.

Effective communication requires well-trained staff and an environment that enables sensitive discussions, as these discussions might lead to emotional distress. The UK PDS published guidance about communication with people with Parkinson's disease and their carers.[33] The recommendations arose from a group of 17 people with Parkinson's disease, with ages ranging from 47 to 67, and their carers.

It is important to communicate with carers, particularly when people with Parkinson's disease have cognitive impairment or depression. Carers need:

- general factual information about the condition
- specific information, if permission is given, about the person with Parkinson's disease
- information about services and entitlements to care assessment and support procedures advice and support both to optimise the quality of the communication interaction and also to continue effective communication with the person with Parkinson's disease as the condition progresses
- advice and support to maintain their health and well-being.

3.1.5 Recommendations

1. **Communication with people with Parkinson's disease should aim towards empowering them to participate in judgements and choices about their own care. [2006]**

2. **In discussions, aim to achieve a balance between providing honest, realistic information about the condition and promoting a feeling of optimism. [2006]**

3. **Because people with Parkinson's disease may develop impaired cognitive ability, communication problems and/or depression, provide them with:**
    - 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. [2006]

4. **Give family members and carers (as appropriate) information about the condition, their entitlement to a Carer's Assessment and the support services available. [2006]**

5. **People with Parkinson's disease should have a comprehensive care plan agreed between the person, the family members and carers (as appropriate), and specialist and secondary healthcare providers. [2006]**

6. **Offer people with Parkinson's disease an accessible point of contact with specialist services. This could be provided by a Parkinson's disease nurse specialist. [2006]**

7. **Advise people with Parkinson's disease who drive that they should inform the Driver and Vehicle Licensing Agency (DVLA) and their car insurer of their condition when Parkinson's disease is diagnosed. [2006]**

4 Information needs of people with Parkinson's disease and their families and carers

This section covers the information needs of people with Parkinson's disease about the risk of developing impulse control disorders (ICDs), and also the specific information needs of women of child bearing age. ICDs are a group of psychiatric conditions linked by their repetitive reward-based behaviours. Their core feature is the failure to resist an impulse, drive, or temptation to perform an act harmful to either oneself or others. ICDs are a recognised feature of Parkinson's disease (PD) with reviews reporting their prevalence as between 14 and 24% in treated patients. Evidence suggests an association with both dopamine agonists (DAs) and levodopa. The most frequently reported behaviours include pathological gambling, hypersexuality, compulsive shopping, hobbyism and binge eating.

The presence of ICDs can lead to severe distress for patients and carers, sometimes leading to financial difficulties and even criminal convictions. ICDs may be covert, with patients taking steps to conceal their behaviour from carers and family.

To reduce unnecessary distress it is essential to discuss the possibility of developing ICDs with the patient and their family members / carers before dopamine agonist therapy is commenced. In terms of summarising any patient / carer discussions it is standard practice for clinicians to send the patient a copy of the clinic letter that covers the risk of developing an ICD prior to starting treatment with DAs. Alternatively a monitoring tool is also available from Parkinson's UK about DAs and their associated risks. This may be a useful source of information to provide patients with, or for clinicians to use as a tool to guide their discussion about ICDs with patients and their family or carers.

Carer and family members need to also be vigilant to any change in behaviour of the person with PD and therefore need to be informed about the risks and signs to look out for. A regular review by healthcare professionals of how the patient is coping on their dopaminergic mediation, especially dopamine agonists, including an assessment of the possible development of any ICDs is very important.

Whilst the overall rates of pregnancy in women with Parkinson's disease are low, the increase in the average age at which women are having children means this number is likely to increase in the future. Whilst the majority of these pregnancies end successfully concerns remain, both about the way Parkinson's disease may affect the standard circulatory and hormonal changes that occur during pregnancy, and whether Parkinson's disease medicines may need to be modified during pregnancy. It is important that healthcare professionals are prepared to discuss these issues with women with Parkinson's disease who become or wish to become pregnant.

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4.1 Impulse control disorders

What are the information needs of people with Parkinson's disease and their families and carers about the potential for impulse control disorder (ICD) when considering or starting dopaminergic treatment?

4.1.1 Introduction

The aim of this review question was to determine the information needs of people with Parkinson's disease and their families and carers about the potential for ICD development when considering starting or on dopaminergic therapy.

The review focused on identifying studies that fulfilled the conditions specified in Table 3.

Table 3: PICO table for information needs for people with Parkinson's disease in relation to impulse control disorders

Population	Patients with a confirmed diagnosis of Parkinson's disease who are considering or about to commence dopaminergic therapy, and their family or carers.
Interventions	Any information needs identified in the literature that are specific to people with Parkinson's disease who are considering dopaminergic therapy, and their carers
Comparators	Not applicable for qualitative studies
Outcomes	Relevant information needs identified by the GDG : • Signs and symptoms of ICD • Pre-existing risk factors in the person with Parkinson's disease • Risks from different therapies i.e. dopamine agonists • Who to contact if an ICD is suspected • Behavioural and therapeutic strategies for management of ICD • Health related quality of life • Patient experience • Carer experience

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For full details of the review protocol, please see Appendix C. All types of primary study design, except case studies, were considered eligible, and the results were narratively synthesised.

4.1.2 Evidence review

An overarching systematic search was conducted to inform review questions 8, 9, and 10 (see appendix I), which identified 3,423 references. The references were screened on their titles and abstracts and full papers of 60 references were obtained and reviewed against the inclusion and exclusion criteria in the review protocol (see appendix C). This review question was not considered in the previous Parkinson's disease guideline (CG35), no further studies were therefore identified.

Overall, 44 studies were excluded as they did not meet the eligibility criteria such as inappropriate study design, narrative review with no primary data, or populations other than Parkinson's disease. A detailed list of excluded studies and reasons for their exclusion is provided in appendix G.

One study met the inclusion criteria for the current review question. Information needs regarding the potential for the development of ICD were also extrapolated from the reviews of the 15 published papers that were included in review questions 8 and 9 on the predictors for development of ICD and strategies for management of ICD. An additional 8 new papers

were identified through rerun searches at the end of the guideline, of which 1 was included for the current review question, 2 were included for review question 8 and 5 were excluded.

4.1.3 Description of included studies

One study (Phu et al., 2014) of 100 people with Parkinson's disease (ICD: N=15, mean age 64.6 years [SD 7.7]; no ICD: N=85, mean age 67.6 years [SD 9.2]) investigated the effects of impulse control and related disorders (ICRD) on quality of life (QoL) and disability in Parkinson's disease. Patients were interviewed by experienced psychiatrists using the expanded structured clinical interview for diagnostic and statistical manual (DSM IV) for a range of ICRDs, including obsessive compulsive disorder, pathological gambling and binge eating disorder. In addition, a mini neuropsychiatric interview was used to assess the presence of manic depressive disorder. Quality of life measurements were assessed using the self-administered Parkinson's disease questionnaire 39 (PDQ-39).

Another study (Mestre et al., 2014) of 469 participants (201 people with Parkinson's disease, 268 physicians) investigated the reluctance to start medication for Parkinson's disease. Patients were interviewed with a structured questionnaire by a study investigator other than the caring physician and physicians were invited to complete an electronic survey consisting of multiple choice questions. The following topics were covered in the questionnaire/ electronic survey: prevalence of reluctance to start medication, causes and drug-specificity for reluctance to start medication and the consequences of reluctance to start medication.

Evidence tables for included studies can be found in Appendix D, with GRADE profiles reported in Appendix E.

4.1.4 Evidence statements

Health-related quality of life

High-quality evidence from 1 study (Phu et al., 2014) reported ICRD to be associated with worse quality of life, as indicated by higher scores on the self-reported PDQ39 (MD=18, 95% CI: 2.24 to 33.76).

Signs and symptoms of ICD

Evidence on the signs and symptoms of ICDs, used to inform the information needs of patients and their families and carers was derived from review question 8. Please see section 10 on managing and monitoring impulse control disorder.

Pre-existing risk factors

Evidence on the pre-existing risk factors for the development of ICDs, used to inform information needs of patients and their families and carers was derived from review question 8. Please see section 10 on managing and monitoring impulse control disorder.

Risks from different therapies

Evidence for the risks of different therapies for the development of ICDs to inform information needs of patients and their families and carers was derived from review question 8. Please see section 10 on managing and monitoring impulse control.

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Behavioural and therapeutic management strategies

Evidence for the behavioural and therapeutic management strategies for ICDs to inform information needs of patients and their families and carers was derived from review question 9. Please see section 10 on managing and monitoring impulse control.

Patient experience

There was moderate-quality evidence from 1 study (Phu et al., 2014), in which the authors reported that ICRD may be associated with a greater incidence of major depressive disorders. However, the data were consistent with no difference between people with an ICRD and those without (OR=3.07, 95% CI: 0.86 to 11.69).

Moderate quality evidence from 1 study (Mestre et al., 2014) reported that the most common reasons for reluctance to start medication for Parkinson's disease were the fear of side effects, non-acceptance of diagnosis, a general dislike for medications, and scepticism regarding the efficacy.

Carer experience

No evidence was found reporting the experience of carers for people with ICDs.

4.1.5 Health economic evidence

No health economic evidence was identified for this question

4.1.6 Evidence to recommendations

Relative value of different outcomes	The GDG considered that providing information about the potential for developing impulse control disorder and monitoring for the development of any ICD to be the most important outcomes of interest for this review.
Trade-off between benefits and harms	The GDG considered it important that explicit written consent should be confirmed when offering dopamine agonists (DAs) - these drugs can have a profound emotional impact and effect on a patient's quality of life, and clinicians need to make sure patients and their families and carers are fully aware. The GDG agreed that this exceeded the normal requirements for discussing the potential harms and benefits of any treatment including potential side effects. There was general agreement that confirming written and/or documentation of verbal consent was best practice. Standard practice is for patients and carers to be informed about the risk of developing an ICD prior to starting DAs. In the experience of the GDG it was normal practice for clinicians to send the patient a letter to summarise this conversation. The GDG noted that in the United States some doctors have been sued by patients who have developed problematic ICDs for not adequately informing them about the risks. The GDG noted that there is a monitoring tool from Parkinson's disease UK about DAs and associated risks that may be a useful source of information to provide patients with, or for clinicians to use as a tool to guide their discussion about ICDs with patients and their carers. It was agreed as being essential to involve families and carers in any discussion, as long as the patient has given consent, because of the implications of ICD on the patient's social and emotional wellbeing, and the fact that patients with ICDs often don't have insight into their condition and may either not recognise or attempt to conceal their ICD. The carer and family members need to also be vigilant to any change in behaviour and therefore need to be informed about the risks and signs to look out for. It was agreed that a regular review by healthcare professionals of how the

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	patient is coping on their dopaminergic mediation, especially dopamine agonists, including an assessment of the possible development of any problematic ICDs is very important. ICDs may develop at any stage while a patient is exposed to any dopaminergic stimulation, and especially dopamine agonists. Follow up appointments should be utilised to make sure both patients and carers remain aware of the risks of developing an ICD. The GDG agreed that patients and carers should be made aware of whom they can contact should they be concerned about the development or impact of any ICDs.
Trade-off between net health benefits and resource use	No economic evidence was identified for this review question, and health economic modelling was not prioritised as it was felt to be unlikely there would be any significant resource implications from any recommendations made. This is because the provision of information is inexpensive, because the recommendations predominantly apply to a limited subgroup of people (those commencing dopamine agonists) and because the recommendations reflect current practice in the care of many people with Parkinson's disease in the NHS. For all these reasons, the marginal cost of standardising practice was believed to be low.
Quality of evidence	The GDG recognised that there was very little direct evidence to inform this review, and therefore the recommendations are derived primarily from the experience and clinical expertise of the group.

4.1.7 Recommendations

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8. When starting dopamine agonist therapy, give people and their family members and carers (as appropriate) oral and written information about the following, and record that the discussion has taken place:

- The increased risk of developing impulse control disorders when taking dopamine agonist therapy, and that these may be covert.
- Different types of impulse control disorders (for example, compulsive gambling, hypersexuality, binge eating and obsessive shopping).
- Who to contact if impulse control disorders develop.
- The possibility that if problematic impulse control disorders develop, dopamine agonist therapy will be reviewed and may be reduced or stopped. [new 2017]

9. Discuss potential impulse control disorders at review appointments, particularly when modifying therapy, and record that the discussion has taken place. [new 2017]

10. Be aware that impulse control disorders can also develop while taking dopaminergic therapies other than dopamine agonists. [new 2017]

4.2 Women of childbearing age

What are the information needs specific to women of childbearing age with a diagnosis of Parkinson's disease?

4.2.1 Introduction

The aim of this review question was to ascertain the information needs specific to women of childbearing age in relation to the diagnosis and management of Parkinson's disease.

The review focussed on identifying studies that fulfilled the conditions specified in Table 4.

Table 4: PICO table for Information needs specific to women of childbearing age with Parkinson's disease

Population	Women of childbearing age with a confirmed diagnosis of Parkinson's disease
Information	Any information needs identified specific to women of childbearing age with Parkinson's disease
Outcomes	• Fertility complications of Parkinson's disease • Contraceptive advice • Genetic counselling • Frequency of antenatal visits and support throughout pregnancy • Breast feeding • Drug treatment changes during pregnancy • Postnatal depression/anxiety • Safety profile of drug treatments suggested

For full details of the review protocol, please see Appendix C. Qualitative studies were considered to be the most appropriate study design to derive information needs of women of childbearing age with Parkinson's disease, and were therefore considered to be the highest quality within a modified-GRADE framework. All study methodologies, with the exception of case reports, were included.

4.2.2 Evidence review

A systematic search was conducted (see appendix I) which identified 443 references. The references were screened on their titles and abstracts and full papers of 7 references were obtained and reviewed against the inclusion and exclusion criteria in the review protocol (see appendix C). This review question was not considered in the previous Parkinson's disease guideline (CG35), no further studies were therefore identified.

Overall, 6 studies were excluded as they did not meet the eligibility criteria such as inappropriate study aims and outcomes, or information reviews with no primary data collection. Studies that examined reproductive factors that may influence the development of Parkinson's disease were also not included within this review as this fell outside the present review protocol. A detailed list of excluded studies and reasons for their exclusion is provided in appendix G.

The 1 remaining published paper did meet eligibility criteria and was included. Evidence table for the included study can be found in appendix D, with GRADE profiles reported in appendix E.

No additional new papers were identified through rerun searches at the end of the guideline.

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The overall quality of the evidence from the 1 published paper was very low due to the presence of bias and small participant numbers.

The included study examined the pregnancy and birth outcomes of 18 women with Parkinson's disease.

4.2.3 Description of included studies

One study (Golbe et al., 1987) used a semi-structured interview design to explore the interaction between Parkinson's disease and pregnancy in 18 women (mean age at time of conception=34.6 (SD 6.1) years) in whom pregnancy occurred after the diagnosis of Parkinson's disease (mean=4.1 (SD 4.2) years after diagnosis). A total of 24 pregnancies were reported after the onset of Parkinson's disease symptoms. Obstetric, neurologic, and foetal complications were examined and reported.

Evidence tables for included studies can be found in Appendix D, with GRADE profiles reported in Appendix E

4.2.4 Evidence statements

Fertility and birth complications

Very low quality evidence reported a total of 17 successful pregnancies (70.8%; mean maternal age 33.1 (6.0) years). A total of 4 elective abortions were reported; 1 because of the detection of trisomy 21; and 3 because of the fear of complications for the mother and/or foetus. A total of 3 women (15%) each had 1 spontaneous miscarriage during the first 4 months of pregnancy and these were not associated with any known gross foetal abnormalities.

Very low quality evidence reported no significant difference in disease duration of those women who had successful pregnancies (mean disease duration=4.2 (4.5)) and those who had spontaneous miscarriage (mean disease duration=3 (2.6) years).

Safety profile of drug treatment during pregnancy

Medications taken during the 3 miscarriages were: amantadine and benzotropine; amantadine and levodopa; and benzotropine and dienhydramine.

Very low quality evidence reported all 4 pregnancies (100%) in which amantadine was being taken to be associated with complications: 2 women had miscarriages; 1 woman had first trimester vaginal bleeding; another women reported proteinuria and hypertension, diagnosed as preeclampsia. In 4/16 (25%) of pregnancies in which amantadine was not taken, complications such as vaginal bleeding or severe nausea were also reported.

Very low quality evidence reported that in all 6 pregnancies (100%) in which levodopa/carbidopa was being taken, no major complications were observed for the mother or her baby, however 4 of these women (66%) did report worsening of their Parkinson's disease symptoms. It is not reported specifically whether these symptoms resolved post-delivery.

Neurological complications

Very low quality evidence reported minor exacerbation of Parkinson's disease symptoms or the development of new symptoms during pregnancy 11/17 (64.7%) pregnancies. In all of these pregnancies that reported worsening of Parkinson's disease symptoms or development of new symptoms (100%), the rate of disease progression during pregnancy was rated as greater during pregnancy compared with the months before or after pregnancy

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(method of measurement of disease progression not reported). In only 1 of these (9.09%) did symptoms improve post-delivery.

No patient reported a significant change in functional disability.

One patient who reported dopa-induced chorea noted transient worsening of that symptom during pregnancy.

Post-natal depression and anxiety

Very low quality evidence reported a total of 4 pregnancies in 3 women to be followed by postpartum depression not requiring drug treatment. Depression was reported de novo in 1 woman and was resolved after pregnancy.

4.2.5 Health economic evidence

No health economic evidence was identified for this review question.

4.2.6 Evidence to recommendations

Relative value of different outcomes	The GDG agreed that the most critical outcomes for women were their needs regarding the impact of being pregnant on the control of the Parkinson's disease symptoms, and the drug safety profiles for the mother and unborn baby. Other important needs were the impact of having Parkinson's disease on being able to have a successful pregnancy.
Trade-off between benefits and harms	The GDG agreed that the main challenge and trade-off between benefit and harm is represented in maintaining optimal health and control of Parkinson's disease symptoms in the mother, while allowing her to have a successful pregnancy. It was also noted as important to weigh-up the cost of potentially harming the mother and child by remaining on Parkinson's disease medications which have an unknown impact on the pregnancy, and the optimal management of the health of both the mother and the unborn foetus. It was highlighted by all members of the GDG that this is a field in which there is no guidance for women or clinicians on the best course of action. The GDG agreed that any information that could be pooled from the evidence review and clinical anecdotal experience would be highly useful. The GDG discussed the limited evidence identified for this review question and agreed that there is no evidence to suggest any benefit of coming off nor any harm of taking Parkinson's disease drugs during pregnancy. There was, however, evidence that suggested worsening of Parkinson's disease symptoms during pregnancy (seen in 11/17 women). The impact of this worsening or whether it is likely to resolve post pregnancy was not clearly reported in the study. Nevertheless, the GDG agreed that the reported deterioration in Parkinson's disease symptoms is unlikely to represent a serious worsening of symptoms as no deterioration in functional disability was reported. The GDG also expressed a consensus agreement that it is very difficult for women who are taking these drugs to know what to do about their drug regime during pregnancy and whether it is safe. The GDG then went on to have a few general discussions, starting with breast feeding as being an important concern for women and noted that the BNF had highlighted many of the Parkinson's disease drugs are expressed in breast milk. The GDG therefore noted that it is worth considering a review of medication dosage as it is likely that women may take lower doses during pregnancy to minimise any risk of drug effects on the foetus. The GDG then went on to discuss the risk of psychosis during pregnancy in people with Parkinson's disease and highlighted that the risk is 20 times higher than in people without Parkinson's disease during pregnancy . This is

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	compounded by the fact that many Parkinson's disease drugs also increase the risk of psychosis. The GDG therefore agreed that it is important for people with Parkinson's disease to be monitored during pregnancy. The GDG also discussed anecdotal evidence of safe use of ropinirole and sinemet in women with Parkinson's disease who successfully carried their babies to term and did not report any complications for the mother or her baby. Other dopamine agonists have been used to treat prolactinoma and was associated with safe pregnancies. From their own experience the GDG agreed that levodopa was innocuous in pregnancy and that in people without Parkinson's disease, no toxicity has been shown. However, there exists no clear research to support this. The GDG also highlighted that the summary of drug characteristics do not always contain sufficient information to cover all concerns clinicians may have, and expressed the belief that if healthcare professionals don't know the risks, they are likely to recommend avoidance to align with the principle of do no harm. It was also noted that for amantadine the SPC states that it is contraindicated during pregnancy. The GDG lastly discussed the role of genetic testing. Women who have young onset Parkinson's disease are potentially much more likely to have a genetic basis to their disease. The presence of genetic abnormalities may indicate a risk of carrying that genetic mutation in future offspring, therefore any women with a positive family history of Parkinson's disease and a high likelihood of a genetic basis to their disease may wish to undergo genetic counselling, with or without testing before deciding on whether to have a child.
Trade-off between net health benefits and resource use	No economic evidence was identified for this review question, and health economic modelling was not prioritised as it was felt to be unlikely there would be any significant resource implications from any recommendations made.
Quality of evidence	The GDG discussed in depth the lack of evidence for this question, and that the very low quality evidence that was found was of limited value. This population was considered to be rare, which impedes the ability of high quality research being done in this area. The GDG discussed the need for more collaborative sharing of data on women of childbearing age with a diagnosis of Parkinson's disease in order to increase the feasibility and quality of research in this area. The GDG felt that the evidence base in this area was so poor that, despite the need for guidance discussed above, it was not possible for them to make any evidence based recommendations. Consideration was given to making a research recommendation, but it was felt that the best evidence to answer this question would come from registry data, and would not require a separate primary study to be set up to collect additional data.

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4.2.7 Recommendations

No recommendations made

5 Parkinson's disease diagnosis

'It knocked me for six . . . I became very low . . . I thought it can't be me . . . it's just elderly people who got it.' (patient)[2]

'I found it hard to cope with life . . . I didn't tell anyone . . .I couldn't face the reality of it.' (patient)[2]

5.1 Definition and differential diagnosis

There are many manifestations of Parkinson's disease but the classical diagnostic symptoms are:

- slowness and poverty of movement
- stiffness
- shaking.

The physical signs of Parkinson's disease 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.

At diagnosis, these signs are usually unilateral, but they 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 (OH).

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).

Parkinson's disease is traditionally defined, pathologically, by the finding of Lewy bodies and degeneration of catecholaminergic neurones at post-mortem. Using a pathological definition of Parkinson's disease 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 Parkinson's disease; it is presumed that these are pre-clinical cases.
- Lewy bodies have not been found in otherwise typical individuals with Parkinson's disease with Parkin mutations, although such rare young-onset genetic cases of Parkinson's disease might be said not to have idiopathic Parkinson's disease.

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

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

The decline in dopaminergic neurones identified by radionuclide positron emission tomography (PET) or single photon emission computed tomography (SPECT) has also been

proposed as a method of defining Parkinson's disease. Unfortunately, this decline is seen in conditions other than Parkinson's disease such as MSA and PSP.

Given these difficulties, it is generally accepted that the diagnosis of Parkinson's disease should be based on clinical findings. The most widely accepted clinical criteria for the diagnosis of Parkinson's disease are those introduced by the UK PDS Brain Bank Criteria (Table 5.1).[35]

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

Parkinson's disease must also be differentiated from other conditions presenting with tremor (Table 5.2). This can be particularly difficult as Parkinson's disease can present with a postural and action tremor similar to that seen in essential tremor.

In addition, Parkinson's disease must be differentiated from other causes of a parkinsonian syndrome or parkinsonism (Table 5.3). 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.[34]

Table 5.1 UK PDS Brain Bank Criteria for the diagnosis of PD[35]

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 PD

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 3 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 PD

Three or more required for diagnosis of definite PD:

- 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 5 years
- clinical course of over 10 years.

Table 5.2 Common causes of tremor

Rest tremor
Parkinson's disease
Postural and action tremor
Essential tremor
Exaggerated physiological tremor
Hyperthyroidism
Drug-induced (eg -agonists)
Dystonic tremor
Intention tremor
Cerebellar disorders

Table 5.3 Causes of a parkinsonian syndrome

Parkinson's disease

Alzheimer's disease

Multiple cerebral infarction

Drug-induced parkinsonism (eg phenothiazines)

Other degenerative parkinsonian syndromes:

- progressive supranuclear palsy (Steele–Richardson–Olszewski syndrome)
- multiple system atrophy (previously Shy–Drager syndrome, olivopontocerebellar atrophy and striatonigral degeneration)

5.1.1 Recommendation

11. Suspect Parkinson's disease in people presenting with tremor, stiffness, slowness, balance problems and/or gait disorders. [2006]

5.1.2 Methodological limitations of the diagnostic studies

When interpreting the literature about Parkinson's disease diagnosis, the following methodological issues should be considered:

- lack of long-term prospective clinical and pathological follow-up as a 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
- Parkinson's disease trial age groups are often young as studies were performed by neurologists who see a younger population of people with Parkinson's disease
- most studies included people with established disease lasting some years
- varying geographical locations
- some studies are in specialised units and may not reflect the diagnostic accuracy of other units in the UK
- exclusion of some studies using magnetic resonance volumetry and magnetic resonance spectroscopy (MRS) as they lacked appropriate population, intervention and outcome criteria
- lack of statistical details of diagnostic accuracy such as sensitivity, specificity and positive predictive values
- lack of economic evaluations of SPECT.

5.1.3 Clinical versus post-mortem diagnosis

Most experienced specialists have adopted the UK PDS Brain Bank Clinical Criteria (Table 5.1) for the diagnosis of Parkinson's disease.

How do these compare with the accuracy of pathological diagnosis?

5.1.4 Methodology

Three diagnostic studies were found that assessed the accuracy of clinical diagnosis in parkinsonism compared with autopsy.[36–38] 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 PDS Brain Bank Criteria (Table 5.1) in two of three studies.[37,38] A third study determined a diagnosis of Parkinson's disease when at least two of the three cardinal signs (bradykinesia, rigidity and resting tremor) were present.[36]

5.1.5 Evidence statements

Two studies (N=59[36] and N=100[37]) examined people with a terminal diagnosis of Parkinson's disease and found the frequency of people misdiagnosed with Parkinson's disease (i.e. they did not meet the pathological criteria at post-mortem) was 35% and 24% respectively.[36,37] When recommended diagnostic criteria (UK PDS Brain Bank) were retrospectively applied, diagnostic accuracy increased from 70% to 82%.[37] **(DS II)**

A more recent UK PDS Brain Bank study[38] examined the brains of 143 people with Parkinsonism. 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 Parkinson's disease or alternative parkinsonian condition. The clinical diagnosis was later revised in 44 of 122 cases where full follow-up information was available after a mean of 3.4 (range 0.5–12) years. The sensitivity of the final Parkinson's disease clinical diagnosis was 91%, a specificity of 98% and a positive predictive value of 99% (72 out of 73 correctly diagnosed). **(DS II)**

5.1.6 From evidence to recommendation

The pathological studies emphasise the need for particular care in making a clinical diagnosis of Parkinson's disease. There is limited evidence to suggest that the UK PDS Brain Bank Criteria have adequate sensitivity and specificity in comparison with post-mortem findings. The accuracy of diagnosis using the Brain Bank criteria increases as the condition progresses.

The availability of Parkinson's disease brain tissue has fostered much valuable research in recent years and should be encouraged in the future. Diagnostic information derived from post-mortem examination can also be of value to the families of individual patients.

5.1.7 Recommendations

12. **Diagnose Parkinson's disease clinically, based on the UK Parkinson's Disease Society Brain Bank Clinical Diagnostic Criteria. [2006]**

13. **Encourage healthcare professionals to discuss with people with Parkinson's disease the possibility of donating tissue to a brain bank for diagnostic confirmation and research. [2006]**

5.2 Expert versus non-expert diagnosis

The diagnosis of Parkinson's disease could be made in primary care by the person's GP or in secondary care by a neurologist, geriatrician or general physician. More recently, PDNSs

and other health professionals are developing diagnostic skills. Each may have different levels of expertise in evaluating people with possible Parkinson's disease.

What is the evidence that someone with special expertise is more accurate in diagnosing Parkinson's disease than someone with little experience?

5.2.1 Methodology

Four diagnostic studies[39–42] were found looking at the accuracy of Parkinson's disease diagnosis in a community-based population. The specialist diagnosis was based on the UK PDS Brain Bank criteria in four of the studies.[39,40,42] In one study[41] the expert diagnosis was based on the investigator's confidence in the diagnosis of Parkinson's disease, 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 Parkinson's disease populations.

5.2.2 Evidence statements

One study[39] (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 standard for comparison was diagnosis according to strict clinical diagnostic criteria (the UK PDS Brain Bank Criteria) after a detailed neurological interview and examination. 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. While the positive predictive value of specialists was greater than for other doctors, negative predictive values were equivalent. **(DS II)**

Another study[40] applied the UK PDS Brain Bank criteria to 402 cases derived from a computerised list of people with Parkinson's disease receiving anti-parkinsonian medication from 74 general practices in North Wales. In 59% of cases, the GP made the initial diagnosis of Parkinson's disease. The people with Parkinson's disease were seen either at home or in a specialist movement disorder clinic where a neurological examination was performed. A definite Parkinson's disease diagnosis was made in 53% of all cases, thus the error rate in the community-ascertained cases was 47%. **(DS II)**

DATATOP (Deprenyl and Tocopherol Antioxidative Therapy of Parkinsonism) was a large, multi-site clinical trial[41] in the USA and Canada involving 800 people with early-stage Parkinson's disease who were cared for by 34 investigators with a major interest in movement disorders. A secondary analysis examined the number of people with Parkinson's disease with a change in diagnosis after a mean follow-up of 6 years. The study showed that only 8% had a revised diagnosis. The revised diagnosis was clinical and not based on strict criteria or pathology. **(DS II)**

The UK-PDRG study,[42] which investigated the long-term effectiveness of bromocriptine, selegiline and levodopa therapy, found a total of 49/782 people with Parkinson's disease (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 Parkinson's disease. The authors do not state whether the revised diagnosis was made by one of the specialists performing the study, although this is likely. The authors also do not state whether a specialist or non-specialist conducted the initial diagnostic examination. **(DS II)**

5.2.3 From evidence to recommendation

These studies provide only circumstantial evidence on the diagnostic ability of experts versus non-experts. However, they show that the diagnosis of Parkinson's disease is wrong in around 47% of community-ascertained cases, 25% of non-expert secondary care diagnosed cases, and 6–8% of cases diagnosed by an expert in movement disorders.

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

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 that has, initially, been made by a non-expert can be stressful for patients.

The GDG acknowledges the timeline that the Department of Health and NHS are currently working towards for completion of diagnosis and treatment (18-week target). However, the GDG felt that in the case of Parkinson's disease it should not necessarily mean that patients would have to 'start' treatment within 18 weeks from GP referral but rather that this was when a 'treatment decision' was made for initial consultation and diagnosis.

5.2.4 Recommendations

14. If Parkinson's disease is suspected, refer people quickly and untreated to a specialist with expertise in the differential diagnosis of this condition.[a] [2006]

5.2.5 Review of diagnosis

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

What is the most appropriate frequency of follow-up after an initial diagnosis of Parkinson's disease?

5.2.6 Methodology

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

5.2.7 Evidence statements

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

5.2.8 From evidence to recommendation

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 Parkinson's disease who may not even be on treatment yet, follow-up to check on the diagnosis and the need for treatment may be infrequent (every 6–12 months). Once treatment is commenced,

a The Guideline Development Group considered that people with suspected mild Parkinson's disease should be seen within 6 weeks, but new referrals in later disease with more complex problems require an appointment within 2 weeks

follow-up may need to be more frequent (every 2–3 months) to assess the response to medication, titrate dosage and re-visit the diagnosis. In later disease, people with Parkinson's disease have more complex problems which require changes in medication. This may require review at frequent intervals (every 2–3 months).

5.2.9 Recommendations

15. Review the diagnosis of Parkinson's disease regularly, and reconsider it if atypical clinical features develop.[b] [2006]

5.3 Single photon emission computed tomography

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 Parkinson's disease by intravenous injection. The labelled cocaine derivatives ^{123}I- -CIT and ^{123}I-FP-CIT (N- -fluoropropyl-2 -carboxymethoxy-3 -(4-iodophenyl)tropane) have most commonly been used, although only the latter is licensed in the UK. These label the presynaptic dopamine re-uptake site and thus the presynaptic neurone, which can be visualised in two-dimensional images. These demonstrate normal uptake in the caudate and putamen in controls and in people with essential tremor, neuroleptic-induced parkinsonism or psychogenic parkinsonism, but reduced uptake in those with Parkinson's disease, Parkinson's disease with dementia, MSA or PSP.

How useful is SPECT in discriminating Parkinson's disease from alternative conditions?

5.3.1 Methodology

Fifteen studies addressed the diagnostic accuracy of SPECT scanning.[43–58] The reference standard was clinical diagnosis: eight out of the 16 studies[43,45–51] used the UK PDS Brain Bank Criteria, five studies[44,52–55] used 'established' clinical criteria and three studies[56–58] did not state the clinical criteria used to determine the diagnosis. Although many tracers are listed in the evidence statements, only ^{123}I-FP-CIT is licensed for use in the UK. The ^{123}I- -CIT studies were included as it has a similar structure and labels the same receptors as the ^{123}I-FP-CIT tracer. The GDG agreed that this evidence is supportive of ^{123}I-FP-CIT studies and provides a consistency of effect.

5.3.2 Health economic methodology

Only one study met quality criteria that addressed the economic evaluation of SPECT.[59] This study was based on ^{123}I-FP-CIT SPECT effectiveness data, specificity and sensitivity of clinical examination and prevalence of Parkinson's disease were based predominantly on UK data. However, costs were based on German 2002 data.[59]

5.3.3 Evidence statements

For the differentiation of people with parkinsonism (i.e. Parkinson's disease, 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%).[43,45,49,52,53] A summary of the evidence produced in these five studies is provided in Table 5.4 and Table 5.5. **(DS Ib)**

Three studies (N=80,[47,48,54] N=17,[47,48,54] N=183[47,48,54]) attempting to differentiate Parkinson's disease from other parkinsonian conditions (e.g. MSA, PSP) had insufficiently high levels of sensitivity (range 77% to 97%) and specificity (range 75% to 83%).[47,48,54] **(DS Ib)**

One study[58] found, by comparing the ^{123}I- -CIT SPECT imaging diagnosis for people with parkinsonian syndrome with a clinical diagnosis (based on 6 months' follow-up), that there was disagreement between only three out of 35 cases (8.6%) with visual diagnosis and two out of 35 cases (5.7%) with quantitative imaging diagnosis. **(DS Ib)**

Table 5.4 Diagnostic accuracy of SPECT imaging: differentiation of tremulous disorders

	Number of				
^{123}I-FP-CIT SPECT (institutional read)[45]	158 PD	27 ET	97	100	Ib
^{123}I-FP-CIT SPECT (consensus read)[45]	Same as above		95	93	Ib
^{123}I-FP-CIT SPECT[43]	38 PD	38 Non-PD	87	–	Ib
^{123}I- -CIT SPECT [49]	60 PD and PSP	36 ET and controls	98	83	Ib
^{123}I- -CIT SPECT: Striatum/cerebellum and putamen/	29 PD	62 controls and ET	98.3	–	Ib
cerebellum binding ratio factors[52]	29 PD	32 ET	96.7		
^{123}I- -CIT SPECT: Visual imaging analysis[58] Visual imaging analysis[58]	35 suspect PD		96	80	Ib
^{123}I- -CIT SPECT: Quantitative imaging analysis[58]	Same as above		90	100	Ib

Institutional read = visual assessment of ^{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.

PD = parkinsonian syndrome; PSP = progressive supranuclear palsy; ET = essential tremor.

Table 5.5 Diagnostic accuracy of SPECT imaging: differentiation of Parkinson's disease and controls

	Number of participants				
Test	**PD**	**Controls**	**Sensitivity (%)**	**Specificity (%)**	**Grade**
^{123}I- -CIT SPECT: Striatum/cerebellum binding ratio alone[52]	29	32	94.9	–	Ib
^{123}I-FP-CIT SPECT: Binding index in putamen contralateral to initially clinically affected side[50]	76	20	95	86	II
TRODAT-1 SPECT: Binding index in putamen contralateral to initially clinically affected side[50]	Same as above		92	70	II

TRODAT-1 SPECT: Logistic discriminant parametric mapping[53]	42	23	100	95	II
TRODAT-1 SPECT: Visual inspection[55]	188	45	98	86	Ib
TRODAT-1 SPECT: Quantitative analysis[55]	Same as above		98	88	Ib
TRODAT-1 SPECT: Contralateral putamen/occipital and contralateral putamen/caudate[57]	78	40	100	100	II
TRODAT-1 SPECT: Quantitative imaging analysis. Mean uptake in ipsilateral and contralateral posterior putamen[51]	29	38	0.79	0.92	II

TRODAT-1 = selective dopamine transporter technetium-99m labelled.
Logistic discriminant parametric mapping = technique to distinguish sets of data with maximum accuracy.

5.3.4 Health economic evidence statements

The economic findings indicated:[59]

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

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 Parkinson's disease diagnosis in people with a positive clinical examination before the initiation of treatment.[59] Adequate treatment month equivalents (ATME) were used to reflect both duration of adequate treatment and severity of incorrect treatments. The authors indicated that a 0.55 ATME gain per patient is equivalent to approximately 17 additional days of treatment to a Parkinson's disease patient or withholding approximately 2 days of treatment and side effects to a patient who does not have Parkinson's disease.

The specificity of clinical examination and frequency of Parkinson's disease in the clinic population of Parkinson's disease had the greatest relative impact on the incremental cost-effectiveness ratio (ICER) of SPECT following positive clinical examination compared with 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).[59] This suggests that as more non- Parkinson's disease cases are incorrectly classified as Parkinson's disease cases in clinical examination, the greater the cost-effectiveness of SPECT. When the frequency of Parkinson's disease in the clinic population is increased to 74% (from 53%) the ICER increases to €2,411 (approximately £1,697).[59] This suggests that the cost-effectiveness of SPECT decreases when the frequency of Parkinson's disease in the clinic population increases. In these populations, there may be fewer false-negative

results and therefore fewer people incorrectly being treated for Parkinson's disease. This would mean there are fewer cost-savings from withholding incorrect treatment and therefore an increase in the relative cost-effectiveness of SPECT.

5.3.5 From evidence to recommendation

Considerable evidence supports the use of ^{123}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}I-FP-CIT SPECT cannot, with high accuracy, differentiate Parkinson's disease 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.

Several clinical trials using SPECT or PET to follow the progression of Parkinson's disease found that 4%,[60] 11%[61] and 14%[62] with a clinical diagnosis of Parkinson's disease had normal imaging at the start of the trial. Further long-term clinical follow-up of these people is required.

Due to the subjectivity of the effectiveness measurement, the GDG decided the economic study[59] does not support or refute the clinical recommendations. Further development of comparable effectiveness outcomes in diagnostic economic evaluations is required.

5.3.6 Recommendations

16. **Consider ^{123}I-FP-CIT single photon emission computed tomography (SPECT) for people with tremor if essential tremor cannot be clinically differentiated from parkinsonism. [2006, amended 2017]**

17. **^{123}I-FP-CIT SPECT should be available to specialists with expertise in its use and interpretation. [2006]**

5.4 Positron emission tomography

In positron emission tomography (PET), a positron-emitting radioactive isotope is tagged to a tracer molecule, which is administered by intravenous injection. The most frequently used positron-emitting isotope in this field is ^{18}fluorine, which is attached to dopa or deoxyglucose. ^{18}F-fluorodopa is taken up by the presynaptic 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.

How valuable is PET in the differential diagnosis of parkinsonism?

5.4.1 Methodology

Six diagnostic studies[63–68] 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 Parkinson's disease from essential tremor.

5.4.2 Evidence statements

In one study[68] the diagnostic accuracy of ^{18}F-desmethoxy-fallypride 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%. **(DS Ib)**

In one study[67] the multi-diagnosis group discriminate analysis from ^{18}F-FDG PET scan images found sensitivity of 75% and specificity of 100% in the Parkinson's disease group (N=8), sensitivity of 100% and specificity of 87% in the MSA group (N=9), and sensitivity of 86% and specificity of 94% in the PSP group (N=7). **(DS II)**

One study,[69] using ^{18}F-FDG uptake, reported 74% of all participants (early Parkinson's disease (N=15), atypical Parkinson's disease (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 patterns in individual people with Parkinson's disease. **(DS II)**

One study (N=90),[63] using ^{18}F-fluorodopa uptake, found people with clinically diagnosed Parkinson's disease Parkinson's disease were correctly classified by PET in 64% of the cases and those with atypical parkinsonism (MSA or PSP) in 69% of the cases. **(DS II)**

In another study[70] the probability of the correct diagnosis by ^{18}F-fluorodopa PET was ≥99% for the majority of people with Parkinson's disease (40/41) and controls (26/28). **(DS II)**

5.4.3 From evidence to recommendation

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 Parkinson's disease from other parkinsonian conditions using FDG requires further confirmation. No work was found on PET's ability to differentiate Parkinson's disease from essential tremor. This lack of evidence stems from the high cost and poor availability of PET. Further research is required in this area.

5.4.4 Recommendations

18. **Do not use (positron emission tomography) PET in the differential diagnosis of parkinsonian syndromes, except in the context of clinical trials. [2006, amended 2017]**

5.4.5 Magnetic resonance imaging

Structural magnetic resonance imaging (MRI) provides two- and three-dimensional images of intracranial structures using high magnetic field strengths to excite the hydrogen atoms in water molecules. In Parkinson's disease 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.

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

5.4.6 Methodology

Eight diagnostic studies[64,66,71–76] were found which addressed the effectiveness of MRI compared with long-term clinical follow-up in diagnosing people with a parkinsonian syndrome. Various MRI scanning sequences were used.

5.4.7 Evidence statements

Seven of these studies[64,71–76] provided diagnostic accuracy data for MRI using various techniques. The results are summarised in Table 5.6.

Table 5.6 Diagnostic accuracy of MRI

Abnormal putaminal T2 hypointensity[71,72,74]	MSA-P (24) versus PD (27)	87.5	88.89	DS Ib
T1 MRI: midbrain superior profile[75,76]	PD (27) versus PSP (25)	68	88.8	
T1 MRI: midbrain atrophy[75,76]	Same as above	68	77.7	DS Ib
Putaminal T2 hypointensity and T2 hyperintensity combined[73,74,76]	MSA (28) versus PD (32)	32	100	
Putaminal T2 hypointensity and T2 hyperintensity combined[73,74,76]	MSA (28) versus PSP (30)	32	93	
Putaminal T2 hypointensity and T2 hyperintensity combined[73,74,76]	MSA (28) versus CBD (26)	32	85	DS II
Overall MRI abnormalities[73,74,76]	PD (32) versus MSA (28)	71	91	
Overall MRI abnormalities[73,74,76]	PD (32) versus PSP (30)	70	91	
Overall MRI abnormalities[73,74,76]	PD (32) versus CBD (26)	92	91	
T1 MRI: voxel-based morphometry of cerebral peduncles and midbrain[74–76]	PSP (12) versus PD (12) and controls (12)	83	79	DS II
Diffusion-weighted MRI Putaminal rADC[72,73,75]	PSP (10), PD (13) and MSA-P (12) versus clinical diagnosis	96	100	DS II

rADC = regional apparent diffusion coefficient; PSP = progressive supranuclear palsy; MSA-P = multiple system atrophy parkinsonian type; MSA-C = multiple system atrophy cerebellar type; CBD = corticobasalganglionic degeneration.

Another study[66] found non-concordance between neuroradiological diagnosis and clinical diagnosis in 2/21 people with Parkinson's disease, 5/14 people with MSA-P and 1/4 people with MSA-C. **(DS II)**

One study[75] reported only 15% of people with Parkinson's disease and 24% of those with PSP had abnormal T2 hypointensity in the posterolateral putamen and none had abnormal putaminal proton density hyperintensity. **(DS Ib)**

One study[74] 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 Parkinson's disease). **(DS II)**

5.4.8 From evidence to recommendation

In expert hands structural MRI has proved of some value in differentiating Parkinson's disease from other types of parkinsonism, but further research is required before it can be recommended in routine clinical practice.

5.4.9 Recommendations

19. Do not use structural MRI to diagnose Parkinson's disease. [2006, amended 2017]

20. Structural MRI may be considered in the differential diagnosis of other parkinsonian syndromes. [2006]

5.5 Magnetic resonance volumetry

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 Parkinson's disease.

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

5.5.1 Methodology

Two studies[76,77] addressed the diagnostic effectiveness of magnetic resonance volumetry against retrospective clinical diagnosis in determining an accurate diagnosis in people with parkinsonian syndrome.

5.5.2 Evidence statements

One study[77] (N=61) found no differences between people with Parkinson's disease and controls on any of the magnetic resonance volume measures. However, individuals with PSP were distinguished from people with Parkinson's disease and controls with a sensitivity of 95.2% and a specificity of 90.9% (mainly due to frontal grey matter volume measure). **(DS Ib)**

Another study[76] (N=53) found that mean superior cerebellar peduncle volume atrophy on visual image analysis differentiated PSP from Parkinson's disease, 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 were 74% and 77%. **(DS II)**

5.5.3 From evidence to recommendation

While two studies suggest that volumetric MRI can help in the differentiation of Parkinson's disease from other types of parkinsonism, further work is required before it can be recommended.

5.5.4 Recommendations

21. Do not use magnetic resonance volumetry in the differential diagnosis of parkinsonian syndromes, except in the context of clinical trials. [2006, amended 2017]

5.6 Magnetic resonance spectroscopy

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

Can MRS be helpful in the correct diagnosis of parkinsonism?

5.6.1 Methodology

A systematic review[78] of mixed study designs assessed the diagnostic accuracy of MRS against a clinical diagnosis of a range of parkinsonian syndromes.

5.6.2 Evidence statements

The review[78] 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. **(DS II)**

5.6.3 From evidence to recommendation

Contradictory results have been found on the value of MRS in differentiating Parkinson's disease from controls and other types of parkinsonism.

5.6.4 Recommendations

22. Do not use magnetic resonance spectroscopy in the differential diagnosis of parkinsonian syndromes. [2006, amended 2017]

5.7 Acute levodopa and apomorphine challenge tests

Many people with Parkinson's disease respond to single doses of oral levodopa and/or subcutaneous apomorphine.

Can such responses be assessed using clinical rating scales to provide a diagnostic test for Parkinson's disease?

5.7.1 Methodology

A systematic review[79] and an additional diagnostic study[80] addressed the effectiveness of acute levodopa and apomorphine testing in determining an accurate diagnosis of people with a parkinsonian syndrome. Another review[81] published prior to the included systematic review[79] was excluded because it summarised the same papers.

5.7.2 Evidence statements

The systematic review[79] included 13 studies, four of which examined people with de novo Parkinson's disease and nine others which examined people with well-established Parkinson's disease and with other parkinsonian syndromes. These two groups are presented separately in Table 5.7 and Table 5.8. The diagnostic study[80] followed people with Parkinson's disease for 3 years to investigate whether an acute challenge of carbidopa/levodopa had better diagnostic accuracy compared with the acute apomorphine challenge test. These results are also included in Table 5.8.

The systematic review used logistic regression analysis to determine whether there was a significant difference between the three tests for the misclassification of participants. Two studies[82,83] demonstrated no significant difference between the acute apomorphine challenge test and chronic levodopa therapy. However, two other studies[82,84] provided evidence that there was a difference between the acute levodopa challenge test and chronic levodopa therapy, in favour of chronic levodopa ($p<0.001$). **(DS II)**

The diagnostic study[80] 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 Parkinson's disease. 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. **(DS III)**

Table 5.7 Diagnostic accuracy of acute apomorphine and levodopa challenge testing in *de novo* Parkinson's disease cases[79]

		Positive predictive value	
Acute apomorphine (1.5–5 mg)	187	0.63 (95% CI 0.56 to 0.70)	DS II
Acute levodopa (125–275 mg)	67	0.69 (95% CI 0.59 to 0.80)	

5.7.3 From evidence to recommendation

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 Parkinson's disease 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 outpatients. This does not preclude the use of acute apomorphine challenges to assess whether a person with later Parkinson's disease will still respond to dopaminergic medication.

Table 5.8 Diagnostic accuracy of acute apomorphine and levodopa challenge testing in established Parkinson's disease cases[79,80]

			Sensitivity (%) (95% confidence	Specificity (%) (95% confidence
	PD	Non-PD		

Acute apomorphine 0.7–10 mg[79]	236	126	86 (95% CI 0.78 to 0.94)	85 (95% CI 0.74 to 0.96)	DS II
Acute levodopa 275 mg[79]	135	39	75 (95% CI 0.64 to 0.85)	87 (95% CI 0.77 to 0.97)	
Acute carbidopa/ levodopa 250/25 mg[80]	83	51	77.1	71.7	DS III
Acute apomorphine 1.5 mg[80]	83	51	70.5	65.9	

5.7.4 Recommendations

23. Do not use acute levodopa and apomorphine challenge tests in the differential diagnosis of parkinsonian syndromes. [2006, amended 2017]

5.8 Objective smell testing

Around 80% of people with Parkinson's disease may have an impaired sense of smell (hyposomia).[85]

Since smell can be objectively tested with a battery of different odours, is it possible that objective smell identification may be useful in Parkinson's disease differential diagnosis?

5.8.1 Methodology

We found six diagnostic studies looking at the effectiveness of smell testing in Parkinson's disease differential diagnosis. Two techniques were employed: the 'Sniffin Sticks' test[86] and the University of Pennsylvania Smell Identification Test (UPSIT). The tests were used to differentiate parkinsonian syndromes[86–88] and people with Parkinson's disease from healthy controls.[85,89,90]

5.8.2 Evidence statements

A separate summary of the five diagnostic accuracy studies is listed in Table 5.9 and Table 5.10. One study[90] 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 Parkinson's disease in males than in females. **(DS II)**

Another study[89] reported that of the 40 odorants in the UPSIT test, the combined smell of pizza and wintergreen was the best discriminator. In addition, pizza (oregano smell) alone specifically indicates anosmia for people with Parkinson's disease with a very high sensitivity and specificity (Table 5.10). **(DS II)**

A third study[85] found abnormal olfactory function in 82% of the Parkinson's disease participants tested compared with 23% of controls. **(DS II)**

1213

Table 5.9 Diagnostic accuracy of smell-testing techniques in differentiating parkinsonian syndromes

Technique	Groups (N)	Mean age (years)	Disease duration (years)	Cut-off score	Sensitivity (%)	Specificity (%)	Grade
'Sniffin Sticks'[86]	PD (7) versus MSA (8)	57.7	5.8	19.5 24.8	78 100	100 63	DS Ib
UPSIT test[87]	PD (118) versus MSA (29), PSP (15) and CBD (7)	59.4 63.7	–	25	77	85	DS III
UPSIT test[91]	PD (18) versus VP (14)	70.6 74.1	9.1 6.6	>22	85.7	88.9	DS II
UPSIT test[91]	PD (NR) versus VP (8)	65–75	–	≤23	100	85.7	DS II
UPSIT test[91]	PD (NR) versus VP (6)	76–88	–	≤22	85.7	80	DS II

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Table 5.10 Diagnostic accuracy of smell-testing techniques in differentiating parkinsonian syndromes from non-parkinsonian syndromes

Technique	Groups (N)	Mean age (years)	Disease duration (years)	Cut-off score	Sensitivity (%)	Specificity (%)	Grade
B-SIT test[85]	PD (49) versus control (52)	68 71	5	–	82	82	DS II
UPSIT test[90]	Male: PD (52) versus controls (76)	61 to 70	5 (3 months-48 years)	25	81	82	DS II
UPSIT test[90]	Female: PD (20) versus control (104)	61 to 70	See above	30	80	88	DS II
UPSIT test[90]	Male: PD (32) versus controls (128)	≤60	See above	31	91	88	DS II
UPSIT test[90]	Female: PD (28) versus control (112)	≤60	See above	33	79	85	DS II
UPSIT test[90]	Male: PD (25) versus controls (100)	≥71	See above	22	76	78	DS II
UPSIT test[90]	Female: PD (23) versus control (92)	≥71	See above	25	78	82	DS II
Pizza and wintergreen[89]	IPD (96) versus controls (96)	62	Not stated	NA	90	86	DS II
Pizza (oregano		45.6			76	90	DS II

5.8.3 From evidence to recommendation

Objective smell testing has a moderate sensitivity and specificity in differentiating people with Parkinson's disease from controls. However, there are few data on its ability to differentiate Parkinson's disease from other parkinsonian syndromes. Smell is also diminished in Alzheimer's disease.[92] At present, smell identification adds little in the differential diagnosis of parkinsonism but this situation may change with further research.

5.8.4 Recommendations

24. Do not use objective smell testing in the differential diagnosis of parkinsonian syndromes, except in the context of clinical trials. [2006, amended 2017]

6 Pharmacological management of motor symptoms

Parkinson's disease is a progressive neurodegenerative condition resulting from the death of the dopamine containing cells of the substantia nigra. There is no consistently reliable test that can distinguish Parkinson's disease from other conditions that have similar clinical presentations. The diagnosis is primarily a clinical one based on the history and examination. People with Parkinson's disease classically present with the symptoms and signs associated with parkinsonism, namely hypokinesia (i.e., poverty of movement), bradykinesia (i.e., slowness of movement), postural instability, rigidity and sometimes a rest tremor.

There is no single drug of choice in the initial pharmacotherapy of early Parkinson's disease, particularly as no two Parkinson's disease patients present the same and they often do not respond to medication in the same way. The clinical question to be addressed is the comparative effectiveness of first-line treatments of motor symptoms e.g. levodopa, dopamine agonists, monoamine oxidase B (MAO-B) inhibitors and amantadine, as these medications have been used as first line treatments, but their comparative effectiveness is unclear.

Levodopa is converted into dopamine by the body, and therefore helps to replace the dopamine that is lost as part of Parkinson's disease. Dopamine agonists stimulate nerve cells in the brain in a similar way to dopamine. MAO-Bs reduce the amount of dopamine broken down in the brain, by blocking the enzyme which does so. Finally, amantadine both increases dopamine release and blocks dopamine reuptake. These are no known theoretical reasons why one class of drugs should be more effective than another.

As levodopa is currently the most commonly prescribed treatment for the motor symptoms of Parkinson's disease, but its effectiveness decreases with time, it is also important to answer the clinical question of the best pharmacotherapy adjuvants to oral levodopa. Clinicians often aim to keep the dose of levodopa as low as possible to maintain good function and reduce the development of motor complications, and so it is important to assess the effectiveness of drug therapy adjuvants to levodopa as they are likely to be used as the condition progresses. In addition to the drugs described above (dopamine agonists, MAO-Bs and amantadine), catechol-O-methyltransferase (COMT) inhibitors and anticholinergics have also been used at this stage in the treatment pathway.

COMT inhibitors block an enzyme which breaks down levodopa, thereby prolonging its effect and enabling lower levodopa doses to be used. Anticholinergics are most commonly used in the earlier stages of Parkinson's disease, with the aim of improving motor symptoms.

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6.1 First-line treatment of motor symptoms

What is the comparative effectiveness of levodopa preparations, monoamine oxidase B (MAO-B) inhibitors, dopamine agonists and amantadine as first-line treatment of motor symptoms?

6.1.1 Introduction

The aim of this review question was to determine the effectiveness of levodopa preparations, MAO-B inhibitors, dopamine agonists and amantadine as first-line treatment of motor symptoms associated with drug-naive Parkinson's disease. This updated review incorporates studies that were included in the previous guideline together with newly published evidence.

The review focused on identifying studies that fulfilled the conditions specified in Table 5.

Table 5: PICO table for the first-line treatment of motor symptoms

Population	People with a diagnosis of Parkinson's disease and commencing pharmacotherapy (drug-naive Parkinson's disease population)

Interventions	• Levodopa:
	  ○ Co-beneldopa
	  ○ Co-careldopa
	• MAO-B inhibitors:
	  ○ Selegiline
	  ○ Rasagiline
	• Non-ergot dopamine agonists:
	  ○ Ropinirole
	  ○ Pramipexole
	  ○ Rotigotine
	• Amantadine
	• Combinations of the above interventions

Comparators	• Placebo • Each other
Outcomes	• Adverse events (at individual drug level) • Disease severity: motor symptoms - UPDRS • UPDRS ADL • Non motor symptoms: hallucinations, delusions, psychoses, ICD • Off time • Dyskinesia • Health related quality of life • Carer quality of life

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Only non-ergot dopamine agonists were considered in this review, as the GDG agreed that the higher monitoring requirements for ergot agonists meant they were highly unlikely to be routinely used as first-line treatment. For full details of the review protocol, please see Appendix C. Randomised controlled trials (RCTs) were considered to be the most appropriate study design to estimate treatment effects, and were therefore considered to be the highest quality within a GRADE framework. All other study designs were excluded from this review, including case–control studies, cohort studies and case reports.

6.1.2 Evidence review

A systematic search was conducted (see appendix I), which identified 2,248 references. The references were screened on their titles and abstracts and full papers of 82 references were

obtained and reviewed against the inclusion and exclusion criteria in the review protocol (see appendix C). Additionally, the 30 studies that were included in the previous Parkinson's disease guideline (CG35) were reviewed against the current protocol; and reference lists of identified systematic reviews (both from the old guideline and the new search) were checked for additional eligible studies. An additional 4 new papers were identified through rerun searches at the end of the guideline, of which 1 was included and 3 excluded.

Studies were excluded if they did not meet the eligibility criteria, such as not being a randomised-control design or not assessing an included intervention. A detailed list of excluded studies and reasons for their exclusion is provided in appendix G.

Included studies were divided into 2 pools, the first including those which directly met the inclusion criteria of a treatment-naive population (defined as less than 1 month of prior treatment for Parkinson's disease). Six studies were included which met this criterion. Evidence tables for the included studies can be found in appendix D, with GRADE profiles reported in appendix E.

The second pool comprised studies with a population which was not fully treatment naive. These studies were included as the GDG agreed that they could contain useful information, provided that either more than 75% of the study population were treatment naive, or the following 2 conditions were met:

- Less than 6 months of prior levodopa or dopamine agonist therapy, plus a washout period of at least 2 weeks before study treatment was started.
- If patients were on other medications at baseline (e.g. beta-blockers, anti-cholinergics, amantadine) these needed to be on stable doses at baseline and these doses maintained for the entire period of the study.

Twenty-four studies met these criteria. Evidence tables for the included studies can be found in appendix D, with GRADE profiles reported in appendix E.

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6.1.3 Description of included studies (treatment naive)

All the studies identified in a treatment-naïve population were published after the previous version of the Parkinson's disease guideline was published.

Levodopa vs. placebo (n=1)

People with a confirmed diagnosis of Parkinson's disease within the last 2 years (n=361) were randomly assigned to 4 groups, consisting of 3 different doses of levodopa/carbidopa (150/37.5 mg/day, 300/75 mg/day or 600/150 mg/day) or placebo, to determine whether levodopa treatment affects the rate of progression of Parkinson's disease (Fahn et al., 2005). No participants were on any anti-parkinsonian medication at the time of enrolment. The trial duration was 40 weeks, followed by a 2-week withdrawal period at the end of the trial. The study was conducted in 38 sites in the US (n=33) and Canada (n=5). Full details of the study are found in the evidence tables (see Appendix D).

Monoamine oxidase B (MAO-B) inhibitors (n=3)

Two randomised, double-blind trials examined the safety and effectiveness of selegiline compared with placebo in a total of 177 patients with previously untreated idiopathic Parkinson's disease (Mally et al., 1995; Palhågen et al., 1998). One of the trials was conducted in Sweden and the trial duration depended on when additional therapy (levodopa) was required (Palhågen et al., 1998). Median trial duration was reported to be 12.7 months in the treatment group and 8.6 months in the placebo group. The location of the second trial was not reported but the trial duration was 6 weeks (Mally et al., 1995). Selegiline dosing

was 10 mg/day in both studies. Details of the included studies are found in the evidence tables (see Appendix D)

One further trial examined the safety and effectiveness of early versus delayed rasagiline initiation in a total of 1,176 patients who had not previously received any anti-parkinsonian medication for more than 3 weeks (Olanow et al., 2009). This was a double-blind, placebo-controlled, multicentre trial that used a delayed-start design consisting of 2 phases. Only the first phase (early rasagiline vs. delayed rasagiline [placebo]) was relevant for this review. The trial duration for phase 1 was 18 months and this study was carried out in 14 countries. Rasagiline was administered at a dose of either 1 mg/day or 2 mg/day. Full details of the study are found in the evidence tables (see Appendix D).

Dopamine agonists (n=2)

A total of 535 patients with a confirmed diagnosis of Parkinson's disease within the last 2 years participated in 1 randomised, double-blind, placebo-controlled, delayed-start trial to examine the safety and effectiveness of early versus delayed pramipexole initiation (Schapira et al., 2013). The trial duration for phase 1 (early pramipexole vs. delayed pramipexole [placebo]) ranged from 6 to 9 months and the dosing was up-titrated over 4 weeks from 0.125 mg 3 times a day to 0.5 mg 3 times a day. This study was carried out in 10 countries (Austria, Finland, France, Germany, Italy, Japan, Spain, Sweden, the UK and the USA). Full details of the study are found in the evidence tables (see Appendix D).

A total of 60 patients with previously untreated idiopathic Parkinson's disease participated in 1 randomised, double-blind trial, comparing the effectiveness of ropinirole and pramipexole (Thomas et al., 2006). The study was carried out in 2 Parkinson's disease clinics in Italy. The trial duration was 24 months. The dosing for ropinirole was from 3–5 mg/day to 15 mg/day during the first 3 months. This could be further increased to a maximum of 24 mg/day in the following year according to patients' needs. The dosing for pramipexole was from 0.7 mg/day to 2.1 mg/day during the first 3 months. This could be further increased to a maximum of 4.2 mg/day in the following year according to patients' needs. Full details of the study are found in the evidence tables (see Appendix D).

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Amantadine

No evidence was found on first-line treatment with amantadine.

6.1.4 Description of included studies (early Parkinson's disease)

Of the additional 24 studies meeting the criteria of including participants with early Parkinson's disease but who were not fully treatment naïve (15 of which were included as part of the previous Parkinson's disease guideline, and 9 of which have been published since), the following treatment comparisons were identified:

- 1 study comparing extended-release levodopa with placebo
- 10 studies comparing dopamine agonists with placebo
- 3 studies comparing MAO-B inhibitors with placebo
- 6 studies comparing levodopa with dopamine agonists
- 1 studies comparing levodopa with MAO-B inhibitors
- 1 study comparing dopamine agonists with MAO-B inhibitors
- 1 study comparing levodopa with levodopa plus a dopamine agonist
- 1 study comparing levodopa, dopamine agonists and MAO-B inhibitors (this study – PDMED – was a long-term, independently funded study conducted in the UK, and hence was given particular consideration during GDG discussions)

6.1.5 Health economic evidence

Literature searches were undertaken to find any existing cost–utility analyses (CUAs) comparing any initial or adjuvant drug treatments for people with Parkinson's disease that have been published since the literature reviews in CG35. In total, 925 articles were returned, of which 16 were selected as potentially relevant and retrieved for full text review. Additionally, the 5 studies that were included in CG35 were reviewed against the current protocol. In total, 8 studies were included. Of these, 2 compared initial therapies. Studies that met the eligibility criteria were assessed using the quality appraisal criteria as outlined in the NICE guidelines manual (NICE, 2012).

Two CUAs based on the same model structure met the NICE reference case (NICE, 2012). Farkouh et al. (2012) compared 5 treatments (rasagiline, pramipexole, ropinirole standard and extended release and levodopa) and based their model on that done by Haycox et al. (2009) who compared rasagiline and pramipexole. The primary outcome was delaying the emergence of treatment-related dyskinesias.

Treatment sequences were specified and only monotherapies were modelled. By modelling an additional treatment in the rasagiline arms, the models automatically biased towards taking longer to reach the dyskinesia states for this arm.

Both models used treatment-based states with or without dyskinesias to model a 5-year time horizon. State transitions – occurring when existing treatment no longer adequately controlled symptoms – were taken from single RCTs but no evidence was given for the reasons for selecting the single RCTs rather than undertaking a systematic review of the literature. Separate RCTs were used for each comparator – no attempt was made to appropriately synthesise the RCTs.

The RCTs used in Haycox et al. (2009) exhibited different baseline population characteristics, with the rasagiline RCT showing less severe Parkinson's disease. The RCTs also had differing treatment protocols, with the rasagiline RCT having a longer requirement to exclude levodopa treatment (26 weeks versus 10 weeks in the pramipexole RCT). Both these differences contributed to much lower transition probabilities to other drugs, again slowing the progress to the dyskinesia states for this arm.

Haycox et al. (2009) took an NHS and PSS perspective, but included private medical costs from their source costs paper. Costs were assumed from Hoehn and Yahr stage-based costs and do not appear to have been inflated appropriately and no cost was given for levodopa. The authors chose not to model mortality as they felt there would be no difference between arms. Costs were discounted at 6% per annum and utilities at 1.5% per annum.

Farkouh et al. (2012) took an American managed-care perspective. They applied a cost multiplier (1.7, from European studies) to states with dyskinesias. Both costs and utilities were discounted at 3% per annum.

Both papers took their utility values from the same paper reporting visual analogue scale and standard gamble utility scores for an American convenience sample. The papers assumed the Hoehn and Yahr stages appropriate to their treatment-based states with and without dyskinesias.

Haycox et al. (2009) found rasagiline dominated pramipexole. Sensitivity analyses were limited to pramipexole dosing and varying utility inputs; in both cases rasagiline remained dominant. No probabilistic sensitivity analysis (PSA) was reported.

Farkouh et al. (2012) presented pairwise comparisons between rasagiline and the other treatments. It was not possible to calculate incremental results as each pairwise comparison reported different costs for rasagiline. In pairwise comparisons, rasagiline dominated pramipexole, ropinirole extended release and levodopa. Compared with ropinirole standard

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release, rasagiline produced an ICER of $25,900 per QALY. Sensitivity analyses were only presented for rasagiline compared with ropinirole standard release. One-way sensitivity analyses only varied input parameters by 10%, which may not sufficiently capture parameter uncertainty. The ICER was found to be most sensitive to the utility weights used (ICER $52,400 if standard gamble utility weights used) and the dyskinesia cost multiplier (ICER $52,500 if costs were no higher in the dyskinesia states). In PSA, rasagiline was cost effective compared with ropinirole standard release in 61% of iterations at a $50,000 per QALY threshold.

6.1.6 Evidence statements (treatment naive)

6.1.6.1 Adverse events

Monoamine oxidase B (MAO-B) inhibitors

Low-quality evidence from 1 RCT (Olanow et al., 2009) suggested that, compared with placebo, rasagiline has a small lowered risk of any adverse events (IRR=0.80, 95% CI: 0.65 to 0.99). Rasagiline was found to be associated with lower levels of depression and anxiety, compared with placebo.

Very low-quality evidence from 1 RCT (Olanow et al., 2009) reported no meaningful relationship between rasagiline and the risk of adverse events related to dopaminergic therapy, compared with placebo (IRR=0.72, 95% CI: 0.49 to 1.07).

Levodopa/carbidopa

Low-quality evidence from 1 RCT (Fahn et al., 2005) reported no meaningful relationship between levodopa/carbidopa and the risk of any adverse events, compared with placebo (150/37.5 mg/day dose: IRR=1.00 [95% CI: 0.84 to 1.20]; 600/150 mg/day dose: IRR=1.18 [95% CI: 0.97 to 1.43]). However, increasing doses of levodopa/carbidopa were found to be associated with increasing rates of dyskinesia, hypertonia, infection and nausea but decreasing rates of fracture and leg pain.

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Dopamine agonists

Low-quality evidence from 1 RCT (Shapira et al., 2013) reported no meaningful relationship between pramipexole and the risk of any adverse events, compared with placebo (RR=1.04, 95% CI: 0.94 to 1.15). Pramipexole was however associated with higher levels of nausea, somnolence, peripheral oedema and hallucination, compared with placebo.

Low-quality evidence from 1 RCT (Thomas et al., 2006) reported no meaningful difference between ropinirole and pramipexole on the risk of adverse events (RR=1.67, 95% CI: 0.44 to 6.36).

6.1.6.2 UPDRS total

Low-quality evidence from 2 RCTs (Palhågen et al., 1998; Olanow et al., 2009) suggested that, compared with placebo, MAO-B inhibitors significantly reduce parkinsonian symptoms as assessed by the UPDRS total rating scale (MD=−3.07, 95% CI: −3.78 to −2.37), although the mean difference was below the minimal clinically important difference as defined by Schrag et al., 2006.

A network meta-analysis pooling 5 RCTs using UPDRS total rating scale to measure parkinsonian symptoms suggested that levodopa/carbidopa has a large effect in reducing symptoms, and appears to be the optimal option in this domain, followed by the dopamine

agonist pramipexole and MAO-B inhibitors (selegiline and rasagiline). Evidence was moderate quality.

6.1.6.3 UPDRS II (ADL)

A network meta-analysis pooling 4 RCTs reporting the activities of daily living in people with Parkinson's disease using the UPDRS ADL subscale suggested that levodopa/carbidopa is likely to be the optimum option. There is low probability that a MAO-B inhibitor (selegiline) is the best treatment, in this domain. Evidence was low quality.

6.1.6.4 UDRS III (motor)

A network meta-analysis pooling 4 RCTs using UPDRS motor subscale to measure motor symptoms in people with Parkinson's disease suggested that a higher dose of levodopa/carbidopa (600 mg/day) has the highest probability of being the optimum option in this domain, followed by dopamine agonist (pramipexole), a lower dose of levodopa/carbidopa (150/300 mg/day) and lastly MAO-B inhibitors (selegiline). Evidence was low quality.

6.1.6.5 Non-motor symptoms

Low-quality evidence from 1 RCT (Schapira et al., 2013) using the Beck depression inventory to measure the severity of depression suggested that, compared with placebo, pramipexole significantly improves depression and depressive symptoms (MD=−1.40, 95% CI: −2.23 to −0.57).

6.1.6.6 Dyskinesia

Low-quality evidence from 1 RCT (Fahn et al., 2005) found increasing doses of levodopa/carbidopa to be associated with increasing rates of dyskinesia ($p<0.001$).

6.1.6.7 Off time

No evidence for off time was identified.

6.1.6.8 Health-related quality of life

No evidence for health-related quality of life was identified

6.1.6.9 Carer quality of life

No evidence for carer quality of life was identified.

6.1.7 Evidence statements (full population)

6.1.7.1 Levodopa versus placebo

Low-to-moderate-quality evidence from 2 RCTs indicates that levodopa is associated with significant improvements, versus placebo, in UPDRS scores (total, ADL and motor), and the PDQ-39, although the mean differences on all UPDRS scores were below and/or the confidence intervals crossed the line of minimal clinically important differences as defined by Schrag et al., 2006 and Horvath et al., 2015.

Very low- to low-quality evidence from 2 RCTs could not differentiate between levodopa and placebo in overall rates of adverse events, serious adverse events, dopaminergic adverse events or adverse events requiring discontinuation:

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- Levodopa was associated with higher rates of dyskinesia, hypertonia, infection and nausea, but lower rates of fracture and leg pain.

6.1.7.2 Dopamine agonist versus placebo

Very low- to moderate-quality evidence from 8 RCTs indicates that dopamine agonists are associated with significant improvements, compared with placebo, in UPDRS total, motor and ADL scores, although the mean differences were below and/or the confidence intervals crossed the line of minimal clinically important differences as defined by Schrag et al., 2006.

High quality evidence from 1 RCT indicates that dopamine agonists are associated with significant improvements, compared to placebo, in depression (BDI).

Low-to-moderate quality evidence from 2 RCTs indicates that dopamine agonists are associated with significant improvements, compared with placebo, in Parkinson's-specific quality of life (PDQ-39), although the confidence intervals from 1 RCT crossed the line of minimal clinically important change on the PDQ-39 questionnaire as defined by Peto et al., 2001.

Low quality evidence from 2 RCTs indicates that dopamine agonists are associated with a significant worsening, compared with placebo, in sleepiness (ESS).

Low-quality evidence from 2 RCTs could not differentiate health-related quality of life (EQ-VAS) levels between dopamine agonists and placebo.

Very low-quality evidence from 5 RCTs could not distinguish between pramipexole and placebo in rates of adverse events, serious adverse events, dopaminergic adverse events or adverse events requiring discontinuation.

- Pramipexole was associated with higher levels of nausea, somnolence, constipation, fatigue, dizziness, dry mouth, peripheral oedema and hallucination, compared with placebo.

Very low- to low-quality evidence from 4 RCTs indicates rotigotine is associated with significantly higher rates of adverse events and adverse events requiring discontinuation, but could not distinguish rates of serious adverse events.

- Rotigotine was associated with higher levels of application site disorders, lower leg pain, nausea, vomiting, somnolence and fatigue, compared with placebo.

Very low- to low-quality evidence from 2 RCTs indicates ropinirole is associated with significantly higher rates of adverse events requiring discontinuation, but could not distinguish rates of adverse events or serious adverse events.

- Ropinirole was associated with higher levels of nausea, dizziness, somnolence and syncope, compared with placebo.

6.1.7.3 Monoamine oxidase B (MAO-B) inhibitors versus placebo

Very low- to moderate-quality evidence from 4 RCTs indicates that MAO-B inhibitors are associated with significant improvements, compared with placebo, in UPDRS (total, motor and ADL scores) and the Parkinson's disease quality of life scale (PDQUALIF), although the mean differences were below and/or the confidence intervals crossed the line of minimal clinically important differences as defined by Schrag et al., 2006 and Horvath et al., 2015.

Low-quality evidence from 1 RCT could not differentiate depression (BDI) levels between MAO-B inhibitors and placebo.

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Very low- to low-quality evidence from 2 RCTs indicates rasagiline is associated with significantly lower rate of adverse events, but could not differentiate rates of serious adverse events or dopaminergic adverse events.

- Rasagiline was associated with higher levels of asthenia, but lower rates of depression and anxiety.

6.1.7.4 Levodopa versus dopamine agonists

Low-to-moderate-quality evidence from 3 RCTs indicates that levodopa is associated with significant improvements, compared with dopamine agonists, in UPDRS scores (total, motor and ADL), although the mean differences were below and/or the confidence intervals crossed the line of minimal clinically important differences as defined by Schrag et al., 2006 and Horvath et al., 2015.

Moderate-quality evidence from 1 RCT indicates people with Parkinson's disease taking levodopa are significantly more likely to experience dyskinesia than those taking dopamine agonists.

Very low- to low-quality evidence from 1 RCT indicates that levodopa is associated with lower rates of adverse events than pramipexole, but could not differentiate rates of serious adverse events.

- Pramipexole is associated with higher rates of somnolence, hallucinations, cellulitis, oedema and peripheral oedema than levodopa, but lower rates of urinary frequency and hernia

Very low-quality evidence from 2 RCTs could not differentiate rates of adverse events, serious adverse events or adverse events requiring discontinuation between levodopa and ropinirole.

- Ropinirole is associated with higher rates of nausea, hallucinations and somnolence than levodopa.

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6.1.7.5 Long-term data

Low-to-moderate-quality evidence from 2 RCTs indicates that people with Parkinson's disease taking levodopa have significantly better UPDRS (total, motor and ADL) scores than those taking dopamine agonists, although the mean differences were below and/or the confidence intervals crossed the line of minimal clinically important differences as defined by Schrag et al., 2006 and Horvath et al., 2015.

Moderate-quality evidence from 2 RCTs indicates that people with Parkinson's disease taking levodopa are significantly more likely to experience dyskinesia than those taking dopamine agonists.

6.1.7.6 Levodopa versus monoamine oxidase inhibitors

Low-quality evidence from 1 RCT indicates that levodopa is associated with significant improvements, compared with MAO-B inhibitors, in UPDRS motor score, although the mean difference was below the minimal clinically important difference as defined by Schrag et al., 2006.

Low-quality evidence from 1 RCT could not find any meaningful difference between levodopa and MAO-B inhibitors in UPDRS ADL score.

6.1.7.7 Long-term data

Moderate-quality evidence from 1 RCT indicates that people taking levodopa are significantly less likely to require add-on therapy than those taking MAO-B inhibitors.

Moderate-quality evidence from 1 RCT indicates that people taking levodopa experience higher rates of motor fluctuations than those taking MAO-B inhibitors.

Low-quality evidence from 1 RCT could not differentiate rates of dyskinesia between those taking levodopa and MAO-B inhibitors.

6.1.7.8 Dopamine agonists versus monoamine oxidase inhibitors

Moderate-quality evidence from 1 RCT indicates that people taking dopamine agonists had significantly greater problems with somnolence, as measured by the ESS, than those taking MAO-B inhibitors.

Very low-quality evidence from 1 RCT could not differentiate rates of adverse events, serious adverse events or adverse events requiring discontinuation between pramipexole and rasagiline.

6.1.7.9 Network meta-analyses

Low-quality evidence found MAO-B inhibitors, dopamine agonists and levodopa are all associated with benefits in UPDRS (ADL) scores versus placebo, with levodopa at higher doses being significantly better than MAO-B inhibitors, although the mean differences were below and/or the confidence intervals crossed the line of the minimal clinically important difference as defined by Schrag et al., 2006.

Low-quality evidence found MAO-B inhibitors, dopamine agonists and levodopa are all associated with benefits in UPDRS (motor) scores versus placebo, though the benefits with MAO-B inhibitors may not persist, although the mean differences were below and/or the confidence intervals crossed the line of the minimal clinically important difference as defined by Schrag et al., 2006 and Horvath et al., 2015.

Moderate-quality evidence found MAO-B inhibitors, dopamine agonists and levodopa are all associated with benefits in UPDRS (total) scores versus placebo, with levodopa at higher doses being significantly better than MAO-B inhibitors, although the mean differences were below and/or the confidence intervals crossed the line of the minimal clinically important difference as defined by Schrag et al., 2006.

Low-quality evidence found dopamine agonists are associated with a significant worsening in ESS scores, relative to placebo.

6.1.8 Levodopa versus dopamine agonists versus monoamine oxidase inhibitors (PD MED)

6.1.8.1 Efficacy (levodopa versus levodopa-sparing)

Moderate-quality evidence from 1 RCT indicates that levodopa is associated with significantly better long-term outcomes for mobility, ADL, stigma and bodily discomfort than levodopa-sparing therapy, although the mean differences are below the trial's defined minimally important differences.

Moderate-quality evidence from 1 RCT indicates that levodopa is associated with significantly better long-term Parkinson's specific (PDQ-39) and health-related (EQ-5D) quality of life than levodopa-sparing therapy.

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Moderate-quality evidence from 1 RCT could not differentiate long-term levels of emotional wellbeing, social support, cognition or communication between levodopa and levodopa-sparing therapy.

6.1.8.2 Efficacy (dopamine agonists versus monoamine oxidase inhibitors)

Moderate-quality evidence from 1 RCT indicates that MAO-B inhibitors are associated with significantly better long-term outcomes for cognition than dopamine agonists, although the mean difference is below the trial's defined minimally important difference.

Moderate-quality evidence from 1 RCT could not differentiate long-term levels of mobility, ADL, emotional wellbeing, stigma, social support, communication, bodily discomfort or health-related quality of life between MAO-B inhibitors and dopamine agonists.

6.1.8.3 Safety

Moderate-quality evidence from 1 RCT indicates that levodopa is associated with significantly higher long-term rates of dyskinesia than levodopa sparing-therapy.

Moderate-quality evidence from 1 RCT indicates that levodopa is associated with significantly lower rates of drug discontinuation, both due to side effects and lack of efficacy, than levodopa-sparing therapy.

6.1.9 Evidence statements (economics)

Two partially applicable cost–utility analyses with very serious limitations found rasagiline to be cost effective compared with alternative treatments. However, the model structure on which both are based appears to bias results towards rasagiline in a number of areas, costs were not necessarily representative and utilities were assumed from a non EQ-5D source. No economic evidence was found for initial treatment with selegiline, rotigotine, amantadine or combinations of treatments.

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6.1.10 Evidence to recommendations

Relative value of different outcomes	The GDG agreed that the key trade-off for this question was better control of motor symptoms against the risks of adverse events, in particular the long-term development of motor fluctuations and dyskinesia, which also significantly impact on quality of life for both the person with Parkinson's disease and their carer(s). The best outcome measure to address this question would therefore be one that combined the impacts of these separate components in one measure (that is, patient and carer quality of life). Where such combined evidence was not available, the GDG agreed that it was important to weigh up the balance between symptom control and long-term adverse events.
Trade-off between benefits and harms	The GDG discussed the appropriate inclusion criteria for studies to include in the decision making on first-line treatments of motor symptoms associated with treatment-naive Parkinson's disease. It was agreed that it was appropriate to not only consider people with treatment-naive Parkinson's disease but to also consider people with early Parkinson's disease in this review question. This decision was based on the fact that the choice of treatment for treatment-naive and early Parkinson's disease are similar from a clinical perspective. Additionally the majority of trials in this area were not conducted in people with Parkinson's disease who were entirely treatment naive, and therefore restricting study inclusion to this population would severely narrow the evidence base available. The GDG therefore discussed and agreed that if the population in the trials had less than 6 months' exposure to previous dopaminergic therapy and had at least a 2-week

washout period before study entry, the study would be considered for inclusion. The GDG agreed that any drug–drug interactions were likely to be rare. Therefore, any concomitant drugs, such as anticholinergics or beta-blockers, were also considered to be acceptable as long as these were at stable doses prior to inclusion in the trial and maintained throughout the study period. The GDG agreed that any recommendations arising from the evidence and directed at the treatment of early Parkinson's disease would apply to both treatment-naive and early stage Parkinson's disease.

The GDG noted that, although MAO-B inhibitors, dopamine agonists and levodopa are all associated with symptomatic benefit in people with treatment-naive or early Parkinson's disease, there is a consistent trend towards higher doses of levodopa being more effective than the other 2 classes of drugs in all aspects of symptomatic control, but particularly in controlling motor symptoms. This difference was demonstrated in both short-term and long-term trials (up to 7 years). Specifically, the GDG noted that, in a long-term pragmatic trial in the UK comparing initial therapy with levodopa, dopamine agonists and MAO-B inhibitors (PDMED), there were long-term quality of life gains associated with initial levodopa therapy (which included the long-term disutilities of dyskinesia), implying that for this population the balance of benefits and harms favours initial treatment with levodopa. The GDG agreed that these findings had clinical face validity. Moreover, it was noted that, although there is no statistical significant difference in symptom control (motor symptoms as well as activities of daily living) between MAO-B inhibitors and dopamine agonists, the point estimate of dopamine agonist is more effective than MAO-B inhibitors.

The GDG discussed and recognised that high levodopa dose (>600 mg/day) is preconceived to be associated with an increased risk of developing levodopa-induced dyskinesia. Although there is some evidence to suggest this, there is limited evidence to indicate how severe dyskinesia is (i.e. the impact it has on quality of life) in people with Parkinson's disease on levodopa. The GDG therefore agreed not to make a recommendation on the initial dosage of levodopa. Instead the GDG agreed that the risk of developing levodopa-induced dyskinesia and their potential severity in the future should be weighed against current quality of life gains, which is seen in evidence from higher levodopa doses. The GDG noted the importance of changing people's preconceptions that levodopa is harmful, especially at higher doses (greater than 600 mg/day) for people with Parkinson's disease. In the GDG's experience such preconceptions lead clinicians to avoid prescribing higher doses of levodopa but there is a lack of evidence to support this practice.

Whilst levodopa was associated with the greatest improvement in symptomatic control, particularly in motor function, the GDG noted the symptomatic benefit provided by dopamine agonists and MAO-B inhibitors. The GDG therefore agreed that people with treatment-naive or early Parkinson's disease without motor symptoms impacting their quality of life, should be offered a choice of treatment options depending on their individual concerns or circumstances. This should take place after the clinician has had a discussion with the person on their clinical and lifestyle characteristics as well as the potential benefits and harms of the different drug classes. The GDG agreed that it is important to inform the person about the different dosing regimen involved for each drug to ensure people adhere to their medication regimen.

The GDG agreed that, before commencing pharmacological treatment for people with treatment-naive or early Parkinson's disease, the specific adverse events related to each class of drugs should be discussed with the person and their carer – in particular, the relative increased risk of developing impulse control disorder, somnolence and hallucinations, which is noted in the evidence. Evidence that such a discussion has taken place should be documented in the consultation summary letter that is sent out to

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	the patient after the consultation. The GDG discussed whether to make a recommendation that non-ergot dopamine agonists should be prefered to ergot agonists, because of their lower monitoring requirements. It was noted that both are valid treatment options, and clinicians will often try an ergot agonist if a non-ergot one has not proven effective. The GDG agreed that the difficulties with ergot agonists were now well known amongst Parkinson's' disease clinicians, and therefore there was not a need for specific guidance on this issue.
Trade-off between net health benefits and resource use	The GDG agreed that the published economic evidence discussed was not sufficiently relevant or of a high enough standard to directly inform their decision making. However, it was noted that, for each of the 3 main classes of drugs under discussion, at least 1 prescribable, out-of-patent option was available, and all 3 classes of drugs were in common use in the UK for this population. Therefore, the GDG agreed that is was unlikely their recommendations would add a substantial resource impact to the NHS, and were confident to make recommendations without any directly applicable economic evidence being available.
Quality of evidence	Based on the clear and consistent findings for levodopa, dopamine agonists and MAO-B inhibitors, the GDG were confident in making two 'offer' recommendations for first-line treatment of motor symptoms associated with treatment-naive and early Parkinson's disease. Although the efficacy findings for dopamine agonists and MAOBs sometimes did significantly exceed the defined minimal important differences for UPDRS scores, it was noted that these MIDs were based on short-term changes in health state. However, the benefits of treatment were expected to persist in the long-term, and therefore the GDG were satisfied they did correspond to a meaningful change in patient quality of life. It was also noted that, because the treatments showed benefits to people across multiple domains (motor symptoms, activities of daily living, depression etc.), the total benefit was likely to be greater than that measured on any of the individual outcome measures.

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6.1.11 Recommendations

25. Offer levodopa to people in the early stages of Parkinson's disease whose motor symptoms impact on their quality of life. [new 2017]

26. Offer a choice of dopamine agonists, levodopa or monoamine oxidase B (MAO-B) inhibitors to people in the early stages of Parkinson's disease whose motor symptoms do not impact on their quality of life, after a discussion with the person about their:

- clinical and lifestyle circumstances
- preferences, taking into account the potential benefits and harms of the different drug classes (see table 4). **[new 2017]**

Table 4 Potential benefits and harms of dopamine agonists, levodopa and MAO-B inhibitors

	Levodopa	Dopamine agonists	MAO-B inhibitors
Motor symptoms	More improvement in motor symptoms	Intermediate improvement in motor symptoms	Less improvement in motor symptoms
Activities of daily living	More improvement in activities of daily living	Less improvement in activities of daily living	Less improvement in activities of daily living

	Levodopa	Dopamine agonists	MAO-B inhibitors
Motor complications	More motor complications	Fewer motor complications	Fewer motor complications
Adverse events	Fewer specified adverse events*	More specified adverse events*	Fewer specified adverse events*

Abbreviation: MAO-B, monoamine oxidase B.

* Excessive sleepiness, hallucinations and impulse control disorders (see the summary of product characteristics for full information on individual medicines).

27. When starting treatment for people in the early stages of Parkinson's disease, give people and their family members and carers (as appropriate) oral and written information about the following risks, and record that the discussion has taken place:

- Impulse control disorders with all dopaminergic therapy (and the higher risk with dopamine agonists). Also see recommendations 8-10, 80-81, and 82-85.
- Excessive sleepiness and sudden onset of sleep with dopamine agonists. Also see recommendations 32-34.
- Psychotic symptoms (hallucinations and delusions) with all Parkinson's disease treatments (and the higher risk with dopamine agonists). Also see recommendations 42-49. **[new 2017]**

6.1.12 Research recommendation

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1. What is the effectiveness of initial levodopa monotherapy versus initial levodopa-dopamine agonist combination therapy?

Why this is important

Initial therapy with levodopa has been shown to provide better control of motor symptoms and improvement in activities of daily living than dopamine agonist monotherapy, but with a higher risk of long-term motor complications/dyskinesia. Initial combination therapy with levodopa and a dopamine agonist may make it possible to achieve good symptom control using lower doses of levodopa, therefore reducing the rate at which motor complications develop. Whilst a number of randomised controlled trials have allowed the addition of levodopa to initial dopamine agonist therapy (or vice versa) over time, few trials have included a specific trial arm looking at combination treatment. Well conducted randomised controlled trials comparing initial levodopa monotherapy with initial levodopa-dopamine agonist combination therapy would fill in this gap in the evidence base.

6.2 Adjuvant treatment of motor symptoms

What is the comparative effectiveness of pharmacological interventions as adjuvants to oral levodopa preparations?

6.2.1 Introduction

The aim of this review question was to determine the effectiveness of pharmacological interventions as adjuvants to oral levodopa preparations in people with Parkinson's disease who are experiencing inadequate symptomatic control. This updated review incorporates studies that were included in the previous guideline together with newly published evidence.

The review focused on identifying studies that fulfilled the conditions specified in Table 6.

Table 6: PICO table for adjuvant treatment of motor symptoms

Population	People with Parkinson's disease on oral levodopa monotherapy preparations who are experiencing inadequate symptomatic control, such as exhibiting signs of wearing off or increasing motor symptoms.

Interventions	Oral levodopa preparations plus:
	• Modified release levodopa preparations
	• MAO-B inhibitors:
	  ○ Selegiline
	  ○ Rasagiline
	• Dopamine agonists:
	  ○ Ropinirole
	  ○ Pramipexole
	  ○ Rotigotine
	  ○ Pergolide
	  ○ Cabergoline
	  ○ Bromocriptine
	• Amantadine
	• COMT inhibitors
	  ○ Entacapone
	  ○ Tolcapone
	• Anticholinergics (anti-muscarinics)
	  ○ Benzhexol (Trihexyphenidrl)

Comparators	• Levodopa plus placebo • Levodopa monotherapy • Each other
Outcomes	• Adverse events (at individual drug level) • Disease severity: motor symptoms - UPDRS • UPDRS ADL • Non motor symptoms: hallucinations, delusions, psychoses, ICD • Off time • Dyskinesia • Health related quality of life • Carer quality of life • Mortality • Time to institutional care

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For full details of the review protocol, please see Appendix C. Randomised controlled trials (RCTs) were considered to be the most appropriate study design to estimate treatment effects, and were therefore considered to be the highest quality within a GRADE framework. All other study designs were excluded from this review, including case–control studies, cohort studies and case reports.

6.2.2 Evidence review

A systematic search was conducted (see appendix I), which identified 2,248 references. After removing duplicates the references were screened on their titles and abstracts and full papers of 113 references were obtained and reviewed against the inclusion and exclusion criteria in the review protocol (see appendix C).

Overall, 46 studies were excluded as they did not meet the eligibility criteria, such as not being a randomised-control design or not assessing an included intervention. A detailed list of excluded studies and reasons for their exclusion is provided in appendix G. The remaining 67 studies were identified as being relevant. However, none of these directly met the inclusion criteria of the population of interest (defined as people with Parkinson's disease on oral levodopa monotherapy preparations) but the GDG agreed that they would provide useful information and were therefore included in the evidence review. Of these, 41 were already included in relevant Cochrane reviews (Stowe et al., 2010; Dean et al., 2004; Clarke & Dean, 2001) identified from the search strategy.

Additionally, the 23 studies included in the previous Parkinson's disease guideline (CG35) were reviewed against the current protocol. Of these, 16 studies were already included in a Cochrane review (Stowe et al., 2010) and the remaining 7 studies did not meet the inclusion criteria in the current protocol and were therefore excluded. A detailed list of excluded studies and reasons for their exclusion is provided in appendix G.

Reference lists of identified systematic reviews (both from the old guideline and the new search) were also checked for any eligible studies that had not been identified in the search. No further additional studies were identified. Furthermore, no additional new papers were identified through rerun searches at the end of the guideline. Therefore, a total of 4 Cochrane reviews and 22 RCTs were included in the evidence review. Evidence tables for the included studies can be found in appendix D, with GRADE profiles reported in appendix E.

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6.2.3 Description of included studies

See appendix D for a summary of included studies.

6.2.3.1 Dopamine agonists (DAs)

A total of 41 studies on dopamine agonists as add-on treatments for people experiencing inadequate symptomatic control associated with Parkinson's disease were included in the evidence review. The following treatment comparisons, where all arms were on a background of levodopa/DDCI therapy, were identified:

6.2.3.1.1 *Dopamine agonists versus placebo*

- 1 Cochrane review (Stowe et al., 2010) included 20 RCTs (1 RCT had 2 agonist arms – bromocriptine and pramipexole):
  - 7 studies comparing pramipexole with placebo
  - 5 studies comparing bromocriptine with placebo
  - 4 studies comparing cabergoline with placebo
  - 4 studies comparing ropinirole with placebo
  - 1 study comparing pergolide with placebo

- 1 study comparing pramipexole with placebo (PSG, 2007)
- 1 study comparing extended- and immediate-release pramipexole with placebo (Schapira et al., 2011)
- 3 studies comparing rotigotine with placebo (Nomoto et al., 2014; Nicholas et al., 2014; LeWitt et al., 2007)
- 4 studies comparing ropinirole with placebo (Watts et al., 2010; Pahwa et al., 2007; Mizuno et al., 2007; Lieberman et al., 1998)

6.2.3.1.2 *Dopamine agonists versus dopamine agonists*

- 1 Cochrane review (Clarke and Dean, 2001a) included 3 studies comparing ropinirole with bromocriptine
- 1 Cochrane review (Clarke and Dean 2001b) included 5 studies comparing cabergoline with bromocriptine
- 1 study comparing pramipexole with pergolide (Rektorova et al., 2003)
- 1 3-arm study comparing rotigotine with pramipexole and placebo (Poewe et al., 2007)
- 1 3-arm study comparing pramipexole with bromocriptine and placebo (Mizuno et al., 2003)
- 1 3-arm study comparing transdermal rotigotine with ropinirole and placebo (Mizuno et al., 2014)

6.2.3.2 Catechol-O-methyltransferase (COMT) inhibitors

A total of 25 studies on COMT inhibitors as add-on treatments for people experiencing inadequate symptomatic control associated with Parkinson's disease were included in the evidence review. The following treatment comparisons, where all arms were on a background of levodopa/DDCI therapy, were identified:

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6.2.3.2.1 *COMT inhibitors versus placebo*

- 1 Cochrane review (Stowe et al., 2010) included 18 RCTs:
  - 11 studies comparing entacapone with placebo
  - 7 studies comparing tolcapone with placebo

6.2.3.2.2 *COMT inhibitors versus levodopa*

- 1 study comparing entacapone with levodopa/carbidopa (Tolosa et al., 2014)
- 1 study comparing entacapone with levodopa dose fractionation (Destee et al., 2009)

6.2.3.2.3 *COMT inhibitors versus DAs*

- 1 Cochrane review (Dean et al., 2004) included 2 RCTs:
  - 1 study comparing tolcapone with pergolide
  - 1 study comparing tolcapone with bromocriptine
- 1 study comparing entacapone with cabergoline (Deuschl et al., 2007)
- 1 study comparing entacapone with levodopa plus a dopamine agonist (Fenelon et al., 2003)

6.2.3.2.4 *COMT inhibitors versus COMT inhibitors*

- 1 study comparing entacapone with tolcapone (ESS, 2007)

6.2.3.3 Monoamine oxidase type B (MAO-B) inhibitors

A total of 9 studies on MAO-B inhibitors as add-on treatments for people experiencing inadequate symptomatic control associated with Parkinson's disease were included in the

evidence review. The following treatment comparisons, where all arms were on a background of levodopa/DDCI therapy, were identified:

6.2.3.3.1 *MAO-B inhibitors versus placebo*

- 1 Cochrane review (Stowe et al., 2010) included 7 RCTs:
  - 3 studies comparing rasagiline with placebo
  - 4 studies comparing selegiline with placebo
- 1 study comparing rasagiline with placebo (Zhang et al., 2013)
- 1 study comparing selegiline orally disintegrating tablets (ODT) with placebo (Ondo et al., 2007)

6.2.3.4 Amantadine

A total of 2 studies of amantadine as an add-on treatment for people experiencing inadequate symptomatic control associated with Parkinson's disease were included in the evidence review. The following treatment comparisons, where all arms were on a background of levodopa/DDCI therapy, were identified:

6.2.3.4.1 *Amantadine versus placebo*

- 2 studies on amantadine versus placebo (Pahwa et al., 2015; da Silvia-Junior et al., 2005)

6.2.3.5 Anticholinergics

No studies assessed the effectiveness of anticholinergics in people with inadequate symptomatic control associated with Parkinson's disease.

6.2.4 Health economic evidence

Literature searches were undertaken to find any existing cost–utility analyses (CUAs) comparing any initial or adjuvant drug treatments for people with Parkinson's disease that have been published since the literature reviews in CG35. In total, 925 articles were returned, of which 16 were selected as potentially relevant and retrieved for full text review. Additionally, the 5 studies that were included in CG35 were reviewed against the current protocol. In total, 8 studies were included. Of these, 6 compared adjuvant therapies. Studies that met the eligibility criteria were assessed using the quality appraisal criteria as outlined in the NICE guidelines manual (NICE, 2012).

Three CUAs (one from the UK, one from the USA and one from Finland) looked at entacapone as an adjunct to levodopa for people with Parkinson's disease and motor fluctuations. All 3 studies used Markov models; 2 models contained states defined by Hoehn & Yahr scores and 1 used states defined by the percentage of off-time. They all used clinical evidence from selected RCTs, rather than a full review of the literature, with 2 of the studies basing resource use and costs on clinical opinion rather than solely data. In all 3 studies, entacapone plus levodopa was found to either dominate or be cost-effective compared with levodopa monotherapy.

Two CUAs (1 from the USA and 1 from Finland) looked at both entacapone and rasagiline as possible adjuncts to levodopa for people with Parkinson's disease and motor fluctuations. Both used Markov models with states defined by the percentage of off-time. They all used clinical evidence from selected RCTs, rather than a full review of the literature, with resource use and costs based on clinical opinion rather than solely data. In both studies, entacapone plus levodopa was found to be cost-effective compared with levodopa monotherapy, and

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rasagiline plus levodopa was found to either dominate or be cost-effective compared with both levodopa monotherapy and levodopa plus entacapone.

One CUA (from the Netherlands) compared prolonged release and immediate release ropinirole as an adjunct to levodopa for people with Parkinson's disease and motor fluctuations. It used a Markov model with states defined by Hoehn & Yahr status and the percentage of off-time. It used clinical evidence from a selected RCT, rather than a full review of the literature, with resource use and costs based on clinical opinion rather than solely data. Prolonged release ropinirole was found to dominate immediate release ropinirole as an adjunct to levodopa.

6.2.5 Evidence statements – pairwise meta-analyses

The below statements refer to pharmacological treatments as adjuvants to oral levodopa preparations versus oral levodopa preparation monotherapy (with or without a placebo adjuvant) or each other.

6.2.5.1 Dopamine agonists versus placebo

Low quality evidence from 19 RCTs indicates that dopamine agonists are associated with significant improvements, versus placebo, in off time.

Very low-to-low quality evidence from 15 RCTs indicates that dopamine agonists are associated with significant improvements, versus placebo, in UPDRS motor and ADL scores, although the mean differences were below and/or the confidence intervals crossed the line of minimal clinically important differences as defined by Schrag et al., 2006 and Horvath et al., 2015.

Very low quality evidence from 3 RCTs could not differentiate health-related quality of life (PDQ-39 and PDQUALIF) levels between dopamine agonists and placebo.

Very low-to-moderate quality evidence from 9 RCTs indicates that, compared with placebo, ropinirole is associated with significantly higher rates of hallucination and adverse events, but could not distinguish rates of dyskinesia, serious adverse events, adverse events requiring discontinuation or mortality.

Very low-to-moderate quality evidence from 5 RCTs indicates that, compared with placebo, rotigotine is associated with significantly higher rates of dyskinesia and hallucinations, but could not distinguish rates of adverse events, serious adverse events, adverse events requiring discontinuation, mortality or impulse control disorder.

Very low-to-moderate quality evidence from 10 RCTs indicates that, compared with placebo, pramipexole is associated with significantly higher rates of dyskinesia, hallucinations and adverse events, but could not distinguish rates of serious adverse events or adverse events requiring discontinuations.

Very low-to-moderate quality evidence from 3 RCTs indicates that, compared with placebo, cabergoline is associated with significantly higher rates of dyskinesia and adverse events, but could not distinguish rates of hallucinations, adverse events requiring discontinuations or mortality.

Low-to-moderate quality evidence from 5 RCTs indicates that, compared with placebo, bromocriptine is associated with significantly higher rates of dyskinesia and adverse events, but could not distinguish rates of hallucination and adverse events requiring discontinuation.

Low-to-moderate quality evidence from 1 RCT indicates that, compared with placebo, pergolide is associated with significantly higher rates of dyskinesia and hallucinations, but could not distinguish rates of adverse event requiring discontinuation and mortality.

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6.2.5.2 Catechol-O-methyltransferase (COMT) inhibitors versus placebo

Moderate quality evidence from 13 RCTs indicates that COMT inhibitors are associated with significant improvements, compared with placebo, in off time.

Low-to-moderate quality evidence from 15 RCTs indicates that COMT inhibitors are associated with significant improvements, compared with placebo, in UPDRS motor and ADL scores, although the mean differences were below the minimal clinically important differences as defined by Schrag et al., 2006 and Horvath et al., 2015.

Low-quality evidence from 1 RCT could not differentiate health-related quality of life (PDQ-39) levels between COMT inhibitors and placebo.

Very low-to-moderate quality evidence from 14 RCTs indicates that, compared with placebo, entacapone is associated with significantly higher rates of dyskinesia, adverse events and adverse event requiring discontinuation, but could not distinguish rates of hallucinations, serious adverse events or mortality.

Very low-to-moderate quality evidence from 6 RCTs indicates that, compared with placebo, tolcapone is associated with significantly higher rates of dyskinesia, hallucinations and adverse events, but could not distinguish rates of adverse events requiring discontinuation.

6.2.5.3 Monoamine oxidase B (MAO-B) inhibitors versus placebo

Moderate quality evidence from 4 RCTs indicates that MAO-B inhibitors are associated with significant improvements, compared with placebo, in off time.

Moderate quality evidence from 2 RCTs indicates that MAO-B inhibitors are associated with significant improvements, compared with placebo, in UPDRS motor and ADL scores, although the mean differences were below the minimal clinically important differences as defined by Schrag et al., 2006 and Horvath et al., 2015.

Low quality evidence from 3 RCTs could not distinguish the rates of dyskinesia, hallucinations, adverse events, serious adverse events or adverse events requiring discontinuation between rasagiline and placebo.

Very low-to-low evidence from 3 RCTs could not distinguish the rates of dyskinesia, hallucinations, adverse events, serious adverse events or adverse events requiring discontinuation between selegiline and placebo.

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6.2.5.4 Amantadine versus placebo

Low quality evidence from 1 RCT could not differentiate the effect on motor and ADL symptoms (UPDRS) as well as hyperkinesia and dystonia symptoms (CDRS) between amantadine and placebo.

6.2.5.5 Dopamine agonists versus COMT inhibitors

Very low-to-low quality evidence from 2 RCTs could not differentiate the effect on off time, health-related quality of life (PDQ-39), motor and ADL symptoms (UPDRS) between dopamine agonists and COMT inhibitors.

Very low quality evidence from 1 RCT could not distinguish the rates of hallucinations, adverse events, serious adverse events or adverse events requiring discontinuation between cabergoline and entacapone.

Very low quality evidence from 1 RCT could not distinguish the rates of dyskinesia or hallucinations between bromocriptine and tolcapone.

Low-quality evidence from 1 RCT indicates that pergolide is associated with significantly lower rates of dyskinesia when compared with tolcapone, but higher rates of adverse events requiring discontinuation.

6.2.5.6 Dopamine agonists versus dopamine agonists

Low-to-moderate quality evidence from 1 RCT indicates that ropinirole is associated with significantly lower rates of adverse events when compared with rotigotine, but could not differentiate rates of dyskinesia, hallucinations, serious adverse events or adverse events requiring discontinuation.

Very low quality evidence from 2 RCTs could not distinguish the rates of dyskinesia or hallucinations between ropinirole and bromocriptine.

Low-to-moderate quality evidence from 2 RCTs indicates that pramipexole is associated with significantly lower rates of dyskinesia when compared with bromocriptine, but could not differentiate rates of hallucinations, adverse events, serious adverse events or adverse events requiring discontinuation.

Low quality evidence from 1 RCT could not distinguish the rates of dyskinesia, hallucinations, adverse events or adverse events requiring discontinuation between rotigotine and pramipexole.

Very low quality evidence from 1 RCT could not distinguish the rates of adverse event or adverse event requiring discontinuation between pramipexole and pergolide.

Low-to-moderate quality evidence from 5 RCTs indicates that cabergoline is associated with significantly higher rates of dyskinesia when compared with bromocriptine, but could not distinguish rates of hallucinations.

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6.2.5.7 COMT inhibitors versus COMT inhibitors

Low quality evidence from 1 RCT could not distinguish the rates of dyskinesia, hallucinations, adverse events, serious adverse events or adverse event requiring discontinuation between entacapone and tolcapone.

6.2.5.8 Carer quality of life

No evidence for carer quality of life was identified.

6.2.5.9 Time to institutional care

No evidence for time to institutional care was identified.

6.2.6 Evidence statements – network meta-analyses

The below statements refer to pharmacological treatments as adjuvants to oral levodopa preparations versus oral levodopa preparation monotherapy (placebo) and each other.

6.2.6.1 Off time

Moderate quality evidence from a network-meta analysis found that COMT inhibitors, MAO-B inhibitors and dopamine agonists all provide a significant lowering of off time compared with placebo, with dopamine agonists providing significantly more lowering than the other 2 drug classes.

6.2.6.2 UPDRS II (ADL)

Low quality evidence from a network-meta analysis found that COMT inhibitors, MAO-B inhibitors and dopamine agonists all provide significant improvements in UPDRS II scores compared with placebo, although the mean differences were below the minimal clinically important differences as defined by Schrag et al., 2006.

6.2.6.3 UPDRS III (motor)

Low quality evidence from a network-meta analysis found that COMT inhibitors, MAO-B inhibitors and dopamine agonists all provide significant improvements in UPDRS III scores compared with placebo, although the mean differences provided by COMTI and MAO-B inhibitors were below the minimal clinically important differences as defined by Schrag et al., 2006 and Horvath et al., 2015.

6.2.6.4 PDQ-39

Very low quality evidence from a network-meta analysis could not differentiate PDQ-39 scores between people taking COMT inhibitors, dopamine agonists or placebo.

6.2.6.5 Dyskinesia

Moderate quality evidence from a network-meta analysis found that COMT inhibitors and dopamine agonists both significantly increase rates of dyskinesia compared with placebo.

6.2.6.6 Hallucinations

Moderate quality evidence from a network-meta analysis found that dopamine agonists significantly increase rates of hallucination compared with both placebo and COMT inhibitors.

6.2.6.7 Mortality

Moderate quality evidence from a network-meta analysis could not differentiate rates of mortality between people taking COMT inhibitors, dopamine agonists or placebo.

6.2.6.8 Any adverse events

Moderate quality evidence from a network-meta analysis found that COMT inhibitors and dopamine agonists both significantly increase adverse events rates compared with placebo, with COMT inhibitors also increasing adverse event rates compared with MAO-B inhibitors and dopamine agonists.

6.2.6.9 Serious adverse events

Moderate quality evidence from a network-meta analysis could not differentiate rates of mortality between people taking COMT inhibitors, dopamine agonists, MAO-B inhibitors or placebo.

6.2.6.10 Adverse event requiring discontinuation

Moderate quality evidence from a network-meta analysis found that COMT inhibitors significantly increase rates of discontinuation due to adverse events compared with placebo.

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6.2.7 Evidence statements – economics

Evidence from 5 partially applicable cost-utility analyses with very serious limitations suggests that entacapone as an adjunct to levodopa is either dominant or cost-effective compared with levodopa monotherapy.

Evidence from 2 partially applicable cost-utility analyses with very serious limitations suggests that rasagiline as an adjunct to levodopa is either dominant or cost-effective compared with levodopa monotherapy.

Evidence from 2 partially applicable cost-utility analyses with very serious limitations suggests that rasagiline as an adjunct to levodopa is either dominant or cost-effective compared with entacapone as an adjunct to levodopa monotherapy.

Evidence from 1 partially applicable cost-utility analysis with very serious limitations suggests that prolonged release ropinirole is dominant compared with immediate release ropinirole as an adjunct to levodopa monotherapy.

6.2.8 Evidence to recommendations

Relative value of different outcomes	The GDG agreed that the key trade-off for this question was between better symptomatic control, including motor symptoms, dyskinesia and/or "wearing off" time, against the risks of adverse events, which all significantly impact on quality of life for both the person with Parkinson's disease and their carer(s).
Trade-off between benefits and harms	The GDG agreed that it is important for people with Parkinson's disease who develop problems with levodopa to receive advice from a healthcare professional with expertise in Parkinson's disease before modifying therapy. The GDG is aware that some people with Parkinson's disease and motor fluctuations may stay on levodopa indefinitely without appropriate review by a specialist in Parkinson's disease and then consequently develop further complications. The GDG therefore stressed the importance of encouraging healthcare professionals to seek specialist advice if a person with Parkinson's disease develops inadequate symptomatic control such as motor fluctuations and/or dyskinesia, including "wearing off", to ensure the person receives the specialist support they need in order to control their symptoms. The GDG noted that dopamine agonists, MAO-B inhibitors, and COMT inhibitors were all supported by evidence to be effective as adjunctive treatments to levodopa in significantly improving daily off time, motor symptoms and activities of daily living in people with Parkinson's disease and inadequate symptomatic control. However, the GDG also identified a couple of important points to note and consider when interpreting the evidence. First, the GDG raised concerns regarding the large benefit reported in daily off time with MAO-B inhibitors (rasagiline) in comparison to placebo. From their clinical experience, MAO-B inhibitors do not generally tend to show much benefit in off time. Similarly in their experience when people with Parkinson's disease are taken off MAO-B inhibitors, for example rasagiline, they seldom notice any difference. The GDG therefore agreed that the evidence presented did not truly reflect what GDG members have seen in clinical practice. The GDG also noted that the majority of the included studies did not specify whether the included population were experiencing early wearing off symptoms or later unpredictable on and off fluctuations. In their experience, people with Parkinson's disease experiencing early wearing off, i.e. when levodopa wears off before the next dose is due, is more common as well as an easier study population to recruit and manage in studies. If the majority of participants in the included studies were experiencing early wearing off symptoms rather than later on and off fluctuations the GDG agreed that this may explain the reason for the large estimated benefit in off time for rasagiline vs placebo. People with Parkinson's disease who are

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	experiencing early wearing off tend to respond better to MAO-B inhibitors in comparison to people with later on and off fluctuations, who are more difficult to manage. The GDG also discussed the possible impact in that the trials may have only recruited people who met a certain level of off time where such a study population had more scope to demonstrate benefit than the average patient. Secondly, the GDG discussed and noted that the risk of dyskinesia was suggested to be increased with all treatments. However, in their experience the GDG agreed that this may have been due to the fact that many of the included studies did not allow for changes in the levodopa dose throughout the study duration unless a patient experienced an adverse event thought to be the result of excessive dopaminergic stimulation. The GDG highlighted that in common clinical practice, these drugs are used to treat dyskinesia (by allowing the levodopa dose to be reduced) and they only tend to increase the rate of dyskinesia when the dose of levodopa is kept constant, which is the case in many of the included studies in the review. The GDG therefore agreed that the included studies did not truly reflect the way these drugs would be used in clinical practice for people with Parkinson's disease and inadequate symptomatic control, and hence the evidence should be interpreted with caution. Regardless of the above, the GDG agreed with the available evidence that all drug classes apart from amantadine are effective in improving off time, motor symptoms and activities of daily living in people with Parkinson's disease and inadequate symptomatic control. It agreed that people with Parkinson's disease who have developed dyskinesia and/or motor fluctuations despite optimal levodopa therapy should be offered a choice of treatment options depending on their individual symptoms. This should take place after the clinician has discussed individual clinical and lifestyle characteristics as well as the potential benefits and harms of the different drug classes. The GDG discussed whether to make a recommendation that non-ergot dopamine agonists should be prefered to ergot agonists, because of their lower monitoring requirements. It was noted that both are valid treatment options, and clinicians will often try an ergot agonist if a non-ergot one has not proven effective. The GDG agreed that the difficulties with ergot agonists were now well known amongst Parkinson's' disease clinicians, and therefore there was not a need for specific guidance on this issue. Although no evidence of benefit was identified for anticholinergics as an adjunct treatment to levodopa for people with Parkinson's disease and inadequate symptomatic control, the GDG discussed and strongly agreed that anticholinergics have significant potential for causing adverse cognitive effects and hallucinations as well as increased risk of falls and/or urinary retention and should therefore not be offered to people with Parkinson's disease who have developed dyskinesia and/or motor fluctuations. The GDG felt that in the absence of any evidence of benefits, it was appropriate to recommend that amantadine not be routinely used as an adjunctive therapy, when options with clear evidence of benefit exist. However, because of the specific uses amantadine may have in certain people (e.g. to treat dyskinesia), they did not feel it appropriate to make a stronger "do not use" recommendation.
Trade-off between net health benefits and resource use	The GDG agreed that the economic evidence presented was subject to considerable limitations, both because it was commonly based on very simple model structures that are unlikely to capture all the important effects of treatment (e.g. a model based solely on off-time and no other treatment related changes), and because the included evidence only captured a small proportion of the relevant comparator treatments. However, the fact that all of the studies consistently showed adjuvant treatment to be cost-effective helped to improve confidence in the overall decision to offer treatment, even

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	if the evidence was not robust enough to help inform the choice of which adjuvant should be preferred for different individuals.
Quality of evidence	The GDG agreed that the majority of the included studies may have been subject to publication bias (potential selective reporting of adverse events). Nevertheless, based on the consistency of the available evidence and using their clinical experience and expertise, the GDG was confident in making 3 recommendations, including one "offer" and one "do not offer" recommendation. Although the efficacy findings for dopamine agonists, MAOBs and COMTIs sometimes did not significantly exceed the defined minimal important differences for UPDRS scores, it was noted that these MIDs were based on short-term changes in health state. However, the benefits of treatment were expected to persist in the long-term, and therefore the GDG were satisfied they did correspond to a meaningful change in patient quality of life. It was also noted that, because the treatments showed benefits to people across multiple domains (motor symptoms, activities of daily living, off time etc.), the total benefit was likely to be greater than that measured on any of the individual outcome measures.

6.2.9 Recommendations

28. If a person with Parkinson's disease has developed dyskinesia and/or motor fluctuations, including medicines 'wearing off', seek advice from a healthcare professional with specialist expertise in Parkinson's disease before modifying therapy. [new 2017]

29. Offer a choice of dopamine agonists, MAO-B inhibitors or catechol O methyl transferase (COMT) inhibitors as an adjunct to levodopa to people who have developed dyskinesia and/or motor fluctuations despite optimal levodopa therapy, after a discussion with the person about their:

- clinical and lifestyle circumstances
- preferences, taking into account the potential benefits and harms of the different drug classes (see table 5) **[new 2017]**

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Table 7: Potential benefits and harms of dopamine agonists, MAO-B inhibitors, COMT inhibitors and amantadine

	Dopamine agonists	MAO-B inhibitors	COMT inhibitors	Amantadine
Motor symptoms	Improvement in motor symptoms	Improvement in motor symptoms	Improvement in motor symptoms	No evidence of improvement in motor symptoms
Activities of daily living	Improvement in activities of daily living	Improvement in activities of daily living	Improvement in activities of daily living	No evidence of improvement in activities of daily living
Off time	More off-time reduction	Off-time reduction	Off-time reduction	No studies reporting this outcome
Adverse events	Intermediate risk of adverse events	Fewer adverse events	More adverse events	No studies reporting this outcome
Hallucinations	More risk of hallucinations	Lower risk of hallucinations	Lower risk of hallucinations	No studies reporting this

	Dopamine agonists	MAO-B inhibitors	COMT inhibitors	Amantadine
				outcome

Abbreviations: MAO-B, monoamine oxidase B; COMT, catechol-O-methyl transferase.

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30. Do not offer anticholinergics to people with Parkinson's disease who have developed dyskinesia and/or motor fluctuations. [new 2017]

31. Do not offer amantadine to people with Parkinson's disease who have developed dyskinesia and/or motor fluctuations. [new 2017]

7 Pharmacological management of non-motor symptoms

Parkinson's disease is defined by the effects that it has on movement and posture. These are referred to as motor features. But Parkinson's disease causes a wide range of other difficulties. People with Parkinson's disease often, for example, notice many changes in their mood, behaviour, cognition, sleep, sense of smell, and bowel-, bladder-, saliva- and blood pressure-control, and may experience otherwise-unexplained pain. Often these non-motor symptoms precede the motor ones by many years: two examples of this are the impairment in olfaction, and a sleep disorder involving dream-enactment called REM sleep behaviour disorder, which may occur more than a decade before any discernible physical change.

The extent to which an individual person experiences non-motor symptoms is very variable, both in terms of the number of symptoms and the severity of each one. Numerous studies have shown that non-motor symptoms are generally very important to the quality of life of people with Parkinson's disease and their families. For many people with Parkinson's disease, non-motor symptoms are more disabling than the motor ones. Anxiety, depression, apathy, cognitive impairment, pain and orthostatic hypotension causing falling or fainting are all common examples of disabling non-motor symptoms.

Although the importance of non-motor symptoms is now widely acknowledged, we are still hampered by a lack of well-conducted research into effective treatments. A few symptoms have no known treatment, such as the impaired sense of smell. Many other symptoms are managed by strategies that are time-honoured but have never been scientifically assessed. These traditional approaches typically begin with non-pharmacological strategies, followed by pharmacological treatment, often using off-license drugs. An example of this would be the management of drooling, which might start with advice to suck sweets or chew gum, and move on if necessary to the use of drugs with anticholinergic effects.

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7.1 Daytime hypersomnolence

What is the comparative effectiveness of pharmacological interventions to treat daytime hypersomnolence associated with Parkinson's disease?

7.1.1 Introduction

The aim of this review question was to establish the comparative effectiveness of pharmacological interventions to treat daytime hypersomnolence, also referred to as excessive daytime sleepiness (EDS), associated with Parkinson's disease.

The review focussed on identifying studies that fulfilled the conditions specified in Table 8.

Table 8: PICO table for pharmacological interventions for hypersomnolence in Parkinson's disease

Population	Patients with a confirmed diagnosis of Parkinson's disease suffering from daytime hypersomnolence
Interventions	Modafinil Amantadine Selegiline Sodium oxybate Pitolisant
Comparators	Placebo
Outcomes	sleep scale outcome measures, adverse events, health related quality of life, carer burden

For full details of the review protocol, please see Appendix C

Randomised controlled trials (RCTs) were considered to be the most appropriate study design to derive comparative effectiveness odds ratio measures, and were therefore considered to be the highest quality within a GRADE framework. All other study designs were excluded from this review, including case–control studies, cohort studies, and case reports.

7.1.2 Evidence review

A systematic search was conducted (see appendix I) which identified 2,380 references. The references were screened on their titles and abstracts and full papers of 12 references were obtained and reviewed against the inclusion and exclusion criteria in the review protocol (see appendix C). The 3 studies included in CG35 were also reviewed against the current protocol. A total of 15 studies were assessed in full-text.

Of these, 11 studies were excluded as they did not meet the inclusion criteria specified in the review protocol such as inappropriate study design (prospective open-label cohort study, descriptive narrative, opinion, etc.), and studies in which the population was not those with Parkinson's disease. A detailed list of excluded studies and reasons for their exclusion is provided in appendix G.

One newly published paper met the inclusion criteria.. All 3 of the studies previously included in the original guideline (CG 35) met the inclusion criteria for the current guideline and were also included in the analyses. Evidence tables for the included studies can be found in appendix D, with GRADE profiles reported in appendix E.

No additional new papers were identified through rerun searches at the end of the guideline.

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The overall quality of the evidence from the 4 published papers was rated low.

The 4 included studies examined the effectiveness of modafinil to treat hypersomnolence in Parkinson's disease. No studies were identified which examined the effectiveness of amantadine, selegiline, sodium oxybate, or pitolisant to treat the symptoms of daytime hypersomnolence in Parkinson's disease.

7.1.3 Description of included studies

Four placebo-controlled double-blind RCTs that examined the effectiveness of modafinil to treat daytime hypersomnolence in Parkinson's disease were included in this analyses (total N=101; mean age=65 years). Three of the studies used a 200 mg/d dose (Lou et al., 2009; Adler et al., 2003; Hogl et al., 2002), while the third (Ondo et al., 2005) increased the dose to 400mg after 1 week. Sample sizes were very small, ranging from 15 (Hogl et al., 2009) to 40 (Ondo et al., 2005) people with Parkinson's disease.

7.1.4 Evidence statements

Epworth sleepiness scale (ESS)

A meta-analysis of 4 RCTs reported that modafinil had a beneficial effect in reducing mean ESS score in those taking 200–400 mg/d of modafinil compared with those taking placebo. The evidence was of low quality.

Adverse events

A meta-analysis of 4 RCTs reported no significant differences in the rate of adverse events between modafinil and placebo. The quality of the evidence was low.

Health-related quality of life

No evidence was identified for this outcome.

Carer burden

No evidence was identified for this outcome.

7.1.5 Health economic evidence

No health economic evidence was identified for this review question.

7.1.6 Evidence to recommendations

Relative value of different outcomes	The GDG deliberated on the different outcomes presented and were mindful of the fact that the ESS scale is used routinely in clinical practice and as such is important in clinical decision making and should be considered as a critical outcome. However, the GDG were unable to identify what would be a clinically meaningful change on the ESS scale. The GDG considered that it would be highly subjective and very much dependent on what level on the ESS scale the person was initially assessed at. While adverse effects were a consideration this was more in relation to the sustained use of some of these pharmacological interventions, especially modafinil. The GDG considered that if these drugs were prescribed for a defined period of time that they were likely to confer more benefit than harm if used in the appropriate clinical situations. Health related quality of life was considered to be of critical importance if it included a consideration of the social interaction aspect, as

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	hypersomnolence reduces the opportunity for meaningful social interaction with family and friends with a detrimental effect on quality of life.
Trade-off between benefits and harms	The GDG recognised the benefit for modafinil (in improving ESS scores) reported in the included evidence. However the GDG experience was that modafinil can have a dramatically beneficial effect in some patients, and not in others. It was raised as difficult to identify a priori which people may derive the greatest benefit. It was noted that a MHRA warning exists for modafinil related to long-term and/or inappropriate use. Modafinil is currently only licensed for narcolepsy following appropriate diagnosis.
Trade-off between net health benefits and resource use	No economic evidence was identified for this treatment. The GDG discussed the negligible cost of modafinil, and agreed that any recommendations were unlikely to have a significant resource impact
Quality of evidence	The GDG agreed that the quality of the evidence was low. All included studies only examined modafinil. No evidence for any other potential drugs of interest was identified. The GDG noted that the response to modafinil is typically quite heterogeneous such that there are strong responders and those for which the drug does not work at all. The GDG agreed that this may affect the overall effect observed in the studies. The included studies did not include older people beyond 75 years (mean age of included people within the trials was 65 years) who may be more affected by hypersomnolence. The studies did not consider overall sleeping patterns and possible causes of hypersomnolence. There was a lack of clarity of the minimally important difference (MID) in ESS scores in order to qualify the magnitude of the benefits as part of the trade-off between benefits and harms. A limitation of the evidence is that the studies do not highlight how the ESS score is reached – is it a composite of many repeats of the test or from just one test? You may improve on one aspect of the score but lose on other components of it which loses the importance in the aggregate score. While used widely in clinical practice, the Epworth sleep scale (ESS) is hard to interpret in a study context. This scale is made up of many different domains and is not a linear scale, and therefore a change from 17 to 14 may not necessarily be equivalent to a change from 7 to 4. The GDG considered that the number of daytime naps may be a more appropriate outcome as it is easier to interpret. Falling asleep during the daytime is a very significant consequence of hypersomnolence. Of particular concern is the impact on driving, with the GDG feeling it appropriate to make a specific recommendation that people be advised not to drive whilst suffering from hypersomnolence. For those who experience this condition, daytime sleep has a detrimental effect on people's ability to engage in the activities of daily life, in particular time with family and friends. Health related quality of life need to be included as a social care quality of life aspect A limited number of adverse events were reported as many of the studies had very short follow up periods (up to 4 weeks), although it was reported that participants in the studies continued on modafinil. The short follow-up time of these trials means that there is limited data on the wider efficacy of this drug in people with Parkinson's disease. It must also be kept in mind that the licensing of modafinil means that it is only indicated for narcolepsy. The GDG noted that there are MHRA safety alerts regarding the potentially severe side effects of use over the long term (the warning relates to risk of Stevens Johnson syndrome after starting the drug). REM sleep disorders were not considered in the evidence base.
Other considerations	Hypersomnolence is multifactorial and its causes need to be investigated before additional pharmacological interventions are considered. Modafinil needs to be considered in light of other pharmacological interventions being used. Consideration of modafinil and subsequent monitoring for response

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and tolerance needs to be carried out by a healthcare professional with special expertise in Parkinson's disease. In particular, the GDG highlighted that blood pressure and heart rate should be monitored at least annually due to the cardiovascular risks with modafinil. However, the GDG were mindful that there was variation across the NHS and this may unwittingly restrict modafinil as a treatment option in some NHS trusts.

The GDG noted that clinicians should not just add modafinil because dopaminergic therapy itself can make people sleepy. Clinicians should review dopaminergic therapy first before deciding to add another pharmacological intervention.

Individual circumstances should be considered, for example adding modafinil for younger patients of working age may be acceptable but for older patients this may add little benefit and the benefit-harms profile may no longer be acceptable. It was noted that the mean age of participants in the included studies was 65.

Frequent napping can mean missing out on time with family thereby affecting social quality of life. Sleep could be considered as an outcome in other reviews and we should be considering social benefit as much as clinical benefit. If a person is very sleepy this has a major impact on nutrition and hydration.

Clinical practice is to not regularly treat people with daytime somnolence with stimulants but to take a sleep history and to identify the reason why sleep is disturbed, for example, a side effect of dopaminergic agonists is hypersomnolence; affected sleep patterns due to physical (e.g. frequent urination) or psychological factors (e.g. depression, anxiety, impulse control disorder, REM sleep disorder) which may affect sleep at night time increasing daytime sleepiness.

The GDG added a caveat that a detailed sleep history should be taken before modafinil is considered with the express aim of reducing the 'routine' use of modafinil outside its licensed indication and in people in whom it may be of little benefit.

The GDG noted the lack of evidence for amantadine, selegiline, sodium oxybate and pitolisant and agreed that it could not draft recommendations around the use of these drugs.

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7.1.7 Recommendations

32. Consider modafinil to treat excessive daytime sleepiness in people with Parkinson's disease, only if a detailed sleep history has excluded reversible pharmacological and physical causes. [new 2017]

33. Healthcare professionals with specialist expertise in Parkinson's disease should review people who are taking modafinil at least every 12 months. [new 2017]

34. Advise people with Parkinson's disease who have daytime sleepiness and/or sudden onset of sleep not to drive (also see recommendation 7) and to consider any occupation hazards. Adjust their medicines to reduce its occurrence, having first sought advice from a healthcare professional with specialist expertise in Parkinson's disease. [2017]

7.2 Nocturnal akinesia

What is the effectiveness of pharmacological intervention to treat nocturnal akinesia compared with placebo in people with Parkinson's disease?

7.2.1 Introduction

The aim of this review question was to assess the efficacy of pharmacological interventions compared with placebo to treat nocturnal akinesia in people with Parkinson's disease. The review focused on identifying studies that fulfilled the conditions specified in **Table 9**.

Table 9: PICO table for effectiveness of pharmacological interventions for treating nocturnal akinesia in Parkinson's disease

Population	Patients with a confirmed diagnosis of Parkinson's disease who are experiencing nocturnal akinesia sleep disturbance
Interventions	• Immediate-release levodopa • Controlled-release levodopa • Prolonged-release dopamine agonist (including transdermal patch) • Standard-release dopamine agonist ○ rotigotine • Apomorphine • Mirtazapine • Benzodiazepine: Clonazepam • Pregabalin • Melatonin • Rivastigmine • Gabapentin
Comparators	• Placebo • Each other
Outcomes	• Adverse events • Resource use and cost • PD sleep scale • NADCS (nocturnal akinesia, dystonia, cramps score) • PD non-motor scale • UPDRS scores • Health related quality of life • Carer related quality of life

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For full details of the review protocol, please see Appendix C. Randomised controlled trials (RCTs) were considered to be the most appropriate study design to derive treatment effect metrics, and were therefore considered to be the highest quality within a GRADE framework. All other study designs were excluded from this review, including case–control studies, cohort studies, and case reports.

7.2.2 Evidence review

A single systematic search was conducted (see appendix I) for 2 of the sleep study review questions (nocturnal akinesia and REM sleep behaviour disorder) which identified 3,596 references. The references were screened on their titles and abstracts and full papers of 25 references were obtained and reviewed against the inclusion and exclusion criteria in the review protocol (see appendix C).

Overall, 21 studies were excluded as they did not meet the eligibility criteria such as not utilising a randomised-control design.

The 4 remaining published papers did meet eligibility criteria and were included in the appropriate sleep disorder review questions. One of the 4 included papers (Trenkwalder et al., 2011) addressed pharmacological treatment for nocturnal akinesia, and was included within the present review question.

Evidence from the previous guideline (CG35) was also reviewed against the present inclusion and exclusion criteria and 1 study (UK Madopar study group, 1989) was included in the present review.

One additional paper was identified through rerun searches at the end of the guideline but was excluded because it did not meet the eligibility criteria for this review.

Evidence tables for the included studies can be found in appendix D, with GRADE profiles reported in appendix E.

7.2.3 Description of included studies

Rotigotine to treat early morning motor dysfunction and sleep disturbance

One double-blind placebo-controlled RCT (Trenkwalder et al., 2011) of 287 participants with Parkinson's disease (mean age=64 years, SD=9.9; mean time since diagnosis=4.8 years, SD=4.4) assessed the effectiveness of transdermal rotigotine to treat the symptoms of nocturnal akinesia. Twenty-four-hour transdermal rotigotine dosage was set at 2–16 mg/24 hr and titrated to optimal dose over 1–8 weeks with subsequent dose maintenance for 4 weeks.

Controlled and immediate-release co-beneldopa to treat motor dysfunction and sleep disturbance

One double-blind RCT (Madopar study group, 1989) of 103 people with Parkinson's disease (mean age=68 years [no SD reported], mean disease duration=8 years [no SD reported]) compared controlled-release levodopa and benserazide (co-beneldopa) with immediate-release co-beneldopa in the treatment of nocturnal and early morning disability. Controlled-release co-beneldopa or immediate-release co-beneldopa was given at a dose of 125 mg/day immediately before going to bed. There were serious methodological limitations of this study, which reported results in figure-form only, with no indication of standard deviation from mean score. For this reason, the results of this study can be presented in narrative form only.

7.2.4 Evidence statements

Evidence for rotigotine

Nocturnal akinesia

Moderate-to-high quality evidence from 1 RCT suggests that, compared with placebo, rotigotine significantly reduces symptoms of nocturnal akinesia as assessed by the nocturnal akinesia disability scale (NADS) total score (MD=−0.41, 95% CI: −0.79 to −0.04). There was no reduction in the number of nocturias (MD=−0.02, 95% CI: −0.29 to 0.25).

Sleep quality (PDSS)

High-quality evidence from 1 RCT suggests that, compared with placebo, rotigotine significantly improves sleep quality as assessed by the Parkinson's disease sleep scale (PDSS) total score (MD=−4.26, 95% CI: −6.08 to −2.45).

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UPDRS motor symptoms (UPDRS III)

Moderate-quality evidence from 1 RCT suggests that, compared with placebo, rotigotine significantly reduces motor symptoms of Parkinson's disease as assessed by the UPDRS III subscale (MD=−3.55, 95% CI: −5.37 to −1.73), although the confidence intervals of the mean difference crossed the line of minimal clinically important difference as defined by Schrag et al., 2006 and Horvath et al., 2015.

Activity of daily living (UPDRS II)

High-quality evidence from 1 RCT suggests that, compared with placebo, rotigotine significantly improves self-reported experience of activities of daily living as assessed by the UPDRS II score (MD=−1.49, 95% CI: −2.32 to −0.65), although the mean difference was below the minimal clinically important difference as defined by Schrag et al., 2006.

Non-motor symptoms (NMS)

High-quality evidence from 1 RCT suggests that, compared with placebo, rotigotine significantly improves non-motor symptoms as assessed by the NMS (MD=−6.65, 95% CI: −11.99 to −1.31).

Health-related quality of life (PDQ-8)

High-quality evidence from 1 RCT suggests that, compared with placebo, rotigotine significantly improves quality of life as assessed by the PDQ-8 total score (MD=−5.74, 95% CI: −8.74 to −2.75).

Adverse events

High quality evidence from 1 RCT reported a small potentially increased risk of adverse events in participants who were exposed to transdermal rotigotine compared with those exposed to placebo (RR=1.27, 95% CI: 1.04 to 1.55).

Evidence for standard-release compared with controlled-release co-beneldopa

Nocturnal and early morning disability

One moderate-quality study reported no meaningful difference between controlled-release and immediate-release co-beneldopa in nocturnal and early morning disability.

Adverse events

A total of 63 adverse events were reported by 37 patients; 32 while on controlled-release co-beneldopa and 31 while on immediate-release co-beneldopa.

7.2.5 Health economic evidence

No health economic evidence was identified for this review question.

7.2.6 Evidence to recommendations

Relative value of different outcomes	The GDG considered the quality of sleep and impact of nocturnal akinesia upon patient quality of life to be the most important outcomes of interest for this review question. The GDG discussed the evidence for the use of the NADCS as an assessment tool and agreed that it is not a good instrument to capture the experience of nocturnal akinesia as this is presented with a limited range (score of 0–4) and does not capture the full spectrum of issues experienced.

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	Nocturnal issues are complex and nocturnal akinesia is just one of the factors that need to be considered. Other issues may be nightmares and REM sleep disturbance, nocturia, restless legs and periodic limb movement.
Trade-off between benefits and harms	The GDG discussed the efficacy of rotigotine in treating nocturnal akinesia as presented in the evidence review and agreed that, in their experience, it is likely that the positive effects could be extrapolated to other dopamine agonists. Therefore the efficacy of rotigotine in treating sleep disturbance is most likely a class effect and true for any oral or transdermal agonist. The GDG discussed the problematic lack of comparative evidence, whereby the efficacy of rotigotine was only assessed against a placebo comparator. No evidence was presented which assessed the use of transdermal dopamine agonists compared with other classes of drugs or to oral dopamine agonists. As the GDG believed that the positive impact of rotigotine represented a class effect it was agreed that there was no reason to recommend transdermal dopamine agonists over oral dopamine agonists purely on the basis of a lack of evidence for oral agonists. The GDG noted that nocturnal akinesia is difficult to treat and that no clear guidance on the best way to treat this condition in Parkinson's disease currently exists. The GDG discussed the utility of prolonged versus immediate release dopamine agonists noting that individual patient response was variable. The GDG discussed to the importance of taking comorbid factors into account when assessing treatment options. Transdermal applications were discussed as potentially useful when, for example, patients use apomorphine by day and transdermal rotigotine over night to decrease their apomorphine dosage and improve sleep quality. The GDG described a need to provide dopaminergic stimulation overnight to improve sleep quality. Clinically, dopamine stimulation through the night is key to an optimal management strategy. It was noted that this does not necessarily need to be rotigotine over pramipexole or ropinirole. Transdermal applications are more expensive, and there is a substantial cost implication associated with their use, (£80–120 per month), depending on the strength of the agonist. Despite the moderate quality of the presented evidence the GDG did not consider this evidence as clinically meaningful in the absence of comparative evidence for other classes of drugs or active dopamine agonist drug comparators. The benefit in the NADCS and nocturias was considered as of unclear clinical significance when assessing the impact of dopamine agonists on the treatment of nocturnal akinesia. The GDG discussed that if patients are already on levodopa, the treating consultant is likely to adjust their dosage schedule so that they receive more dopaminergic stimulation in the evening when they are experiencing nocturnal problems. (Normally by adding a controlled release preparation at bedtime) Nocturnal akinesia manifests as people with Parkinson's disease waking in the night and being unable to move. Patients need dopaminergic control throughout the night, but don't want to have to take levodopa in the middle of the night to alleviate their symptoms, particularly as there is a time delay of up to 40 minutes before the drug becomes effective. Dopamine agonists may increase or exacerbate nightmares and hallucinations in elderly patients. It is important for clinicians to take this into account when discussing treatment options. Immediate release preparations were considered as not suitable for nocturnal benefit, whereby patients need a longer release preparation to ensure night time control of symptoms and dopaminergic stimulation throughout the night. Rotigotine was a new drug at time the included study was undertaken and

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	this may explain why there isn't any evidence for the sleep quality benefit of other dopamine agonists. It is purported by the makers of rotigotine that the mechanism of action for rotigotine is slightly different to other agonists as it targets the D3 receptor, where oral DAs more commonly target the D2 receptor. The GDG noted that the duration of action of long-acting dopamine agonists was usually 16–18 hours. If taken in the morning this could mean that the drug's efficacy wears off at 3am, meaning that it is not an ideal treatment option for nocturnal akinesia. The GDG noted that it was important to consider that there are other reasons why a patient would take a DA. A treating consultant would not recommend a DA for nocturnal akinesia alone, but would consider nocturnal akinesia alongside any other non-motor symptoms when deciding upon treatment options. The GDG noted that many patients may be taking a DA to augment their levodopa control. The GDG discussed that there was more of a "half-life" effect in favour of rotigotine, whereby the duration of action of rotigotine is longer compared with oral dopamine agonists. Rotigotine is effective; however, it is also expensive. The GDG discussed that it may be more cost effective to first try long-acting oral agonists (perhaps given later in the day). The delivery system of modified release ropinirole was noted as quite sophisticated and potentially enables 24 hour delivery, which is ideal for nocturnal control. However there is currently no evidence for this. Immediate release dopaminergic stimulation at bed time would not be ideal for patients who will experience immediate and ephemeral benefit which will wear off during the night. The GDG was uncomfortable in recommending rotigotine as first line treatment where the evidence presented came from a single study with unclear clinical benefits for the control of the symptoms of nocturnal akinesia. There was no evidence for other dopamine agonists; however the GDG noted that in their experience this does not mean that these treatment options are less effective, there is purely an absence of evidence. Current practice is to try oral dopamine agonists first. Transdermal applications are more expensive and patients can have problems with adverse reactions to the patch. The GDG considered that the optimal strategy was to try oral dopamine agonists or modified-release levodopa as first-line therapy, and if oral drugs are not working, then consider transdermal rotigotine (depending on patient choice). The salient point considered by the GDG was that rotigotine seems to be an optimal treatment, however, there are cost implications for this, and the evidence base is minimal with only one study. Considering the available evidence and using the experience of the GDG it was agreed that rotigotine should be considered only after oral dopamine agonists have been tried.
Trade-off between net health benefits and resource use	No economic evidence was identified for this review question.The GDG discussed the additional cost of rotigotine transdermal patches beyond oral modified-release dopamine agonists. Dopamine agonists are not purely prescribed for nocturnal akinesias and the GDG agreed that there was insufficient comparative evidence of all possible benefits to recommend rotigotine as first-line therapy for nocturnal akinesias alone. The GDG postulated that its recommendations are likely to be cost-neutral – many NHS clinicians already prescribe modified-release agents when nocturnal akinesia develops and, while some additional costs may be incurred by encouraging prescribers who would not currently offer treatment to follow this practice, costs will be saved by discouraging the first-line use of transdermal agents.
Quality of evidence	The 1 study presented was of moderate quality although the GDG questioned its clinical significance. The GDG did not feel it could make any

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strong recommendations based on this limited evidence base.

7.2.7 Recommendations

35. Consider modified-release levodopa preparations or modified-release oral dopamine agonists to treat nocturnal akinesia in people with Parkinson's disease. If the selected option is not effective or not tolerated, offer the other instead. [new 2017]

36. Consider rotigotine if modified-release levodopa preparations and/or modified-release oral dopamine agonists are not effective in treating nocturnal akinesia. [new 2017]

37. Advise people to take modified-release oral dopamine agonists later in the day to ensure nocturnal dopaminergic stimulation (taking into account the half-life of modified-release levodopa preparations and modified-release dopamine agonists). [new 2017]

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7.3 Orthostatic hypotension

What is the comparative effectiveness of pharmacological interventions for orthostatic hypotension associated with Parkinson's disease?

7.3.1 Introduction

The aim of this review question was to assess the efficacy of pharmacological interventions compared with placebo or other drug comparators to treat orthostatic hypotension in people with Parkinson's disease.

The review focused on identifying studies that fulfilled the conditions specified in Table 10.

Table 10: PICO table for effectiveness of pharmacological interventions for treating orthostatic hypotension in Parkinson's disease

Population	Patients with a confirmed diagnosis of Parkinson's disease whom are experiencing symptoms of orthostatic hypotension
Interventions	Salt-retaining steroids • Fludrocortisone Direct-acting sympathomimetic • Domperidone • Droxidopa • Fipamezole • Midodrine • Ephedrine Caffeine NSAIDs
Comparators	Placebo Other comparator drugs
Outcomes	Adverse events Mortality Injury (fracture) Resource use and cost Non-motor features Hypotension-related outcome scales Blood pressure Autonomic symptom scale Falls Heath related quality of life Carer burden

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For full details of the review protocol, please see Appendix C. Randomised controlled trials (RCTs) were considered to be the most appropriate study design to derive treatment effect metrics, and were therefore considered to be the highest quality within a GRADE framework. In the instance that no RCT evidence was identified, observational evidence could be considered. All other study designs were excluded from this review, including case–control studies and case reports.

7.3.2 Evidence review

A single systematic search was conducted (see appendix I) for both autonomic dysfunction review questions – thermoregulatory dysfunction (see section 7.7) and orthostatic hypotension – which identified 2,517 references. The references were screened on their titles and abstracts and full papers of 15 references were obtained and reviewed against the

inclusion and exclusion criteria in the review protocol (see appendix C) for orthostatic hypotension.

Evidence from the previous guideline (CG35) was also reviewed against the present inclusion and exclusion criteria; however no studies met the criteria for the present review.

Overall, 12 studies were excluded as they did not meet the eligibility criteria such as not providing primary evidence. A detailed list of excluded studies and reasons for their exclusion is provided in appendix G. The remaining 3 studies met the inclusion criteria for this review and were therefore included. An additional 4 new papers were identified through rerun searches at the end of the guideline, of which none met the inclusion criteria for this review and were therefore excluded.

Evidence tables for included studies can be found in Appendix D, with GRADE profiles reported in Appendix E.

7.3.3 Description of included studies

Droxidopa

Evidence from 1 parallel-group RCT with 2 papers (Hauser et al., 2014; Hauser et al., 2015) reported on the effectiveness of droxidopa, compared with placebo, to treat orthostatic hypotension in 225 patients with orthostatic hypotension and Parkinson's disease (mean age 72.3; time since diagnosis not reported). Dosage of droxidopa or placebo was titrated for up to 2 weeks, followed by 8 weeks of maintenance treatment.

Fludrocortisone and domperidone

Evidence from 1 crossover RCT (Schoffer et al., 2007) reported on the comparative efficacy of fludrocortisone and domperidone to treat orthostatic hypotension in 17 patients with orthostatic hypotension and Parkinson's disease (mean age 69; mean time since diagnosis 6 years). After a 3-week period of non-pharmacological treatments, patients were randomly assigned 1 of the 2 drugs for a 3-week treatment period; then, after a 1-week washout period, patients would spend 3 more weeks on the alternative treatment.

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7.3.4 Health economic evidence

A single literature search was conducted to identify existing CUAs of relevance to the pharmacological management of orthostatic hypotension and pharmacological interventions for thermoregulatory dysfunction (see appendix I for details). A total of 752 articles was returned; none appeared relevant on review of title and abstracts. However, rerun searches undertaken at the end of guideline development identified 1 relevant CUA, which was included. Relevant details are summarised in an economic evidence profile in appendix F.

François et al. (2016) undertook a 1-year CUA of droxidopa compared with standard care for patients with symptomatic neurogenic orthostatic hypotension caused by primary autonomic failure. The analysis, which was funded by the manufacturer of droxidopa, adopted a US payer's perspective (with assumed patient copayment). The population considered was not explicitly limited to people with Parkinson's disease; however, all critical data inputs were drawn from research in the Parkinson's population. Effectiveness estimates came from the 2 included 10-week RCTs reported by Hauser et al. (2014, 2015). The explicit focus of the analysis was on the potential of droxidopa to reduce falls in people with orthostatic hypotension; however, a general utility benefit was also assumed, in reflection of a claimed improvement in symptomatic control.

The analysis concluded that the modelled 6-month course of droxidopa would cost a little over US$30,000 per person, but would save almost US$15,000 per person per year in fall-

related costs, resulting in a net incremental cost of US$15,500. A health gain of 0.33 QALYs over the year was estimated, leading to an ICER of a little under US$50,000 per QALY. PSA gave a 53.4% probability that the true ICER is US$50,000/QALY or better. A limited range of variables was explored in deterministic sensitivity analysis; lower underlying fall probabilities, shorter fear of falling duration and lower fear disutilities were associated with ICERs greater than US$70,000/QALY.

7.3.5 Evidence statements

Adverse events and mortality

No mortality rates were recorded in any study found.

Very low-quality evidence was found in 2 publications reporting no meaningful relationship between droxidopa and the incidence of adverse events, compared with placebo (OR=0.99, 95%CI 0.51 to 1.94).

Very low-quality evidence from 1 RCT reported no meaningful difference between domperidone and fludrocortisone in the incidence of adverse events (OR=0.73, 95%CI 0.15 to 3.47)

Falls and fall-related injuries

Low-quality evidence was found in 2 publications reporting no meaningful relationship between droxidopa and the incidence of fall-related adverse events, compared with placebo (OR=0.56, 95%CI 0.29 to 1.07).

No evidence was reported for the incidence of falls and fall-related injuries in those taking fludrocortisone or domperidone.

Non-motor features

Low-to-moderate-quality evidence was found in 2 publications reporting a potential benefit of droxidopa compared with placebo on OHQ composite score over 1 week (MD=−0.88, 95%CI −1.65 to −0.11); however, any benefit was not maintained at 2 or 8 weeks.

No evidence was reported for non-motor features in those taking fludrocortisone or domperidone.

Blood pressure

Low-to-moderate-quality evidence was found in 2 publications reporting a potential benefit of droxidopa compared with placebo in standing systolic blood pressure after 1 week's treatment (MD=7.34 mmHg, 95%CI 2.23 to 12.44 mmHg); however, there was no evidence that any benefit was maintained at 8 weeks (MD=3.16 mmHg, 95%CI −1.80 to 8.12 mmHg).

Very low-quality evidence from 1 RCT reported no meaningful difference in supine blood pressure between fludrocortisone and domperidone (MD=−4 mmHg; 95%CI −23.6 to 15.64 mmHg).

Autonomic symptom scale

No evidence was reported for the experience of autonomic symptoms in those who received droxidopa or placebo.

Very low-quality evidence from 1 study reported no meaningful difference in the experience of orthostatic hypotensive symptoms between fludrocortisone and domperidone, as assessed by the COMPASS-OD score (MD=−1; 95%CI −2.96 to 0.96).

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Health-related quality of life

No evidence on health-related quality of life was identified

Carer burden

No evidence on carer burden was identified

7.3.5.1 Health economic evidence statement

One partially applicable cost–utility analysis with very serious limitations suggested that the acquisition costs of droxidopa may be partially offset by a reduction in falls, with consequent cost savings and gains in quality of life, resulting in an ICER of approximately US$50,000 per QALY gained.

7.3.6 Evidence to recommendations

Relative value of different outcomes	Adverse events associated with different pharmacological therapies were a key GDG consideration. The GDG agreed that systolic BP was more important than diastolic in assessing orthostatic hypotension. The GDG noted that the second Hauser et al. trial (2015) had adopted as its primary outcome measure the 1 measure – at the 1 time point – that had shown some effect in the first trial (Hauser et al. 2014). The GDG were unconvinced that treating a single index from a composite measure after 1 week's intervention as the primary target of treatment reflected an appropriate, clinically motivated focus. The GDG considered that the identified trials were long enough to see impact on some outcomes (blood pressure; OH scales) but not others (falls).
Trade-off between benefits and harms	The GDG emphasised that, when treating people for orthostatic hypotension, it is important to monitor for supine hypertension, which may increase stroke and other cardiovascular risks and makes orthostatic hypotension difficult to manage. Midodrine and fludrocortisone, in particular, are known to cause or exacerbate supine hypertension. At the time the GDG discussed this question, midodrine had very recently received UK marketing authorisation for OH due to autonomic disturbance. The GDG clarified that this would include all people with Parkinson's disease and OH. Therefore, midodrine is the only licensed product for the treatment of OH in this population. The GDG discussed that there is some prior experience of prescribing midodrine on a named-patient basis in Parkinson's disease; however, it has not typically been the first choice of drug for people with OH in Parkinson's disease. Although the review did not identify any evidence on the use of midodrine in people with Parkinson's disease, the GDG was aware that NICE has recently published an evidence summary on midodrine for orthostatic hypotension due to autonomic dysfunction. This review looked at evidence for the use of midodrine in a broader population of people experiencing autonomic disturbance, predominantly relying on 2 placebo-controlled RCTs from the 1990s. These trials suggest that midodrine increases standing blood pressure, and may also improve some – but not all – relevant symptoms, while having some reported adverse effects. Without any evidence comparing midodrine with the off-label/unlicensed drugs used in current practice, the GDG were not confident that it clearly represents the optimal choice for people with OH and Parkinson's disease. However, being mindful of the good prescribing practice requirements imposed by regulators and professional bodies, the GDG agreed that it was reasonable that prescribers should consider midodrine, as a licensed product, before resorting to options without a marketing authorisation.

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	The GDG reported that a number of drugs have been used in clinical practice. There is anecdotal experience that some drugs help some people, but it was acknowledged that there is a very limited evidence base to guide treatment decisions. The GDG believed that fludrocortisone has been the most common option in recent NHS use, but noted that using it for this indication represents off-label prescribing. Domperidone is licensed as an antiemetic in the UK, but does not have a marketing authorisation for OH; therefore, its use in this indication is considered off-label. It has a 'black triangle' warning due to QT interval prolongation. Nevertheless, it has been used long-term in some people with Parkinson's disease, as long as regular ECG monitoring is undertaken. The GDG observed that, in the included RCT, domperidone had been used at the upper limit of safe dosage (30 mg/day). Although the 1 small RCT comparing fludrocortisone and domperidone did not detect any difference in adverse events between the 2, the GDG agreed that most prescribers would prefer to use fludrocortisone, in view of the known safety issues with domperidone. For this reason, fludrocortisone was prioritised over domperidone for people who need an off-label alternative to midodrine. The GDG were aware that droxidopa is commonly used to treat OH in Parkinson's disease in Japan and USA. However, it is unlicensed and hard to access in the UK. The evidence identified in this review shows, at best, a very short-term (1-week) benefit that is not sustained at later timepoints. The GDG also noted that a substantial proportion of participants in the 2 droxidopa RCTs were already receiving fludrocortisone and were allowed to continue taking it during the trials. This suggested that those people were likely to be experiencing quite significant, treatment-resistant OH. While the GDG could not exclude the possibility that there may be a role for droxidopa in such cases, there were no grounds to recommend its use in anything other than exceptional circumstances, especially as it is presently unlicensed in the UK.
Trade-off between net health benefits and resource use	The GDG were aware that cost alone cannot be used to prefer an off-label or unlicensed product to one which has a marketing authorisation for the relevant indication. Therefore, the acquisition cost of the drugs under consideration should not be used as an argument not to prescribe midodrine. The GDG emphasised that a review of current medication – an inexpensive step that should already be thought of as best practice – should be undertaken before any medicine directly targeting orthostatic hypotentsion should be considered. The GDG also noted that the consequences of ineffectively treated orthostatic hypotension – especially falls – can impose a nontrivial cost burden on the NHS. Therefore, recommendations that optimise management will recoup some or all of their associated acquisition costs in downstream care savings.
Quality of evidence	The evidence identified was limited in extent, low in quality, and did not address the comparisons of greatest interest. The GDG would have been particularly interested in an RCT of midodrine compared with fludrocortisone, and made a recommendation that such research should be undertaken. The GDG noted that the eligibility criteria of the droxidopa trials made it difficult to draw useful inference from their findings. The fact that a substantial proportion of participants were already receiving fludrocortisone suggested people with advanced, treatment-resistant OH were mixed in with people for whom it was a new problem. Moreover, effect estimates may have been confounded by the fact that there were more people on fludrocortisone in droxidopa arm than placebo (33% -v- 20%). The RCT of fludrocortisone -v- domperidone was very limited (both in

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	participant numbers and in duration) and very low quality. However, the GDG were satisfied that 1 week's washout should have been sufficient in a crossover trial of these 2 agents. The GDG considered it possible that there may be more evidence of the efficacy and safety of some of the drugs under consideration in a broader population of people with autonomic dysfunction. Such trials may include people with Parkinson's disease; however, no trials were found that report a subgroup analysis limited to people with Parkinson's disease.
Other considerations	The GDG noted that OH in Parkinson's disease may be caused or exacerbated by existing medications (Parkinson's disease and/or non-Parkinson's disease). Therefore, the first and most important step in pharmacological management of symptoms is to review current medications. Accordingly, the GDG felt it was important to emphasise this in their recommendations. The GDG chose to draw attention to several classes of medicine that may have an antihypertensive effect; these were ordered by likely magnitude of impact and the importance of reviewing them. The GDG expressed a view that some non-pharmacological interventions can be effective in the treatment of OH; however, these were not within the scope of this review.

7.3.7 Recommendations

38. If a person with Parkinson's disease has developed orthostatic hypotension, review the person's existing medicines to address possible pharmacological causes, including:

- antihypertensives (including diuretics)
- dopaminergics
- anticholinergics
- antidepressants
- proton pump inhibitors. **[new 2017]**

39. Consider midodrine for people with Parkinson's disease and orthostatic hypotension, taking into account the contraindications and monitoring requirements (including monitoring for supine hypertension). [new 2017]

40. If midodrine is contraindicated, not tolerated or not effective, consider fludrocortisone[b] (taking into account its safety profile, in particular its cardiac risk and potential interactions with other medicines) or domperidone[c] (with QT interval monitoring). [new 2017]

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[b] At the time of consultation (October 2016), use of fludrocortisone for this indication would be off-label. The prescriber should follow relevant professional guidance, taking full responsibility for the decision. Informed consent should be obtained and documented. See the General Medical Council's Good practice in prescribing and managing medicines and devices for further information.

[c] At the time of consultation (October 2016), use of domperidone for this indication would be off-label. Medicines and Healthcare products Regulatory Agency (MHRA) guidance (2014) notes that domperidone is associated with a small increased risk of serious cardiac side effects. Domperidone is now contraindicated in certain groups in whom the risk of cardiac effects is higher; its marketing authorisations have also been restricted to its use in the relief of nausea and vomiting only, at the lowest effective dose and for the shortest possible time (usually not more than 1 week): see the MHRA guidance and summaries of product characteristics. The MHRA advises that prescribers should take into account the overall safety profile of domperidone, and in particular its cardiac risk and potential interactions with other medicines (such as erythromycin), if there is a clinical need to use it at doses or durations greater than those authorised. The prescriber should follow relevant professional guidance, taking full responsibility for the decision. Informed consent should be obtained

7.3.8 Research recommendation

2. For people with Parkinson's disease, what is the most effective pharmacological treatment for orthostatic hypotension? Particular interventions and comparisons of interest are:

- midodrine compared with fludrocortisone
- pyridostigmine
- ephedrine
- pseudoephedrine.

Why this is important

The GDG felt that orthostatic hypotension was important practical problem, common in people with Parkinson's disease and a contributor to falls and injuries. The current best pharmacological treatment is not yet established and research in this area would be beneficial to determine this. The randomised controlled trials that have previously been undertaken have only provided low-quality evidence (due to both small sample sizes and weaknesses in the trial designs) and cover only a subset of the comparisons of interest, making future research in this area of value.

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and documented. See the General Medical Council's Prescribing guidance: prescribing unlicensed medicines for further information.

7.4 Depression

It was agreed in the scope to cross refer to the existing NICE guideline on Depression in adults with a chronic physical health problem: recognition and management CG91 for the recommendations relating to depression.

41. For guidance on identifying, treating and managing depression in people with Parkinson's disease, see the NICE guideline on depression in adults with a chronic physical health problem. [new 2017]

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7.5 Psychotic symptoms (hallucinations and delusions)

What is the comparative effectiveness of pharmacological interventions for psychotic symptoms associated with PD?

7.5.1 Introduction

The aim of this review question was to determine the effectiveness of second-generation antipsychotics for psychotic symptoms associated with Parkinson's disease. This updated review incorporates studies that were included in the previous guideline together with newly published evidence.

The review focused on identifying studies that fulfilled the conditions specified in Table 11.

Table 11: PICO table for pharmacological interventions for psychotic symptoms

Population	Patients with a confirmed diagnosis of Parkinson's disease who are experiencing psychosis
Interventions	• Amisulpride • Aripiprazole • Clozapine • Donepezil • Galantamine • Haloperidol • Memantine • Olanzapine • Quetiapine • Risperidone • Rivastigmine
Comparators	• Placebo • Each other

Outcomes	• Adverse events (include worsening of motor symptoms)
	• Mortality
	• Resource use and cost
	• Disease severity (UPDRS motor)
	• Psychosis measures:
	  ○ Psychosis
	  ○ Delusions
	  ○ Hallucinations
	  ○ Positive symptoms

For full details of the review protocol, please see Appendix C. Randomised controlled trials (RCTs) were considered to be the most appropriate study design to estimate treatment effects, and were therefore considered to be the highest quality within a GRADE framework. All other study designs were excluded from this review, including case–control studies, cohort studies and case reports.

7.5.2 Evidence review

A systematic search was conducted (see appendix I), which identified 2,864 references. The references were screened on their titles and abstracts and full papers of 11 references were obtained and reviewed against the inclusion and exclusion criteria in the review protocol (see appendix C).

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Overall, 7 studies were excluded as they did not meet the eligibility criteria such as not being a randomised-control design or not assessing an included intervention. A detailed list of excluded studies and reasons for their exclusion is provided in appendix G.

The 4 remaining published articles met eligibility criteria and were included in the analysis. The 6 studies, reported in 5 publications, that were included in the previous Parkinson's disease guideline (CG35) were reviewed against the current protocol. All of these studies met the inclusion criteria for the current guideline and were included in the analyses.

Evidence tables for included studies can be found in Appendix D, with GRADE profiles reported in Appendix E.

One additional new paper was identified through rerun searches at the end of the guideline but was excluded as it did not meet the eligibility criteria for the current review.

The included studies examined the effectiveness of pharmacological interventions compared with placebo or active comparator for treating psychotic symptoms associated with Parkinson's disease.

Two approaches to the analysis were used, network meta-analysis (NMA) and pairwise meta-analysis. Where, possible, a NMA was conducted to investigate and compare the different second generation antipsychotics to see which is the most effective in reducing psychotic symptoms associated with Parkinson's disease and which is the safest. However, where a NMA could not be formed, data were pooled using pairwise meta-analysis, to assess the effectiveness and safety of second generation antipsychotics used to treat psychotic symptoms associated with Parkinson's disease.

7.5.3 Description of included studies

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Quetiapine vs. placebo (n=3)

A total of 71 people (study size ranged from 16 to 31) with a confirmed diagnosis of Parkinson's disease who were experiencing symptoms of psychosis participated in 3 randomised, double-blind, placebo-controlled trials examining the safety and effectiveness of quetiapine. The RCTs were carried out in the USA (Ondo et al., 2005; Fernandez et al., 2009) and the UK (Shotbolt et al., 2009). The mean age in the 3 studies ranged from 64.6 to 74 years. The mean disease duration in 2 studies ranged from 8 to 12 years, with 1 study not reporting this information (Fernandez et al., 2009). Duration of follow-up in the 3 studies ranged from 6.5 to 14 weeks. The mean final dosing of drug ranged from 58.3 to 169.1 mg/day. Full details of the included studies are found in the evidence tables (see Appendix D).

Olanzapine vs. placebo (n=4)

A total of 213 people (study size ranged from 23 to 83) with a confirmed diagnosis of Parkinson's disease who were experiencing symptoms of psychosis participated in 4 randomised, double-blind, placebo-controlled trials examining the safety and effectiveness of olanzapine. One publication (Breier et al., 2002) reported results from 2 of the 4 trials, 1 carried out in the EU and 1 in the USA. The remaining 2 studies were also carried out in the USA (Ondo et al., 2002; Nichols et al., 2013). The mean age in the 4 studies ranged from 70.5 to 73.5 years. A mean disease duration of 9.6 years was reported in only 1 of the 4 studies (Ondo et al., 2002). Duration of follow-up in the 4 studies ranged from 4 to 9 weeks. The mean final dosing of drug ranged from 2.5 to 4.6 mg/day. Full details of the included studies are found in the evidence tables (see Appendix D).

Clozapine vs. placebo (n=2)

A total of 120 people (study size for each study was 60) with a confirmed diagnosis of Parkinson's disease who were experiencing symptoms of psychosis participated in 2

randomised, double-blind, placebo-controlled trials examining the safety and effectiveness of clozapine. Both studies were carried out in the USA. The mean age in the two studies ranged from 70.8 to 72.8 years, mean disease duration ranged from 10.4 to 12.1 years, and duration of follow-up was 4 weeks in both studies. The mean final dosing of drug ranged from 24.7 to 35.8 mg/day. Details of the included studies are found in the evidence tables (see Appendix D)

Clozapine vs. quetiapine (n=1)

A total of 45 people with a confirmed diagnosis of Parkinson's disease who were experiencing symptoms of psychosis participated in 1 randomised, open-label, blinded-rater, parallel-group trial, compared the effectiveness of clozapine and quetiapine (Morgante et al., 2004). The study was carried out in Italy. The mean age were 69±10.7 years for people receiving clozapine and 70±10.1 years for people receiving quetiapine (mean±SD); mean disease duration was 9.6±3.8 years vs. 8.4±3.8 years, respectively. The follow-up period was 12 weeks and the mean final dosing was 26 ±12 mg/day for clozapine and 91±47 mg/day for quetiapine. Full details of the study are found in the evidence tables (see Appendix D).

7.5.4 Evidence statements

7.5.4.1 Psychosis

Pairwise comparisons

Olanzapine vs. placebo (n=1)

Low-quality evidence from 1 RCT reported no meaningful relationship between olanzapine and the improvement of psychosis symptoms over 4 weeks, compared with placebo (MD=−0.25, 95% CI: −4.81 to 4.31).

Clozapine vs. quetiapine (n=1)

Low-quality evidence from 1 RCT reported no meaningful difference between clozapine and quetiapine on the improvement of psychosis symptoms over 12 weeks (MD=0.1, 95% CI: −1.0 to 1.2).

7.5.4.2 Hallucinations

Network meta-analyses

A network meta-analysis pooling 3 RCTs reporting hallucinations using the BPRS scale suggested that quetiapine has a high probability of being the optimum option. There is low probability that olanzapine is the best treatment, in this domain. Evidence was moderate-to-low quality. No data on clozapine were available.

A network meta-analysis pooling 5 RCTs using different measures of hallucination suggested that quetiapine has a medium-sized effect in reducing symptoms of hallucination, and has a high probability of being the optimal option. There is a low probability that olanzapine is the best treatment in this domain. Evidence was low quality. No data on clozapine were available.

7.5.4.3 Positive symptoms

Network meta-analysis

A network meta-analysis pooling 4 RCTs using different measures of 'positive' symptoms of psychosis suggested that clozapine has a large effect in reducing symptoms, and appears certain to be the optimal option. The evidence shows no possibility that olanzapine is the

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best treatment in this domain. Evidence was moderate-to-low quality. No data on quetiapine were available.

7.5.4.4 Delusions

Pairwise comparisons

Olanzapine vs. placebo (n=2)

Low-quality evidence from 2 RCTs reported no meaningful relationship between olanzapine and the improvement of delusions over 4 weeks, compared with placebo (MD=0.94, 95% CI: −0.08 to 1.96).

7.5.4.5 Disease severity – UPDRS III (motor)

Network meta-analysis

A network meta-analysis pooling 8 RCTs using UPDRS III (motor) subscale suggested that both quetiapine and clozapine may be effective in improving motor function of Parkinson's disease, with quetiapine having the highest probability of being the optimum option, although the confidence intervals of the mean difference crossed the line of minimal clinically important difference as defined by Schrag et al., 2006 and Horvath et al., 2015. The evidence shows that olanzapine worsens motor symptoms; there is no possibility that it is the best treatment in this domain. Evidence was low quality.

7.5.4.6 Adverse events

Network meta-analysis

Treatment discontinuation due to adverse events

A network meta-analysis pooling 8 RCTs suggested no meaningful difference between quetiapine, clozapine and placebo in reducing the risk of treatment discontinuation due to adverse events, although quetiapine had the highest probability of being the optimum option. The evidence shows that olanzapine is associated with a higher rate of dropouts; there is no possibility that it is the best treatment in this domain. Evidence was low quality.

7.5.4.7 Adverse events – Estimate of rate

A network meta-analysis pooling 5 RCTs suggested that quetiapine has the highest probability of being the optimum option in reducing the risk of adverse events, although the effect was small. There is a lower probability for olanzapine or clozapine to be the best treatment in this domain. Evidence was low quality.

7.5.4.8 Mortality

Across all 10 included RCTs, a total of 3 deaths were reported; it is not possible to draw any conclusions about the effect of clozapine, olanzapine or quetiapine on short-term mortality.

7.5.5 Health economic evidence

No health economic evidence was identified for this review question.

7.5.6 Evidence to recommendations

Relative value of different outcomes	The GDG considered that the measures of hallucinations and delusions were the most important effectiveness outcomes of those presented. The GDG agreed that it would be useful to separate hallucinations vs. delusions as

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	their treatments may be different. However, only 1 treatment (olanzapine) measured hallucinations and delusions in isolation. It was therefore only possible to comment on the differential efficacy of olanzapine on those 2 outcomes. For the other psychosis outcome measures, the GDG noted that the 'positive symptoms' scales (PANSS positive and SAPS) include both hallucinations and delusions and that the BPRS psychosis scale includes both 'positive symptoms' and 'negative symptoms' (the latter are rare in Parkinson's disease psychosis) as well as other items. There will therefore be some overlap between outcome measures. These different psychosis outcome measures were also considered important, but it was noted that they cover wider psychotic experiences and could therefore not be combined with the measures of hallucination or delusions in isolation, which were of most interest. The GDG noted that there are no measures of psychosis that are specifically designed and validated for people with Parkinson's disease; however, the GDG agreed that it would expect any treatments with meaningful effects to show some differences on the generic instruments used in the included RCTs.
Trade-off between benefits and harms	The GDG discussed how the term psychosis should be defined in Parkinson's disease and agreed that it would be useful to make reference to 'hallucinations and delusions', rather than 'psychosis' in its recommendations, as the latter term is widely misunderstood and could also be associated with stigma leading to under-reporting of symptoms. The GDG discussed the importance of making people with Parkinson's disease and their carers aware that hallucination and delusions are common side-effects of anti-parkinsonian drugs. It is therefore important that these symptoms are assessed at subsequent review appointments. The GDG noted that it is important to ask carers if the person is showing signs of experiencing hallucinations or delusions, as some people with Parkinson's disease may not be aware that they are hallucinating (particularly visual hallucinations). The GDG agreed that a general medical evaluation is indicated for people with Parkinson's disease who are experiencing hallucinations and/or delusions (to exclude infection or biochemical abnormality, or other non-parkinsonian drugs causing adverse effects) and that it should lead to treatment for any precipitating condition. It was agreed that this is an important step before commencing any antipsychotic treatment. As hallucinations and delusions are common side-effects of many anti-parkinsonian medicines, the GDG agreed that clinicians should consider gradually reducing dosages whenever side-effects are perceived to outweigh the benefits of taking the medicine(s). Because some anti-parkinsonian medicines are also known to have significant adverse withdrawal effects, the speed of reduction should be dependent on the drugs prescribed and individual's tolerance to withdrawal, and an appropriate balance between beneficial and adverse effects in each individual case should be sought. The GDG discussed the use of pharmacological management of psychosis for people with Parkinson's disease and agreed that it is not always the best option. If the affected person does not find the hallucinations and/or delusions disturbing and has good insight into their symptoms, their symptoms do not need to be actively treated. The GDG discussed whether it is necessary to recommend a cognitive function assessment in all people who report symptoms associated with hallucination. It was recognised that the results from these tests can be hard to interpret in people who are symptomatic, particularly for non-Parkinson's disease specialists. The GDG emphasised that, although there is a strong association between hallucination and cognitive impairment, there is no necessary causal relationship between the 2. That is, people with Parkinson's disease who experience hallucinations do not always show signs

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of cognitive impairment. Likewise, people with Parkinson's disease and cognitive impairment do not necessarily experience hallucinations. Therefore, the GDG agreed that, although any new cognitive symptoms that were apparent in the general medical evaluation should be investigated further, a specific recommendation for everyone to undergo formal cognitive investigation would not be helpful in the context of treating hallucinations and/or delusions caused by Parkinson's disease.

The GDG discussed the evidence for the individual antipsychotics and unanimously agreed to make a 'do not' recommendation for olanzapine for the treatment of psychosis in people with Parkinson's disease. This was based on clear evidence that olanzapine does more harm than good for most people in this population. The GDG also agreed to carry forward a previous recommendation made in CG35 that other antipsychotic drugs such as phenothiazines and butyrophenones should be used with great caution as they are likely to exacerbate the motor features of Parkinson's disease. It was noted that this recommendation was not based on any specific published evidence; however, the GDG agreed with the previous committee that, while the harms of these treatments are well known among healthcare professionals with a particular interest in Parkinson's disease, there is a risk that they may be inappropriately prescribed by people with less specialist knowledge. Therefore it was agreed that it is appropriate to be clear about the dangers associated with them.

The GDG discussed the evidence base for quetiapine and clozapine and recognised that both drugs appear effective at improving psychosis in people with Parkinson's disease without worsening motor function, and there is little evidence that either is superior to the other. The GDG noted that, whereas the use of quetiapine in people with Parkinson's disease psychosis represents off-label prescribing, clozapine has a marketing authorisation for 'psychotic disorders occurring during the course of Parkinson's disease, in cases where standard treatment has failed'.

The GDG noted that it is unlikely that clozapine would be considered practical for routine first-line use, as it is a prerequisite for use that prescribers and patients must be registered with a mandatory monitoring scheme. This is to monitor the possible development of agranulocytosis and granulocytopenia, which clozapine can cause. Regular blood monitoring is mandatory and this can have significant impacts on the service configuration and the patient. For this reason, the GDG agreed that the 'standard treatment' that should be considered before prescribing clozapine is likely to be off-label prescription of quetiapine, which does not have monitoring requirements. When considering drafting the recommendations for this area the GDG agreed that if clozapine was listed first it may risk people receiving no active treatment due to the mandatory monitoring requirements for clozapine.

The GDG agreed to list quetiapine and clozapine as equal first-line therapy options, noting that registration with a mandatory monitoring scheme is required for clozapine. The GDG agreed that, although this recommendation provides room for prescribers to select clozapine if there are good reasons to do so in any individual case, most prescribers are likely to prefer quetiapine as first-line treatment seeing that it is an option that people can take more easily and is at least as effective. The GDG recognised and agreed that in cases where the selected option is ineffective or not tolerated, the alternative option should be offered as there is value in trying both before moving to other off-label options for which no evidence was found. The GDG agreed that this strategy would encourage clinicians to try both therapies and not just avoid clozapine because of its requirements for ongoing monitoring.

The specific prescribing requirements for clozapine and quetiapine were discussed and the GDG noted that, in their clinical experience, doses of clozapine or quetiapine that are common in people with schizophrenia have caused safety issues in people with Parkinson's disease psychosis. It was noted that there are no direct dosage information in the BNF and SPC for

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	Parkinson's disease psychosis. It was therefore agreed that a recommendation should be made to prevent people from using the same dosages as prescribed for schizophrenia, which are likely to be too high for people with Parkinson's disease psychosis.
Trade-off between net health benefits and resource use	The GDG agreed that clozapine and quetiapine appear to be as clinically effective as each other. Whilst clozapine is licensed for this indication where standard treatments have failed, the GDG noted that clozapine would be likely to incur greater costs (due to drug unit costs and mandatory monitoring costs) but without generating any greater benefits. Also the GDG were unclear what 'standard treatments' consist of – one sensible interpretation would include off-label use of quetiapine. Therefore, the GDG intended that its recommendations would lead to most people being offered quetiapine, which is available in inexpensive generic formulations. For this reason, the group believed that its recommendations would be unlikely to be associated with a significant resource impact (indeed, if some prescribers are using clozapine as a matter of routine, the recommendations would be associated with cost savings).
Quality of evidence	The GDG recognised that the evidence base was low quality. However, based on the clear and consistent evidence for quetiapine, clozapine and olanzapine, the GDG were confident to make an 'offer' recommendation for first line treatment of psychosis as well as a 'do not do' recommendation for olanzapine.

7.5.7 Recommendations

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42. At review appointments and following medicines changes, ask people with Parkinson's disease and their family members and carers (as appropriate) whether the person is experiencing hallucinations (particularly visual) or delusions. [new 2017]

43. Perform a general medical evaluation for people with hallucinations or delusions, and offer treatment for any conditions that might have triggered them. [new 2017]

44. Do not treat hallucinations and delusions if they are well tolerated by the person and their family members and carers (as appropriate). [new 2017]

45. Reduce the dosage of any Parkinson's disease medicines that might have triggered hallucinations or delusions, taking into account the severity of symptoms and possible withdrawal effects. Seek advice from a healthcare professional with specialist expertise in Parkinson's disease before modifying therapy. [new 2017]

46. Offer 1 of the following as first-line pharmacological treatment for people with Parkinson's disease with hallucinations and delusions:

- quetiapine[d]
- clozapine (be aware that registration with the mandatory Clozaril patient monitoring service is required).

d At the time of consultation (October 2016), use of quetiapine for this indication would be off-label. The prescriber should follow relevant professional guidance, taking full responsibility for the decision. Informed consent should be obtained and documented. See the General Medical Council's Good practice in prescribing and managing medicines and devices for further information.

If the selected option is not effective or not tolerated, offer the other instead. [new 2017]

47. **Be aware that lower doses of quetiapine and clozapine are needed for people with Parkinson's disease than in other indications. [new 2017]**

48. **Do not offer olanzapine to treat hallucinations and delusions in people with Parkinson's disease. [new 2017]**

49. **Recognise that other antipsychotic medicines (such as phenothiazines and butyrophenones) exacerbate the motor features of Parkinson's disease. [new 2017]**

7.5.8 Research recommendation

3. **What is the effectiveness of rivastigmine compared with atypical antipsychotic drugs for treating psychotic symptoms (particularly hallucinations and/or delusions) associated with Parkinson's disease?**

Why this is important

Rivastigmine is commonly used in practice for treating people with Parkinson's disease psychosis, because it has shown some effectiveness in improving behavioural symptoms in people with Parkinson's disease dementia. Whilst trials have been conducted looking at the efficacy of atypical antipsychotics versus placebo or each other, at present, no evidence exists to support the efficacy of rivastigmine in the treatment of people with Parkinson's disease whose symptoms are predominantly psychotic. It would be beneficial to undertake primary research in this area in order to determine the most effective treatment options for managing Parkinson's disease psychosis.

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7.6 REM sleep behaviour disorder

What is the effectiveness of pharmacological interventions to treat rapid eye movement (REM) sleep behaviour disorder (RBD) associated with Parkinson's disease?

7.6.1 Introduction

The aim of this review question was to assess the efficacy of pharmacological interventions compared with placebo to treat RBD in people with Parkinson's disease. The review focussed on identifying studies that fulfilled the conditions specified in Table 12.

Table 12: PICO table for pharmacological interventions for RBD

Population	Patients with a confirmed diagnosis of Parkinson's disease whom are suffering from RBD sleep disturbance
Interventions	• Immediate-release levodopa • Controlled release levodopa • Prolonged release dopamine agonist (including transdermal patch) • Standard-release dopamine agonist • Apomorphine • Mirtazapine • Benzodiazepine: Clonazepam • Pregabalin • Melatonin • Rivastigmine • Gabapentin
Comparators	• Placebo • Active Comparative
Outcomes	• Adverse events • Resource use and cost • RBD: reported frequency of episodes • RBD severity scale • PD sleep scale • PD non-motor scale • Health related quality of life • Carer health related quality of life • UPDRS scores

For full details of the review protocol, please see Appendix C. Randomised controlled trials (RCTs) were considered to be the most appropriate study design to derive treatment effect metrics, and were therefore considered to be the highest quality within a GRADE framework. All other study designs were excluded from this review, including case–control studies, cohort studies, and case reports.

7.6.2 Evidence review

A single systematic search was conducted (see appendix I) for 2 of the sleep study review questions (nocturnal akinesia and RBD) which identified 3,596 references. The references were screened on their titles and abstracts and full papers of 25 references were obtained and reviewed against the inclusion and exclusion criteria in the review protocol for each of the 2 sleep study reviews (see appendix C).

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Overall, 21 studies were excluded as they did not meet the eligibility criteria such as not utilising a randomised-control design. A detailed list of excluded studies and reasons for their exclusion is provided in appendix G.

The 4 remaining published papers did meet eligibility criteria and were included in the appropriate analyses. One paper (Di Giacomo et al., 2012) which addressed pharmacological treatment for RBD was included within the present review question.

Evidence table for included study can be found in Appendix D, with GRADE profiles reported in Appendix E.

Evidence from the previous guideline (CG35) was also reviewed against the present inclusion and exclusion criteria; however no studies met the criteria for the present review.

One additional new paper was identified through rerun searches at the end of the guideline but was excluded as it did not meet the eligibility criteria for the current review.

7.6.3 Description of included studies

Rivastigmine to treat RBD

One study (Di Giacomo et al., 2012) of 12 participants with Parkinson's disease (mean age=67.7, SD 7.3; mean disease duration=9.2, SD 3.2) utilised a randomised cross-over trial design to assess the effectiveness of rivastigmine to treat RBD in people in whom conventional therapy (melatonin or clonazepam) had failed. Washout period between interventions was 1 week.

7.6.4 Evidence statements

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Number of RBD episodes

Very low-quality evidence from one study reported rivastigmine to considerably reduce the number of RBD episodes in people with Parkinson's disease compared with those exposed to placebo (median change score=2.5; 25^{th}–75^{th} percentile: 0.00 to 4.5)

Sleep quality (PDSS)

No evidence on the sleep quality of participants was presented

UPDRS motor symptoms (UPDRS II)

No evidence on the motor features of participants was presented

Non motor symptoms

No evidence on the non-motor features of participants was presented

Health related quality of life (PDQ-8)

No evidence on the health related quality of life of participants was presented

Adverse events

Very low-quality evidence from 1 study reported 2 participants to drop out from the study in the rivastigmine condition due to serious adverse events of orthostatic hypotension and asthenia. No participant reported any adverse event in the placebo group.

7.6.5 Health economic evidence

No health economic evidence was identified for this review question.

7.6.6 Evidence to recommendations

Relative value of different outcomes	The GDG recognised that frequency and severity of RBD episodes were the most critical outcomes of interest for this review question.
Trade-off between benefits and harms	The GDG noted that the participants in the rivastigmine trial were people in whom both melatonin and clonazepam and failed – indicating that rivastigmine would not normally be prescribed as first line treatment. The GDG unanimously agreed that group members would not be inclined to prescribe rivastigmine to treat RBD as the evidence presented does not provide convincing support for rivastigmine as a useful treatment option. The GDG noted that the paper presents evidence using 25th to 75th percentile ranges rather than means, and this made the evidence difficult to interpret. The GDG further noted that it is likely that the authors have presented the results with these percentiles to maximise the apparent efficacy of the results and to mask the fact that the data would fall below line of clinical significance if presented to standard 95% confidence limits. Melatonin is licensed for people over 55 to treat sleep disturbance and was discussed to be used more routinely for general sleep disturbance, rather than RBD specifically. Clonazepam was discussed to be more commonly clinically used to treat RBD, although the GDG recognised that practice varies greatly throughout the UK. The GDG discussed observational studies which indicate that melatonin may have fewer side effects than clonazepam, however, it was noted that clonazepam may be more efficacious at treating RBD. The GDG recognised that there is a scarcity of evidence in this area and that further high quality research needs to be undertaken in order to determine the most effective treatment options for managing RBD and have therefore made a research recommendation. The GDG agreed that RBD can be dangerous in that both the patient and their bed partner can sustain serious injury, and it is therefore important to treat RBD in order to minimise the risk of harm. The GDG acknowledged that melatonin access can be difficult for different areas in UK, and that different medical regions had differing melatonin prescription practices in place. It was viewed by the GDG as important to highlight to the medical community that both clonazepam and melatonin are useful treatment options to treat RBD as prescribing practice in the UK is highly variable, and therefore clinical guidance is needed. These two treatments are both used to treat RBD in people with other conditions besides Parkinson's disease, and the GDG did not believe there was any clinical reason to suppose their efficacy would be lower in this group. The GDG noted that there may be a greater benefit of slow release preparations whereby the active substance (melatonin or clonazepam) is released during the night to optimally treat nocturnal symptoms. Both melatonin and clonazepam are unlicensed for RBD, however no other treatments are currently licensed for RBD.
Trade-off between net health benefits and resource use	No economic evidence was identified for this review question, and economic modelling was not prioritised. The GDG noted that clonazepam and melatonin are used to treat RBR in clinical areas other than Parkinson's disease, and there would be no reason to suppose the per person treated resource implications would be greater in this population. The GDG emphasised that a review of current medication – an inexpensive step that

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	should already be thought of as best practice – should be undertaken before any medicine directly targeting RBD should be considered. This, coupled with the fairly low incidence of RBD and the relatively low acquisition costs of clonazepam and melatonin, satisfied the group that its recommendations would not impose a significant resource impact on the NHS.
Quality of evidence	The GDG highlighted that fact that the evidence presented was very low quality due to the low patient numbers and lack of meaningful statistical data and therefore should not be used to inform a recommendation.

7.6.7 Recommendations

50. Take care to identify and manage restless leg syndrome and rapid eye movement (REM) sleep behaviour disorder in people with Parkinson's disease and sleep disturbance. [2017]

51. Consider clonazepam or melatonin to treat REM sleep behaviour disorder if a medicines review has addressed possible pharmacological causes[e]. [new 2017]

7.6.8 Research recommendation

4. What is the best first-line treatment for REM sleep behaviour disorder in people with Parkinson's disease?

Why this is important

The GDG highlighted the importance of minimising sleep behaviour disorder, for both people with Parkinson's disease and their carers, particularly due to potential safety concerns. Only one paper was found to address optimal management, and this contained a population of people who had already failed on first line treatment. With multiple possible treatment options (in particular clonazepam and melatonin) and no current evidence on what the most effective first-line treatment is, research (in the form of randomised controlled trials) in this area would be beneficial. The primary outcomes for such trials should be the frequency and severity of RBD episodes, and the adverse effects from treatment.

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[e] At the time of consultation (October 2016), use of clonazepam or melatonin for this indication would be off-label. The prescriber should follow relevant professional guidance, taking full responsibility for the decision. Informed consent should be obtained and documented. See the General Medical Council's Good practice in prescribing and managing medicines and devices for further information.

7.7 Thermoregulatory dysfunction

What is the comparative effectiveness of pharmacological interventions for thermoregulatory dysfunction / hyperhidrosis associated with Parkinson's disease?

7.7.1 Introduction

The aim of this review question was to assess the efficacy of pharmacological interventions compared with placebo or active drug comparators to treat thermoregulatory dysfunction in people with Parkinson's disease.

The review focused on identifying studies that fulfilled the conditions specified in Table 13.

Table 13: PICO table for pharmacological interventions for thermoregulatory dysfunction in Parkinson's disease

Population	Patients with a confirmed diagnosis of Parkinson's disease whom are experiencing symptoms of thermoregulatory dysfunction
Interventions	Levodopa Dopamine agonists Propantheline bromide Clonidine Anticholinergic drugs Aluminium chloride Glycopyrronium bromide Botulinum toxin
Comparators	Placebo Each other
Outcomes	Adverse events Mortality Resource use and cost Disease severity – UPDRS Health-related QoL (patient) Carer burden and quality of life Thermoregulatory sweat test Silastic sweat imprint Quantitative pseudo-motor axon reflex test to test thermoregulatory pathways Hyperhidrosis severity score

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For full details of the review protocol, please see Appendix C. Randomised controlled trials (RCTs) were considered to be the most appropriate study design to derive treatment effect metrics, and were therefore considered to be the highest quality within a GRADE framework. In the instance that no RCT evidence was identified, observational evidence could be considered. All other study designs were excluded from this review, including case–control studies and case reports.

7.7.2 Evidence review

A single systematic search was conducted (see appendix I) for both autonomic dysfunction review questions – thermoregulation and orthostatic hypotension (see section 7.7) – which identified 2,517 references. The references were screened on their titles and abstracts and full papers of 7 references were obtained and reviewed against the inclusion and exclusion criteria in the review protocol (see appendix C) for thermoregulatory dysfunction.

All 7 studies were excluded as they did not meet the eligibility criteria such as not providing primary evidence. A detailed list of excluded studies and reasons for their exclusion is provided in appendix G.

Evidence from the previous guideline (CG35) was also reviewed against the present inclusion and exclusion criteria; however no studies met the criteria for the present review.

No new studies were identified through rerun searches at the end of the guideline.

7.7.3 Description of included studies

No studies were identified for inclusion in this review.

7.7.4 Evidence statements

No studies were identified for inclusion in this review.

7.7.5 Health economic evidence

No health economic evidence was identified for this review question.

7.7.6 Evidence to recommendations

Relative value of different outcomes	The GDG would have placed emphasis on any treatment that effectively minimised hyperhidrosis and improved quality of life with an acceptable safety profile. However, no evidence was available.
Trade-off between benefits and harms	The GDG was unsurprised that there was no evidence on the pharmacological management of thermoregulatory dysfunction: members advised that medical treatment is not usually offered for this problem. In their experience the GDG see very occasional cases and, if pharmacological treatment is offered, it is often not successful. Botulinum toxin is sometimes used in non-Parkinson's disease cases, but moves rather than solves the issue.
Trade-off between net health benefits and resource use	No economic evidence was identified for this review question.
Quality of evidence	The GDG discussed the possible value of a research recommendation, to plug the gap that the review had identified. However, it was not aware of any pharmacological treatments that have shown particular promise, in this area. In addition, the GDG felt that recruitment to an appropriately powered study would be difficult as, although it can be a big problem for some people with Parkinson's disease, absolute numbers of cases are small.

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7.7.7 Recommendations

No recommendations were made

7.8 Saliva management

What is the comparative effectiveness of pharmacological interventions to manage drooling of saliva in people with Parkinson's disease?

7.8.1 Introduction

This question was addressed using an evidence review undertaken by the National Guideline Centre for **Motor neurone disease: assessment and management** (NG42), considering the most effective options for saliva management in people with motor neurone disease. The Motor neurone disease (MND) guideline committee found insufficient evidence from randomised controlled trials in the MND population and therefore included a broader range of conditions (including Parkinson's disease) as part of their review, meaning all studies that would have been included in a Parkinson's disease specific evidence search were identified as well.

The Parkinson's disease guideline committee agreed with the approach undertaken in the MND guideline during the evidence review, and agreed that the use of indirect evidence from a mixed population was appropriate to address this question in people with Parkinson's disease. This evidence was examined and discussed by the Parkinson's disease guideline committee, as noted in the evidence to recommendations section, and a summary of the evidence is presented below. The evidence statements and evidence to recommendations, although based on the same evidence as the MND guideline, were developed separately for the Parkinson's disease guideline, and therefore there may be differences from the MND guideline due to the different clinical contexts.

Further details, including the clinical evidence summary and unit cost data is presented in chapter 14 of the motor neurone disease guideline. The review protocol, literature search strategy, evidence tables, GRADE tables, forest plots, and excluded studies list are found in **appendices** C, F, G, I, J, and K of the MND guideline respectively.

The review focused on identifying studies that fulfilled the conditions specified in Table 14.

Table 14: PICO table for the effectiveness of pharmacological interventions to manage drooling of saliva

Population	People with drooling of saliva and one of the following conditions: • Parkinson's disease • Motor neurone disease • Cerebral palsy • Spinal muscular atrophy • Multiple system atrophy
Interventions	• Atropine (sublingual) • Benztropine • Hyoscine (oral or sublingual or patch) • Glycopyrrolate (sublingual or syringe driver, orally or via PEG) • Amitriptyline (tricyclic antidepressants [TCAs] as oral solution or tablet) • Clonidine injection (antihypertensive, tablet or patch or via PEG) • Botulinum toxin injections
Comparators	• Placebo • No treatment • Each other
Outcomes	• Health-related quality of life (EQ5D, SF-36, SF-12) for patients and carers • Patient/carer reported outcomes (for example symptoms, satisfaction, pain [VAS])

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	• Aspiration pneumonia • Function measured by disability scores (Ashworth scale) • Hospital admissions (and unplanned admissions) • Adverse effects of treatment (increased muscle weakness negating improved saliva control, side effects which cause cessation of use even if improved saliva control)

7.8.2 Evidence review

A total of 14 studies was identified across the populations considered. Ten RCTs were found on the effectiveness of botulinum toxin (4 in Parkinson's disease, 4 in cerebral palsy, 1 in MND and 1 in a mixed population of Parkinson's disease and multiple system atrophy), 3 on the effectiveness of glycopyrrolate (1 in Parkinson's disease and 2 in children with cerebral palsy or other developmental disorders) and 1 on the effectiveness of benztropine (cerebral palsy). Data from these separate populations were combined into a single analysis.

7.8.3 Evidence statements

7.8.3.1 Botulinum toxin versus placebo

Nine studies compared botulinum toxin versus placebo. The evidence showed that there was a clinical benefit of botulinum toxin for impact of drooling on daily activities, patient and caregiver perceived change in severity of drooling, patient satisfaction, and discontinuation of medication due to side effects. There was no clinical difference between botulinum toxin and placebo for patient assessment of severity of drooling, severity of dysphagia, and aspiration pneumonia. The evidence was of moderate, low or very low quality.

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7.8.3.2 Botulinum toxin versus no treatment

One study compared botulinum toxin versus no treatment. The evidence showed that there was a clinical benefit of botulinum toxin for caregiver assessment of severity of drooling, and no clinical difference between botulinum toxin and no treatment for muscle weakness. The evidence was of very low quality.

7.8.3.3 Glycopyrrolate versus placebo

Three studies compared glycopyrrolate versus placebo. The evidence showed that there was a clinical benefit of glycopyrrolate for caregiver assessment of severity of drooling and caregiver satisfaction with medication. The evidence showed a clinical harm of glycopyrrolate from side effects, as omdocated by discontinuation of medication. There was no clinical difference between glycopyrrolate and placebo for change in motor symptoms. The evidence was of moderate or very low quality.

7.8.3.4 Benztropine versus placebo

One study compared benztropine versus placebo. The evidence showed that there was a clinical benefit of benztropine for caregiver assessment of severity of drooling, and a clinical harm of benztropine for discontinuation of medication due to side effects. The study was of very low quality.

7.8.4 Evidence to recommendations

	GDG discussions
Relative value of different outcomes	The GDG agreed that the outcomes collected as part of the MND guideline - health-related quality of life, patient- and carer-reported outcomes (pain, symptoms, satisfaction) and adverse effects of treatment - were relevant

	outcomes for a population with Parkinson's disease.
Trade-off between benefits and harms	The evidence base included people with Parkinson's disease, motor neurone disease, cerebral palsy, spinal muscular atrophy and multiple system atrophy. The GDG agreed that whilst the mechanisms of action were not always identical between people with these different conditions, the same range of pharmacological interventions would be relevant as treatments. Across the full range of populations, 14 studies were included in the review (with 6 exclusively or mostly in a population with Parkinson's disease). These studies covered 4 comparisons: botulinum toxin versus placebo, botulinum toxin versus no treatment, glycopyrrolate versus placebo and benztropine versus placebo. Nine studies evaluated botulinum toxin versus placebo. Botulinum toxin showed clinical benefits in 4 outcomes, including the impact of drooling on daily activities. In 4 other outcomes where there was no meaningful difference between the treatments. The other evidence for botulinum toxin came from 1 study where it was compared to no treatment. The results were again positive, showing botulinum toxin improves caregiver assessment of drooling while not causing muscle weakness. Three studies comparing glycopyrrolate versus placebo and 1 study comparing benztropine versus placebo found both drugs to be effective in improving caregiver assessment of severity of drooling. However, a clinically significant number of patients discontinued the treatments due to side effects. The GDG noted that anticholinergic medicines are available on prescription and are less invasive than other treatments (for example, botulinum toxin), making them preferable as a first-line treatment, if appropriate. However, whilst no evidence was identified to suggest that the use of anticholinergic medication causes the development of cognitive side effects (although there were significantly increased discontinuations because of adverse events), the GDG noted that their experience of these drugs is that they do cause serious side effects and may not be well tolerated. This may be especially true of people with Parkinson's disease who, unlike those with MND, have a progressively neurodegenerative prognosis, with a particular risk of cognitive dysfunction, psychosis and other non-motor complications that are known to be exacerbated by anticholinergic medicines. When it had considered adjuvant pharmacological treatment of motor symptoms (section 6.2) the GDG was keen to discourage the use of anticholinergics – as, in that context, it agreed that the known harms outweighed the possible benefits – and had therefore made a 'do not offer' recommendation. In the context of management of drooling, the GDG agreed that the balance of benefits and harms may be somewhat different, especially as there are fewer convenient alternative medicines and 1 option in the class that had been shown to be effective, glycopyrrolate, is believed to have fewer central nervous system side-effects, as it is not centrally acting. Therefore, the GDG agreed that, where an anticholinergic medicine is prescribed for patients with Parkinson's disease, glycopyrrolate was the preferred choice, and other anticholinergics should only be considered if prescribers are confident that the patient is very unlikely to experience exacerbated non-motor symptoms as an adverse effect. The GDG was aware that some prescribers advocate sublingual administration of anticholinergic medicines – most commonly, atropine – on the hypothesis that locally delivered medicine is less likely to have CNS effects than an oral formulation. However, no evidence was identified as part of the review to substantiate this view, and GDG members reported personal experience of conspicuous exacerbation of cognitive and psychotic symptoms in people who had received only a few drops of a centrally acting anticholinergic agent. For this reason, the GDG chose not to make any recommendation in favour of sublingual anticholinergics, although it noted that this may be a reasonable route of administration for anyone in whom prescribers would also be confident to offer a centrally acting anticholinergic orally. The GDG discussed circumstances in which the use of any anticholinergic

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	medication, including glycopyrrolate, should not be considered due to the side-effect profile. This would include people with Parkinson's disease who have significant cognitive decline, who are experiencing hallucinations or who have a history of side-effects with anticholinergic treatment. In these people, the potential harms of treatment with anticholinergics are likely to outweigh the benefits, so it would be appropriate to use botulinum toxin as first-line treatment.
Economic considerations	No economic evidence was identified for this review question, and economic modelling was not prioritised. Unit costs of interventions were considered by the GDG, and the costs of the interventions were generally low. As the number of individuals requiring these interventions is small, the economic impact of selecting a particular intervention is likely to be minimal. Where the first choice treatment has not worked or is considered clinically inappropriate (for example due to the side-effect profile), botulinum toxin was considered to be a possible option; health benefits shown by the clinical review were thought to justify its acquisition and administration cost.
Quality of evidence	The quality of the evidence varied from very low to moderate. The majority of the evidence was from indirect populations and all of the outcomes were downgraded by 1 increment accordingly. This is the same approach as adopted in the motor neurone disease guideline, though in this case studies were downgraded for indirectness if they were not in a population of people with Parkinson's disease, as opposed to nbot being in a population of people with motor neurone disease. The outcomes for the indirect evidence of botulinum toxin versus placebo ranged from very low to moderate quality. In addition to indirectness, some outcomes were downgraded for risk of bias and/or imprecision. All other outcomes for the other 3 comparisons (botulinum toxin versus no treatment, glycopyrrolate versus placebo and benztropine versus placebo) were consistently graded low (1 outcome) or very low (7 outcomes). In addition to indirectness, some outcomes were downgraded for risk of bias and/or imprecision and/or inconsistency. The GDG agreed that, given its reliance on group members' own experience in the absence of high-quality evidence, it would not be appropriate to make directive ('offer') recommendations in this area. Therefore, all recommendations suggest that prescribers should consider the available options in the context of potential benefits and harms for individual patients.
Other considerations	The GDG recognised that problems related to saliva can be significant and distressing for people with Parkinson's disease. The GDG highlighted that the relationship between saliva management, swallowing difficulties and respiratory impairment is complex and requires careful assessment by an appropriately trained MDT. The GDG agreed that the appropriate first-line management for drooling of saliva was non-pharmacological, and would involve a referral to speech and language therapy services. Only if such non-pharmacological management is unavailable or not effective should pharmacological management be considered and they made a recommendation to reflect this. The GDG noted that, where prescribed medicine is used, the formulation may need to be considered: liquid preparations or transdermal patches could be appropriate if swallowing difficulties cause adherence problems with oral tablets. The GDG noted that botulinum toxin is not available in all areas and required referral to a specialist service, and therefore is often more difficult to access than other treatment alternatives.

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7.8.5 Recommendations

52. Only consider pharmacological management for drooling of saliva in people with Parkinson's disease if non-pharmacological management (for example, speech

and language therapy; see recommendation 64) is not available or has not been effective. [new 2017]

53. **Consider glycopyrrolate[f] to manage drooling of saliva in people with Parkinson's disease if non-pharmacological management is not available or has not been effective. [new 2017]**

54. **If treatment for drooling of saliva with glycopyrrolate is not effective, not tolerated or contraindicated (for example, in people with cognitive decline, hallucinations or delusions, or a history of adverse effects following anticholinergic treatment), consider referral to a specialist service for Botulinum toxin A[f]. [new 2017]**

55. **Only consider anticholinergic medicines other than glycopyrrolate to manage drooling of saliva in people with Parkinson's disease if their risk of cognitive adverse effects is thought to be minimal. [new 2017]**

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[f] At the time of consultation (October 2016), these medicines did not have a UK marketing authorisation for this indication. The prescriber should follow relevant professional guidance, taking full responsibility for the decision. Informed consent should be obtained and documented. See the General Medical Council's Prescribing guidance: prescribing unlicensed medicines for further information.

8 Pharmacological management of dementia associated with Parkinson's disease

Parkinson's disease is a neurodegenerative condition characterised by deficiency of neurotransmitters within the brain. Lack of dopamine leads to an impaired quality of movement, and low levels of other neurotransmitters can cause development of associated non-motor symptoms, such as serotonergic deficiency associated with depression and loss of cholinergic stimulation causing progressive cognitive impairment. If this develops to the point where the patient, and/or their carer, reports a significant loss of global cognitive function, they are diagnosed as having dementia with Parkinson's disease (PDD).

Dementia (the progressive loss of global cognitive function) is common in Parkinson's disease; 48% to 80% of people may develop dementia at some point in their condition. Traditionally, dementia developing more than 1 year after the onset of the motor symptoms of Parkinson's disease is referred to as Parkinson's disease dementia (PDD). Dementia developing within 1 year of the onset of motor symptoms is referred to as dementia with Lewy bodies (DLB).

The relationship between PDD and DLB is unclear, but they have many common clinical features and some are of the opinion that they may be the same condition. Therefore, the GDG agreed that the population included in this review question should cover people with PDD and DLB. Studies that included people with mild cognitive impairment were excluded.

Update 2017

8.1 Pharmacological management of Parkinson's disease dementia

8.1.1 Introduction

What is the comparative effectiveness of donepezil, galantamine, memantine and rivastigmine for cognitive enhancement in dementia associated with Parkinson's disease?

The aim of this review question was to assess the comparative efficacy of pharmacological interventions for cognitive enhancement in dementia associated with Parkinson's disease, compared with placebo or other active comparator(s). This updates the evidence reviews on:

- Cholinesterase inhibitors for cognitive enhancement in Parkinson's disease from the 2006 guideline on Parkinson's disease (CG35).
- Cholinesterase inhibitors or memantine for the treatment of cognitive symptoms of Dementia with Lewy bodies from the 2006 guideline on Dementia (CG42).
- Cholinesterase inhibitors or memantine for the treatment of non-cognitive symptoms of dementia with Lewy bodies from the 2006 guideline on Dementia (CG42).

This updated review incorporates some studies that were included in the previous guidelines together with newly published evidence.

The review focused on identifying studies that fulfilled the conditions specified in Table 15.

Table 15: PICO table for effectiveness of pharmacological interventions compared with placebo or other active comparator(s) for cognitive enhancement in dementia associated with Parkinson's disease

Population	People with a diagnosis of PDD or DLB
Interventions	• Donepezil • Galantamine • Memantine • Rivastigmine[1] • Memantine plus cholinesterase inhibitor
Comparators	• Placebo • Each other • Combination of memantine plus cholinesterase inhibitor
Outcomes	• Cognitive outcomes, including: ○ Mini Mental State Examination (MMSE) ○ Alzheimer's Disease Assessment Scale – cognitive subscale (ADAS-cog) ○ Montreal Cognitive Assessment (MoCA) • Global outcomes, including: ○ Unified Parkinson's Disease Rating Scale (UPDRS) ○ Global impression of change • Activities of daily living (ADL), including: ○ Unified Parkinson's Disease Rating Scale – activities of daily living scale (UPDRS-ADL) ○ Measures used in DLB research (including those derived from Alzheimer's disease measures) • Other non-cognitive outcomes, including: ○ Neuropsychiatric outcomes, such as the Neuropsychiatric Inventory (NPI) ○ Motor symptoms, such as tremor and rigidity • Adverse events, such as hallucinations • Study withdrawal

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

[1] *Rivastigmine capsules are currently the only intervention that is licensed for mild to moderate dementia in Parkinson's disease*

For full details of the review protocol, please see Appendix C. Randomised controlled trials (RCTs) were considered to be the most appropriate study design to derive treatment effect metrics, and were therefore considered to be the highest quality within a GRADE framework. All other study designs were excluded from this review, including case–control studies, cohort studies, and case reports.

8.1.2 Evidence review

A systematic search of the literature was conducted (see appendix I) which identified 1,152 references. This search was restricted to studies published from 2005 onwards to avoid duplicates of studies considered in the previous Parkinson's disease guideline (CG35). After removing duplicates the references were screened on their titles and abstracts and full papers of 130 references were obtained and reviewed against the inclusion and exclusion criteria in the review protocol (see appendix C).

Overall, 121 studies were excluded as they did not meet the eligibility criteria, such as not utilising a randomised-control design. The 9 remaining published papers met the eligibility criteria and were included in the review. A list of excluded studies and reasons for their exclusion is provided in appendix G.

Five RCTs included in previous guidelines on Parkinson's disease (CG35) and Dementia (CG42) were reviewed. Of these, 2 RCTs were already included from the search (McKeith et al., 2000, Ravina et al., 2005) and 2 RCTs (Aarsland et al., 2002; Emre et al., 2004) met the present inclusion and exclusion criteria and were included. The remaining RCT (Leroi et al., 2004) was excluded as people in the study had mild cognitive impairment associated with Parkinson's disease.

Systematic reviews identified in the literature search were also analysed to identify any published papers meeting the eligibility criteria that had not been identified in the search. No further studies were identified. Furthermore, no additional new papers were identified through rerun searches at the end of the guideline. Therefore, a total of 11 RCTs were included in the evidence review.

Evidence tables for included studies can be found in Appendix D, with GRADE profiles reported in Appendix E.

8.1.3 Description of included studies

See Table 16 for a summary of included studies.

Pharmacological interventions in PDD

4 double-blind placebo-controlled RCTs (reported in 5 publications) assessed the effectiveness of a cholinesterase inhibitor in people with PDD:

- donepezil (Aarsland et al., 2002, Dubois et al., 2012, Ravina et al., 2005)
- rivastigmine (Emre et al., 2004, Dujardin et al., 2006 [secondary publication]).

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1 open-label RCT (Emre et al., 2014) assessed the effectiveness of rivastigmine capsules compared with rivastigmine patches in people with PDD.

2 double-blind placebo-controlled RCTs, reported in 3 publications (Emre et al., 2010; Leroi et al., 2009, Leroi et al., 2014 [secondary publication]) assessed the effectiveness of memantine in people with PDD.

No studies assessed the effectiveness of a combination of cholinesterase inhibitor plus memantine in people with PDD.

Pharmacological interventions in DLB

3 double-blind placebo-controlled RCTs assessed the effectiveness of a cholinesterase inhibitor in people with DLB:

- donepezil (Ikeda et al., 2015, Mori et al., 2012)
- rivastigmine (McKeith et al., 2000).

1 double-blind placebo-controlled RCT (Emre et al., 2010) assessed the effectiveness of memantine in people with DLB.

No studies assessed the effectiveness of a combination of cholinesterase inhibitor plus memantine in people with DLB.

Mixed population (PDD or DLB)

1 double-blind placebo-controlled RCT assessed the effectiveness of memantine in a mixed population of people with PDD or DLB (Aarsland et al., 2009).

Prioritisation of outcomes

A large number of outcomes were reported in the studies, particularly those measuring cognitive function. Some outcomes were reported frequently (for example, MMSE) while others were reported only in a single small RCT. Therefore, the Committee prioritised some key critical outcomes for the analyses.

Key critical outcomes prioritised by the Committee were:

- Adverse events
- Cognitive function, measured by:
  - Mini Mental State Examination (MMSE)
  - Alzheimer's Disease Assessment Scale – cognitive subscale (ADAS-cog)
  - Mattis Dementia Rating Scale (MDRS)
  - Delis-Kaplan Executive Functions System verbal fluency test (D-KEFS)
  - 10-point clock drawing test
  - Cognitive Drug Research computerised assessment system (CDR)
  - Brief test of attention (BTA)
- Global assessment
- Activities of daily living
- Carer-reported outcomes
- Other non-cognitive outcomes, including
  - Neuropsychiatric Inventory (NPI)
  - Unified Parkinson's Disease Rating Scale – motor subscale (UPDRS III)

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Analyses

The following analyses were conducted:

- pharmacological interventions in people with PDD:
  - cholinesterase inhibitors versus placebo
  - memantine versus placebo
  - rivastigmine patches versus capsules
- pharmacological interventions in people with DLB:
  - cholinesterase inhibitors versus placebo
  - memantine versus placebo
- combined analyses – pharmacological interventions in a mixed population (PDD or DLB)
  - cholinesterase inhibitors versus placebo
  - memantine versus placebo
  - network meta-analyses of pharmacological interventions versus placebo

The combined analyses were only carried out for outcomes when data were available for both PDD and DLB populations.

For studies which had more than one active treatment arm, for example different doses, the active treatment arms were combined together to give an overall effect.

Studies were pooled where possible. Not all studies presented adequate data to be included in the meta-analyses; this is reported in the GRADE table footnotes. Mean differences (MDs) were calculated for continuous outcomes and rate ratios (RRs) for dichotomous outcomes, as well as the corresponding 95% confidence intervals (CIs), where sufficient data were available. For some outcomes, when different measures were used for the same outcome, data were analysed using a standardised mean difference.

Data were analysed with fixed effects models. Where there was potentially moderate or substantial heterogeneity between studies ($I^2 \geq 40\%$ for pairwise meta-analysis and $I^2 \geq 50\%$ for NMA), analysis with random effects models was conducted.

The evidence across outcomes was appraised using the GRADE framework and forest plots are presented where appropriate (see appendix E).

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Table 16: Summary of included studies

Study	Population	Intervention	Comparison	Prioritised outcomes
Parkinson's disease dementia (PDD)				
Aarsland et al. (2002)	People aged 45–95 years with cognitive impairment associated with Parkinson's disease (MMSE score 16 to 26 inclusive [mean 20.8])	Donepezil 5mg daily, increased to 10mg daily after 6 weeks if well tolerated	Placebo	• Adverse events • Cognitive outcome: MMSE • Global outcome: CIBIC+ • Non-cognitive outcomes: NPI, UPDRS III
Dubois et al. (2012)	People aged 40 years and older with PDD (MMSE score 10 to 26 inclusive [mean 21.4])	Donepezil 5mg or 10mg daily	Placebo	• Adverse events • Cognitive outcomes: ADAS-cog, MMSE, D-KEFS verbal fluency test, BTA • Global outcomes: CIBIC+ • ADL: DAD • Non-cognitive outcomes: NPI, UPDRS III
Emre et al. (2004)	People aged at least 50 years old with PDD (MMSE 10 to 24 [mean 19.3])	Rivastigmine 1.5mg twice daily, increasing to a maximum well tolerated dose (up to 6mg twice daily)	Placebo	• Adverse events • Cognitive outcomes: ADAS-cog, MMSE, D-KEFS verbal fluency test, CDR, 10-point clock drawing test • Global outcome: ADCS-CGIC • ADL: ADCS-ADL • Non-cognitive outcomes: NPI, UPDRS III
Emre et al. (2010)[1]	People aged 50 years and older with PDD (MMSE score 10 to 24 inclusive [mean 21.1])	Memantine 5mg daily, increasing to a maintenance dose of 20mg daily	Placebo	• Adverse events • Global outcome: ADCS-CGIC • ADL: ADCS-ADL • Non-cognitive outcomes: NPI, UPDRS III • Carer-reported outcome: ZBI
Emre et al. (2014)	People aged 50 to 85 years with PDD (MMSE score 10 to 26 inclusive [mean 20.9])	Rivastigmine 4.6mg/24h patch, increasing to 9.5mg/24h patch	Rivastigmine 1.5mg twice daily, increasing to a maximum well tolerated dose (up to 6mg twice daily)	• Adverse events • Cognitive outcome: MDRS • ADL: ADCS-ADL • Non-cognitive outcome: NPI

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Study	Population	Intervention	Comparison	Prioritised outcomes
Leroi et al. (2009)	People with PDD (MMSE score 10 to 27 [mean 19.1])	Memantine 20mg daily	Placebo	• Adverse events • Cognitive outcomes: MMSE, DRS • Global outcome: CIBIC+ • Non-cognitive outcomes: NPI, UPDRS III
Ravina et al. (2005)	People aged 40 years and older with PDD (MMSE score 17 to 26 inclusive [mean 22.2])	Donepezil 5mg daily or 5mg twice daily	Placebo	• Adverse events • Cognitive outcomes: ADAS-cog, MMSE, MDRS • Global outcomes: CGIC, UPDRS (total score) • Non-cognitive outcomes: UPDRS III
Dementia with Lewy bodies (DLB)				
Emre et al. (2010)[1]	People aged 50 years and older with DLB (MMSE score 10 to 24 inclusive [mean 20.4])	Memantine 5mg daily, increasing to a maintenance dose of 20mg daily	Placebo	• Adverse events • Global outcome: ADCS-CGIC • ADL: ADCS-ADL • Non-cognitive outcomes: NPI, UPDRS III • Carer reported outcome: ZBI
McKeith et al. (2000)	People with DLB (MMSE score over 9 [mean 17.9])	Rivastigmine 1.5mg twice daily, increasing to a maximum well tolerated dose (up to 6mg twice daily)	Placebo	• Adverse events • Cognitive outcome: MMSE • Global outcome: CGC+ • Non-cognitive outcomes: NPI, UPDRS III
Ikeda et al. (2015)	People aged 50 years and older with DLB (MMSE score 10 to 26 inclusive [mean 20.4])	Donepezil 5mg or 10mg daily	Placebo	• Adverse events • Cognitive outcome: MMSE • Global outcome: CIBIC+ • Non-cognitive outcomes: NPI, UPDRS III • Carer-reported outcome: ZBI
Mori et al. (2012)	People aged 50 years and older with DLB (MMSE score 10 to 26 inclusive [mean 19.6])	Donepezil 3mg, 5mg or 10mg daily	Placebo	• Adverse events • Cognitive outcome: MMSE • Global outcome: CIBIC+ • Non-cognitive outcomes: NPI, UPDRS III

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Study	Population	Intervention	Comparison	Prioritised outcomes
				• Carer-reported outcome: ZBI
Mixed population (PDD or DLB)				
Aarsland et al. (2009)	People with PDD or DLB (MMSE score 12 or above [mean 20.0])	Memantine 5mg daily, increasing to a maintenance dose of 10mg twice daily	Placebo	• Adverse events • Cognitive outcomes: MMSE • Global outcome: CGIC • ADL: DAD • Non-cognitive outcomes: NPI, UPDRS III

[1] *Study included people with PDD and DLB; data for PDD, DLB and the mixed population was presented separately in the paper*

ADAS-cog; Alzheimer's Disease Assessment Scale – cognitive subscale
ADCS-ADL; Alzheimer's Disease Assessment Scale – Activities of Daily Living subscale
ADCS-CGIC; Alzheimer's disease Cooperation Study – Clinical Global Impression of Change
ADL; Activities of daily living
BTA; Brief test of attention
CDR; Cognitive Drug research computerised assessment system
CGC-plus; Clinical Global Change-plus
CGIC; Clinical Global Impression of change
CIBIC+; Clinician's interview based impression of change
DAD; Disability assessment for dementia
D-KEFS; Delis-Kaplan Executive Functions System
MDRS; Mattis Dementia Rating Scale
MMSE; Mini Mental State Examination
NPI; Neuropsychiatric Inventory
UPDRS; Unified Parkinson's Disease Rating Scale
ZBI; Zarit caregiver Burden Interview

Update 2017

8.1.4 Health economic evidence

Literature searches were undertaken to find any existing cost–utility analyses (CUAs) assessing pharmacological interventions for cognitive enhancement in dementia associated with Parkinson's disease. In total, 344 articles were returned, of which 2 were selected as potentially relevant and retrieved for full text review. Both were included. Studies were assessed using the quality appraisal criteria as outlined in the NICE guidelines manual (NICE, 2012).

Willan et al. (2006) compared rivastigmine with placebo in people with mild PDD (MMSE 20–24), based on evidence from the EXPRESS RCT (Emre et al. 2004). The analysis concentrated solely on short-term cognitive effect, as measured by MMSE at 24 weeks, which was translated to health-related quality of life (EQ-5D) using a mapping function based on a Scandinavian population with Alzheimer's disease (Jönsson, 2003). The authors' base case adopted a broad societal perspective, including an attempt to value caregiver time; however, disaggregated results are reported, enabling the recalculation of results with a perspective that is consistent with the NICE reference case (that is, NHS and PSS costs only). This suggests that rivastigmine is associated with an ICER of around £58,600 per QALY gained. However, this analysis comes from a time when rivastigmine was only available as a proprietary product; since then, it has become available generically and costs have decreased substantially. Therefore, to approximate the results of this CUA from a present-day perspective, the developer recalculated results by:

- removing costs borne by patients and caregivers;
- re-estimating rivastigmine drug cost, assuming the overall change is proportional to the change in price of a 28 x 3 mg pack (£2004=£34.02 [BNF 47]; £2016=£2.57 [NHS Drug Tariff Feb 2016]; reduction of 92.4%);
- inflating all other costs from £2004/05 to £2015/16 using PSSRU hospital & community health services inflators.

This analysis estimated an ICER of approximately £16,000 per QALY gained.

Gustavsson et al. (2009) simulated a population with DLB (from which people with PDD were explicitly excluded) receiving unspecified cholinesterase inhibitors. The authors drew treatment effects from a UK observational audit for the first 4 months, and extrapolated these to 5 years using a Scandinavian longitudinal study in Alzheimer's disease (Wallin et al., 2007). Additional non-cognitive symptoms (extra-pyramidal symptoms and psychosis) were assumed for DLB. The authors used 3 separate models, and compared results. The first was a reconstruction of the Southampton Alzheimer's disease model (Loveman et al., 2006); the second was a micro-simulation model; and the third was a Markov model with 4 discrete MMSE states. When applied to people with all severities of dementia, ICERs of between £2,700 and £46,800 per QALY were estimated; when the population was limited to people with moderate dementia (MMSE 10–20), cholinesterase inhibitors were dominant in all 3 models (that is, they were predicted to save money and improve health). Again, it was possible to estimate present-day results for these analyses, by:

- re-estimating cholinesterase inhibitor drug costs, assuming the original model used the cost of donepezil 10 mg daily and assumed 2 monitoring visits per year, and that the overall change in drug costs is proportional to the change in price of a 28 x 10 mg pack of donepezil (£2005=£89.06 [BNF 49]; £2016=£1.45 [NHS Drug Tariff Feb 2016]; reduction of 98.4%);
- inflating all other costs from £2005/06 to £2015/16 using PSSRU hospital & community health services inflators

This recalculation estimated that treatment with cholinesterase inhibitors is less costly and more effective than placebo in all analyses, regardless of population modelled or model preferred.

Update 2017

8.1.5 Evidence statements – Parkinson's disease dementia

8.1.5.1 Adverse events

Cholinesterase inhibitors

High-quality evidence from 4 RCTs suggests that, compared with placebo, cholinesterase inhibitors significantly increase the risk of any adverse events (RR=1.12, 95%CI 1.04 to 1.21).

Low- to moderate-quality evidence from 2 RCTs could not differentiate the risk of serious adverse events between cholinesterase inhibitors and placebo (RR=1.13, 95%CI 0.82 to 1.54).

High-quality evidence from 3 RCTs suggests that, compared with placebo, cholinesterase inhibitors significantly increase the risk of study withdrawal due to adverse events (RR=1.76, 95%CI 1.23 to 2.53).

High-quality evidence from 2 RCTs suggests that, compared with placebo, cholinesterase inhibitors significantly reduce the risk of hallucinations (RR=0.54, 95%CI 0.34 to 0.86).

Low-quality evidence from 1 RCT could not differentiate the risk of any adverse events, serious adverse events, study withdrawal due to adverse events or hallucinations between rivastigmine patches and rivastigmine capsules.

Memantine

Low-to-moderate-quality evidence from 2 RCTs could not differentiate the risk of any adverse events, serious adverse events or study withdrawal due to adverse events between memantine and placebo.

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8.1.5.2 Cognitive function

Cholinesterase inhibitors

High-quality evidence from 4 RCTs suggests that, compared with placebo, cholinesterase inhibitors significantly improve cognitive function as assessed by the MMSE (MD=1.36, 95%CI 0.95 to 1.77).

High-quality evidence from 3 RCTs suggests that, compared with placebo, cholinesterase inhibitors significantly improve cognitive function as assessed by ADAS-cog (MD=−2.28, 95%CI −3.40 to −1.15).

Low-quality evidence from 1 RCT could not differentiate the effect on cognitive function between rivastigmine patches and rivastigmine capsules at 24 weeks, as assessed by the MDRS total score, but there was a significant benefit for rivastigmine capsules at 76 weeks (moderate-quality) (MD=−5.30, 95%CI −8.17 to −2.43).

Memantine

Low-to-moderate quality evidence from 1 RCT could not differentiate the effect on cognitive function between memantine and placebo, as assessed by the MMSE and by the 10-point clock drawing test.

8.1.5.3 Global assessment

Cholinesterase inhibitors

High-quality evidence from 4 RCTs suggests that, compared with placebo, cholinesterase inhibitors significantly improve global function as assessed by different measures (SMD=−0.30, 95%CI −0.42 to −0.17).

High-quality evidence from 3 RCTs suggests that, compared with placebo, cholinesterase inhibitors significantly improve global response as assessed by different measures of at least minimal improvement (RR=1.24, 95%CI 1.05 to 1.47).

Memantine

Moderate-quality evidence from 1 RCT could not differentiate the effect on global function between memantine and placebo, as assessed by ADCS-CGIC (MD=−0.20, 95%CI −0.69 to 0.29).

Low-quality evidence from 1 RCT could not differentiate the effect on global response between memantine and placebo, as assessed by at least minimal improvement in CIBIC+ (RR=1.40, 95%CI 0.64 to 3.08).

8.1.5.4 Activities of daily living

Cholinesterase inhibitors

Update 2017

High-quality evidence from 2 RCTs suggests that, compared with placebo, cholinesterase inhibitors significantly improve activities of daily living as assessed by different ADL measures (SMD=0.18, 95%CI 0.05 to 0.31).

Low quality evidence from 1 RCT could not differentiate the effect on activities of daily living between rivastigmine patches and rivastigmine capsules at 24 weeks, as assessed by ADCS-ADL, but there was a significant benefit for rivastigmine capsules at 76 weeks (moderate-quality) (MD=−3.40, 95%CI −5.84 to −0.96).

Memantine

Moderate-quality evidence from 1 RCT could not differentiate the effect on activities of daily living between memantine and placebo, as assessed by ADCS-ADL (MD=0.80, 95%CI −3.22 to 4.82).

8.1.5.5 Carer-reported outcomes

Cholinesterase inhibitors

No evidence was identified.

Memantine

Moderate-quality evidence from 2 RCTs could not differentiate the effect on carer burden between memantine and placebo, as assessed by the Zarit caregiver burden interview (MD=−3.40, 95%CI −7.21 to 0.42).

8.1.5.6 Other non-cognitive outcomes

Cholinesterase inhibitors

High-quality evidence from 2 RCTs suggests that, compared with placebo, cholinesterase inhibitors significantly improve neuropsychiatric symptoms as assessed by the NPI-10 item score (MD=−1.67, 95%CI −3.01 to −0.32).

Low-quality evidence from 1 RCT could not differentiate the effect on neuropsychiatric symptoms between rivastigmine patches and rivastigmine capsules at 24 weeks, as assessed by the NPI-10 item score, but there was a significant benefit for rivastigmine patches at 76 weeks (moderate-quality) (MD=−2.30, 95%CI −4.30 to −0.30).

Low-quality evidence from 2 RCTs could not differentiate the effect on motor symptoms between donepezil and placebo, as assessed by UPDRS III (MD=−1.50, 95%CI −7.87 to 4.87).

Moderate-quality evidence from 1 RCT could not differentiate the effect on motor symptoms between rivastigmine patches and rivastigmine capsules, as assessed by UPDRS III (MD=0.00, 95%CI −2.04 to 2.04).

Memantine

Moderate-quality evidence from 2 RCTs could not differentiate the effect on neuropsychiatric symptoms (NPI-10 item or NPI-12 item scores) or motor symptoms (UPDRS III) between memantine and placebo.

8.1.5.7 Economic evidence statements

One partially applicable cost–utility analysis with very serious limitations explored proprietarily-priced rivastigmine for the treatment of PDD. It concluded that rivastigmine is likely to improve quality-adjusted life expectation and may reduce overall costs. However, when an NHS and PSS perspective is adopted, rivastigmine is no longer cost-saving, with an ICER of £58,600/QALY. An approximation to 2016 costs suggests that, now generic rivastigmine is available at lower cost, it would be associated with an ICER of around £16,000/QALY.

8.1.6 Evidence statements – Dementia with Lewy bodies

8.1.6.1 Adverse events

Cholinesterase inhibitors

Moderate-quality evidence from 3 RCTs could not differentiate the risk of any adverse events, serious adverse events or adverse events requiring treatment withdrawal between cholinesterase inhibitors and placebo.

Memantine

Moderate-quality evidence from 1 RCT could not differentiate the risk of any adverse events, serious adverse events or adverse events requiring treatment withdrawal between memantine and placebo.

Update 2017

8.1.6.2 Cognitive function

Cholinesterase inhibitors

Moderate-quality evidence from 3 RCTs suggests that, compared with placebo, cholinesterase inhibitors significantly improve cognitive function as assessed by the MMSE (MD=1.77, 95%CI 1.06 to 2.47).

Memantine

Moderate-quality evidence from 1 RCT could not differentiate the effect on cognitive function between memantine and placebo, as assessed by the 10-point clock drawing test (MD=1.30, 95%CI −0.51 to 3.11).

8.1.6.3 Global assessment

Cholinesterase inhibitors

High-quality evidence from 1 RCT suggests that, compared with placebo, donepezil significantly improves global response as assessed by CIBIC+ (MD=−1.17, 95%CI −1.66 to −0.68).

High-quality evidence from 1 RCT suggests that, compared with placebo, donepezil significantly improves global response as assessed by at least minimal improvement in CIBIC+ (RR=2.04, 95%CI 1.21 to 3.46).

Memantine

Moderate-quality evidence from 1 RCT could not differentiate the effect on global response between memantine and placebo, as assessed by ADCS-CGIC (MD=−0.60, 95%CI −1.22 to 0.02).

Update 2017

8.1.6.4 Activities of daily living

Cholinesterase inhibitors

No evidence was identified.

Memantine

Moderate-quality evidence from 1 RCT could not differentiate the effect on activities of daily living between memantine and placebo, as assessed by ADCS-ADL (MD=1.60, 95%CI −4.90 to 8.10).

8.1.6.5 Carer-reported outcomes

Cholinesterase inhibitors

High-quality evidence from 2 RCTs suggests that, compared with placebo, donepezil significantly improves carer burden as assessed by the Zarit caregiver burden interview (MD=−4.49, 95%CI −7.64 to −1.34).

Memantine

Moderate-quality evidence from 1 RCT could not differentiate the effect on carer burden between memantine and placebo, as assessed by the Zarit caregiver burden interview (MD=−1.40, 95%CI −6.66 to 3.86).

8.1.6.6 Other non-cognitive outcomes

Cholinesterase inhibitors

Low-quality evidence from 3 RCTs could not differentiate the effect on neuropsychiatric symptoms between cholinesterase inhibitors and placebo, as assessed by the NPI-10 item score (MD=−2.06, 95%CI −7.15 to 3.02).

High-quality evidence from 2 RCTs suggests that, compared with placebo, cholinesterase inhibitors significantly improve neuropsychiatric symptoms (hallucinations, delusions, dysphoria and apathy) as assessed by the NPI-4 item score (MD=−2.49, 95%CI −4.64 to −0.33).

Low-quality evidence from 2 RCTs could not differentiate the effect on neuropsychiatric symptoms (hallucinations, cognitive fluctuation) between donepezil and placebo, as assessed by the NPI-2 item score (MD=−2.30, 95%CI −6.32 to 1.72).

Moderate-quality evidence from 2 RCTs could not differentiate the effect on motor symptoms between cholinesterase inhibitors and placebo, as assessed by UPDRS III (MD=−0.67, 95%CI −2.08 to 0.73).

Memantine

Moderate-quality evidence from 1 RCT could not differentiate the effect on neuropsychiatric symptoms between memantine and placebo, as assessed by the NPI-12 item score (MD=−6.00, 95%CI −12.23 to 0.23).

Moderate-quality evidence from 1 RCT could not differentiate the effect on motor symptoms between memantine and placebo, as assessed by UPDRS III (MD=−1.40, 95%CI −5.52 to 2.72).

8.1.6.7 Economic evidence statements

One partially applicable cost–utility analysis with very serious limitations used multiple models to assess treatment of DLB with unspecified, proprietarily-priced cholinesterase inhibitors compared with none. It concluded that, in all people with DLB, cholinesterase inhibitors improve QALYs at increased cost, with ICERs ranging from £2,700 to £46,800, depending on modelling assumptions. In a subgroup of people with moderate DLB, cholinesterase inhibitors were found to be cost-saving. An approximation to 2016 costs suggests that, now generic cholinesterase inhibitors are available at lower cost, treatment would be dominant in all models and all populations. The study undertook no exploration of uncertainty.

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8.1.7 Evidence statements – mixed population (PDD or DLB)

8.1.7.1 Adverse events

Cholinesterase inhibitors

High-quality evidence from 7 RCTs suggests that, compared with placebo, cholinesterase inhibitors significantly increase the risk of any adverse events (RR=1.12, 95%CI 1.05 to 1.19).

Moderate-quality evidence from 5 RCTs could not differentiate the risk of serious adverse events between cholinesterase inhibitors and placebo (RR=1.10, 95%CI 0.83 to 1.45).

High-quality evidence from 6 RCTs suggests that, compared with placebo, cholinesterase inhibitors significantly increase the risk of adverse events requiring treatment withdrawal (RR=1.50, 95%CI 1.10 to 2.04).

Memantine

Low- to moderate-quality evidence from 2 RCTs could not differentiate the risk of any adverse events, serious adverse events or study withdrawal due to adverse events.

8.1.7.2 Cognitive function

Cholinesterase inhibitors

High-quality evidence from 8 RCTs suggests that, compared with placebo, cholinesterase inhibitors significantly improve cognitive function as assessed by the MMSE (MD=1.46, 95%CI 1.11 to 1.82).

Memantine

Low-quality evidence from 2 RCTs could not differentiate the effect on cognitive function between memantine and placebo, as assessed by the MMSE (MD=1.56, 95%CI −0.17 to 3.28).

8.1.7.3 Global assessment

Cholinesterase inhibitors

Moderate-quality evidence from 5 RCTs suggests that, compared with placebo, cholinesterase inhibitors significantly improve global function as assessed by different measures (SMD=−0.48, 95%CI −0.76 to −0.21).

High-quality evidence from 4 RCTs suggests that, compared with placebo, cholinesterase inhibitors significantly improve global response as assessed by different measures of at least minimal improvement (RR=1.31, 95%CI 1.12 to 1.54).

Memantine

Moderate-quality evidence from 2 RCTs suggests that, compared with placebo, memantine significantly improves global function as assessed by different measures (SMD=−0.27, 95%CI −0.51 to −0.02).

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8.1.7.4 Activities of daily living

Cholinesterase inhibitors

Evidence not available in either PDD and DLB.

Memantine

Moderate-quality evidence from 2 RCTs could not differentiate the effect on activities of daily living between memantine and placebo, as assessed by different ADL measures (SMD=0.13, 95%CI −0.12 to 0.38).

8.1.7.5 Carer-reported outcomes

Cholinesterase inhibitors

Evidence not available in either PDD and DLB.

Memantine

Moderate-quality evidence from 2 RCTs could not differentiate the effect on carer burden between memantine and placebo, as assessed by the Zarit caregiver burden interview (MD=−2.69, 95%CI −5.99 to 0.60).

8.1.7.6 Other non-cognitive outcomes

Cholinesterase inhibitors

High-quality evidence from 5 RCTs suggests that, compared with placebo, cholinesterase inhibitors significantly improve neuropsychiatric symptoms as assessed by the NPI-10 item score (MD=−1.49, 95%CI −2.69 to −0.29).

Moderate-quality evidence from 4 RCTs could not differentiate the effect on motor symptoms between donepezil and placebo, as assessed by UPDRS III (MD=−0.71, 95%CI −2.09 to 0.66).

Memantine

Moderate-quality evidence from 3 RCTs could not differentiate the effect on neuropsychiatric symptoms between memantine and placebo, as assessed by the NPI-10 item or NPI-12 item scores (SMD=−0.16 95%CI −0.40 to 0.07).

High-quality evidence from 3 RCTs could not differentiate the effect on motor symptoms between memantine and placebo, as assessed by UPDRS III (MD=0.28, 95%CI −1.28 to 1.85).

8.1.7.7 Network meta-analyses

High-quality evidence from a network meta-analysis of 9 RCTs showed that cholinesterase inhibitors are associated with a significant increase in any adverse events, compared with placebo, but the data could not differentiate between memantine compared with placebo or cholinesterase inhibitors.

High-quality evidence from a network meta-analysis of 7 RCTs could not differentiate the rates of serious adverse events between any treatment alternative compared with placebo, or between cholinesterase inhibitors and memantine.

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High-quality evidence from a network meta-analysis of 8 RCTs showed that cholinesterase inhibitors are associated with a significant increase in treatment withdrawal due to adverse events, compared with placebo, but the data could not differentiate between memantine compared with placebo or cholinesterase inhibitors.

High-quality evidence from a network meta-analysis of 10 RCTs showed that cholinesterase inhibitors are associated with a significant improvement in cognitive function assessed by the MMSE, compared with placebo, but the data could not differentiate between memantine compared with placebo or cholinesterase inhibitors.

Moderate-quality evidence from a network meta-analysis of 7 RCTs showed that cholinesterase inhibitors are associated with a significant improvement in global function, compared with placebo, but the data could not differentiate between memantine compared with placebo or cholinesterase inhibitors.

High-quality evidence from a network meta-analysis of 8 RCTs showed that cholinesterase inhibitors are associated with a significant improvement in neuropsychiatric symptoms, compared with placebo, but the data could not differentiate between memantine compared with placebo or cholinesterase inhibitors.

Low-quality evidence from a network meta-analysis of 7 RCTs could not differentiate the effect on motor symptoms between any treatment alternative compared with placebo, or between cholinesterase inhibitors and memantine.

8.1.8 Evidence to recommendations

Relative value of different outcomes	Cognitive outcomes were critical to decision-making for this review question. Many different cognitive outcomes were reported in the studies; therefore the Committee prioritised those outcomes where more data were available to inform their decision-making. MMSE and ADAS-cog were the most frequently reported cognitive outcomes. However, it recognised the limitations of, for example, MMSE, as a measure of the effectiveness of medication. Frequently, clinicians may be looking for stability, rather than an actual improvement in cognitive function. The GDG also recognised that treatments for dementia may have important benefits in non-cognitive outcomes, such as global function, activities of daily living, carer burden and behavioural symptoms.
Trade-off between benefits and harms	The GDG highlighted the importance of clinicians being aware that cognitive impairment is common in people with Parkinson's disease. It is therefore essential that they routinely consider whether cognitive function is affecting the patient and to look out for signs which may help with decision-making. This can be done during conversations with the person and their family member or carer, and does not necessarily require an MMSE or other formal cognitive assessment. Some people can have troubling cognitive symptoms, which does not reflect in their MMSE score. The GDG was aware of variation in the provision of Parkinson's disease services with some designed to also assess and manage dementia, but many others do not. It was not able to make a recommendation about identifying cognitive impairment in people with Parkinson's disease, as this was not within the scope of this review question. However, the group did want to emphasise its importance to allow medication to be considered appropriately at the right time and right stage of disease. The GDG agreed that the evidence overall suggests that the effectiveness of pharmacological interventions is similar in people with PDD and DLB. This supports their original assertion about the similarity between these conditions, with diagnosis being dependent on an arbitrary measure of which symptoms present first. The effectiveness of these interventions also appears to be broadly consistent with the effects observed in Alzheimer's

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disease (AD). The GDG suspected that some of the early AD RCTs included a significant proportion of participants with DLB. Most RCTs ranged from 12 to 24 weeks, which the Committee recognised was a short duration for a long-term degenerative disease.

Cholinesterase inhibitors

Overall, evidence from the meta-analyses supported the GDG's view that there is a class effect for cholinesterase inhibitors. No significant differences were observed between donepezil and rivastigmine for any of the outcome measures. No evidence was identified for galantamine, although the GDG did not expect significant differences to be observed, compared with either donepezil or rivastigmine.

The GDG's experience suggests that donepezil is generally better tolerated than rivastigmine, although adverse effects are dose-related, usually appear quickly, and then subside quickly following treatment withdrawal. Rivastigmine is generally better in treating neuropsychiatric symptoms. This is also supported by trends observed in the evidence review, although possible differences observed did not reach conventional levels of statistical significance. Donepezil has a simpler dose titration regime, which may be an important consideration for individual patients. Rivastigmine also has an effect on gait and balance, although this has not been measured as part of this evidence review. The GDG was aware that rivastigmine has a higher licensed dose range in the US and rivastigmine capsules are currently the only product with a UK marketing authorisation for mild to moderate dementia associated with Parkinson's disease.

In clinical practice, there are some patients who respond very well to cholinesterase inhibitors and some that don't respond at all. The GDG recognised that monitoring and reviewing the effectiveness of medication is a difficult balance for clinicians. It was mindful that some people may stay on cholinesterase inhibitors indefinitely without appropriate review. The GDG also highlighted the challenges in assessing whether people who are not improving or getting worse despite treatment would be declining at a much greater rate without medication.

The GDG recognised that the evidence identified was in people with mild to moderate PDD. However, in their experience, some people with PDD present with the condition in the advanced stages. It was very concerned about the detrimental effects observed in many people in clinical practice when cholinesterase inhibitors were stopped. The GDG recognised this required careful discussion and consideration on a case-by-case basis, weighing up the possible risks and benefits of treatment. Previously, when cholinesterase inhibitors were not available as non-proprietary products, clinicians may have felt more pressure to discontinue medication that was no longer improving a person's symptoms.

Rivastigmine is commonly prescribed to treat hallucinations and this was supported by the evidence which showed a significant reduction in hallucinations, compared with placebo. The GDG was concerned that these people often bypass memory clinics and get lost within the system, but were not able to make a recommendation as this was outside the scope of this review question. The GDG agreed that it is important that treatment for hallucinations is integrated within the dementia care pathway.

The RCT (Emre et al., 2014) which compared rivastigmine patches with rivastigmine capsules found that the long-term (76-week) effect on cognitive function was significantly better with capsules. However, the GDG agreed that patient factors such as medicines adherence need to be considered on an individual patient basis. There were no other clinically meaningful differences between patches and capsules, including the risk of adverse effects. Therefore, the GDG could not make a recommendation specifically in relation to rivastigmine patches.

The GDG was confident that there is clear evidence of benefit with

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	cholinesterase inhibitors in improving cognition, global function, activities of daily living, carer burden and neuropsychiatric symptoms at a cost that is dominant over placebo. The GDG concluded that an 'offer' recommendation should be made so that all people with mild or moderate PDD and/or their carer have a conversation with a health professional about the risks and benefits of treatment. The GDG also agreed that the recommendation should inform clinicians that rivastigmine capsules are the only product licensed in the UK for mild to moderate dementia associated with Parkinson's disease. Furthermore, although no RCT evidence was identified, the GDG discussed and agreed by consensus that a consider recommendation should be made for cholinesterase inhibitors in people with severe PDD, to reflect their concerns about stopping treatment without appropriate review. In particular, they felt treatment should not be withdrawn from someone, solely as a result of them having progressed to what is defined as severe dementia. **Memantine** The GDG recognised that there were far less data for memantine versus placebo, compared with cholinesterase inhibitor versus placebo. Memantine was only significantly better than placebo on the global assessment scales. However, the GDG agreed that this was likely to be due to insufficient data being available which resulted in wide 95% confidence intervals. The trends were towards improvement and the network meta-analyses did not show that cholinesterase inhibitors were more effective than memantine for any outcomes measured. Although the available data were in people with mild to moderate PDD, the GDG had concerns about the possible detrimental effects of stopping treatment when people reach the severe stage of the disease. The GDG discussed and agreed that it should not discard a recommendation for memantine on the basis of the poor evidence-base. This is because, from clinical experience, the GDG has seen significant improvements in cognitive function in some people with PDD. The GDG therefore agreed that is was appropriate to make a 'consider' recommendation for memantine for people with PDD who are intolerant of, or have a contraindication to a cholinesterase inhibitor, based on clinical experience and the limited evidence that suggests a trend towards improvement with memantine. The recommendation to consider treatment with memantine applies to all people with PDD, regardless of the severity of the disease to reflect the GDG's concerns about stopping treatment without appropriate review. The GDG also agreed that the recommendation should highlight that memantine is not licensed for dementia associated with Parkinson's disease. In view of the lack of evidence on the effectiveness of memantine in people with PDD, the GDG agreed that this should be a research recommendation. **Combination treatment** Although no studies were identified where participants were randomised to combination treatment with a cholinesterase inhibitor and memantine, the GDG recognised that this option was being used in practice. From clinical experience, some people do respond to combination treatment. As there was no evidence, the GDG agreed this was an important priority for research and therefore made a research recommendation.
Trade-off between net health benefits and resource use	The GDG agreed that the economic evidence presented had very serious limitations, and lacked direct applicability to the question, particularly because they took place at a time before the generic versions of the drugs were available. However, it also noted that, once appropriate adjustments had been made to the price of the drugs, the fact that cholinesterase inhibitors came out as consistently either cost-effective or cost-saving compared with placebo added additional evidence to support the recommendations made.
Quality of	Based on the clear and consistent findings for cholinesterase inhibitors, the

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evidence	GDG were confident in making an 'offer' recommendation for people with mild to moderate PDD. The evidence-base for memantine was of lower quality and, despite the point estimate being in favour of memantine, the GDG could not be as confident of the effectiveness of memantine. Therefore a consider recommendation was made for memantine in situations where a cholinesterase inhibitor was not tolerated or contra-indicated.

8.1.9 Recommendations

56. Offer a cholinesterase inhibitor[g] for people with mild or moderate Parkinson's disease dementia. [new 2017]

57. Consider a cholinesterase inhibitor[h] for people with severe Parkinson's disease dementia. [new 2017]

58. Consider memantine[i] for people with Parkinson's disease dementia, only if cholinesterase inhibitors are not tolerated or are contraindicated. [new 2017]

59. For guidance on assessing and managing dementia, and supporting people living with dementia, see the NICE guideline on dementia[j]. [new 2017]

8.1.10 Research Recommendations

5. What is the effectiveness of memantine for people with Parkinson's disease dementia?

6. What is the effectiveness of combination treatment with a cholinesterase inhibitor and memantine for people with Parkinson's disease dementia if treatment with a cholinesterase inhibitor alone is not effective or no longer effective?

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Why this is important

The GDG felt that cholinesterase inhibitors, memantine, and combination therapy with both treatments are all reasonable clinical options, but noted that some people do not tolerate cholinesterase inhibitors well due to side effects. The evidence base for memantine was considerably weaker than for cholinesterase inhibitors, and therefore there would be value in either additional trials of memantine versus placebo (in people for whom cholinesterase inhibitors are not an option), or non-inferiority studies versus cholinesterase inhibitors. In clinical practice, memantine is often added to a cholinesterase inhibitor when it is no longer

[g] At the time of consultation (October 2016), rivastigmine capsules are the only treatment with a UK marketing authorisation for this indication. Use of donepezil, galantamine or rivastigmine patches for this indication would be off-label. The prescriber should follow relevant professional guidance, taking full responsibility for the decision. Informed consent should be obtained and documented. See the General Medical Council's Good practice in prescribing and managing medicines and devices for further information.

[h] At the time of consultation (October 2016), use of cholinesterase inhibitors for this indication would be off-label. The prescriber should follow relevant professional guidance, taking full responsibility for the decision. Informed consent should be obtained and documented. See the General Medical Council's Good practice in prescribing and managing medicines and devices for further information.

[i] At the time of consultation (October 2016), use of memantine for this indication would be off-label. The prescriber should follow relevant professional guidance, taking full responsibility for the decision. Informed consent should be obtained and documented. See the General Medical Council's Good practice in prescribing and managing medicines and devices for further information.

[j] The NICE guideline on dementia is being updated. It will include recommendations on the pharmacological management of dementia with Lewy bodies.

proving effective, but again there is no evidence base for this and randomised trials to establish if there is additional benefit would be valuable. Both of these questions could potentially be answered in a single study with three arms of memantine monotherapy, cholinesterase inhibitor monotherapy and combination treatment.

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9 Non-pharmacological management of motor and non-motor symptoms

Both motor and non-motor symptoms of Parkinson's affect activities of daily living and quality of life. Many of these cannot be improved by pharmacological intervention alone and many non-pharmaceutical interventions target specific problems. Postural instability, changes in posture and impaired gait are among the motor features that may become increasingly problematic as the condition progresses, and physiotherapy intervention can improve function and maintain independence. Gait problems may include reduced stride length as well as speed, festination and freezing, and intervention may include exercise, cueing and strategies.

Non motor symptoms include cognitive and mood dysfunction (e.g. anxiety, apathy, depression, mild cognitive impairment, and dementia), sleep disturbance, bladder and bowel dysfunction (usually constipation), speech and language changes and swallowing problems and weight loss.

While 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). A recent meta-analysis of 24 papers including 6,378 patients identified nocturia (59.7%), urinary urgency (54.6%), depression (51.7%), constipation (48.5%), anxiety (46.9%), forgetfulness (45.5%) and insomnia (44.7%) as the most prevalent symptoms.

Occupational therapy intervention can address activities of daily living and maintenance of independence, both at home and in the workplace or community. Non motor features of cognitive function and mood may also be addressed.

Speech and language therapy addresses speech intelligibility as well as ability to swallow, which is important in reducing the risk of aspiration. It also addresses the changes to communication stemming from cognitive-linguistic factors.

Dietary advice may be necessary and may include managing weight loss and protein redistribution to ensure efficacy of Parkinson's medication.

The clinical questions that have been addressed in this chapter are:

- Nurse specialist interventions: What is the effectiveness of Parkinson's disease nurse specialist care versus standard medical care in the management of people with Parkinson's disease?
- Physiotherapy: What is the effectiveness of physiotherapy (physical activity) compared with usual care to treat the complications of PD?
- Occupational therapy: What is the effectiveness of occupational therapy compared with usual care to treat the complications of PD?
- Speech and language therapy: What is the effectiveness of speech and language therapy compared with usual care to manage speech and communication difficulty and swallowing difficulty in persons with Parkinson's disease?
- Nutritional support: What is the effectiveness of nutritional support compared with usual care?

The mental health issues of anxiety and apathy in PD were not included in the scope. Management of pain in Parkinson's disease was also not included. Standard treatment therefore applies in these areas – see the NICE guideline entitled: 'Anxiety: management of anxiety (panic disorder, with or without agoraphobia, and generalised anxiety disorder) in adults in primary, secondary and community care'.

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9.1 Parkinson's disease nurse specialist interventions

PDNS care has been pioneered in the UK over the last 10 years supported by the UK PDS. A PDNS's role is defined[360] as a specialist practitioner with essential skills in:

- communication (see Appendix K)
- patient and carer assessment
- symptom management
- medicines management
- providing ongoing support and advice
- referral to other therapists
- education.

A recent report from the UK PDS (2004)[361] 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 Parkinson's disease
- 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 monitoring the effectiveness of changes in medication and treatment
- using the latest information technology (IT) to triage people with Parkinson's disease to the most appropriate health professional
- using IT to identify people at risk and speed up responses to crises.

What is the effectiveness of PDNS care versus standard medical care in the management of people with Parkinson's disease?

9.1.1 Methodology

Three RCTs [362,363,364] 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 [362]
- the effects of nurse practitioner care versus 'standard care' in a population of 40 people with Parkinson's disease recruited from a specialist neurology unit [363]
- the effects of substituted consultant care versus PDNS care in a population of 185 people with Parkinson's disease attending hospital clinics.[364]

Only one study provided data on statistical power.[362] Another study [364] involved only 58% of the 185 enrolled participants who completed the trial, and in a third study [363] the sample size was small (N=40).

The study environment varied considerably between trials. In one study,[362] 438 GP practices were involved from nine randomly selected English health authorities. The practices recruited people who represented the Parkinson's disease population of England and Wales. In another

study,[364] clinics in London and Hull with established PDNS services were selected to participate. This study had large numbers of crossovers (i.e. people receiving care from both consultants and PDNSs), which makes interpretation difficult. Finally, a third study [363] 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.

9.1.2 Health economic methodology

Three economic studies of PDNS care were critically appraised [362,364,365] and one met quality criteria.[362] One study [364] 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 a 42% loss of people during follow-up, which may have led to bias in the economic results. The third study [365] was also excluded as the trial did not consider all costs relevant to the provision of PDNS care to reflect true cost-saving estimates.

The one study [362] that met quality criteria evaluated community-based PDNS care with GP care versus standard GP care in an RCT in the UK.

As part of the guideline development process, we have evaluated the cost-effectiveness of PDNS care in comparison to standard care over a 1-year period from the NHS perspective. Full details of this analysis are shown in Appendix F.

9.1.3 Evidence statements

The PDNS versus GP care study [362] evaluated the results of the Global Health Questionnaire at the end of a 2-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). (1+)

This study also reported non-significant results for the following outcome measures: 2-year and 4-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). (1+)

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 Parkinson's disease taking controlled-release levodopa increased significantly more in the nurse group (p=0.016).
- People in the nurse group had a greater tendency after 2 years to discontinue their use of selegiline (p<0.001).[362] (1+)
- After 1 year, another trial364 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). (1+)
- The nurse practitioner versus standard care RCT [363] assessed people with Parkinson's disease and dystonia over 6 months. For the psychosocial outcome measures, no significant differences were found between the intervention and control groups. (1+)

In addition, the results from an independent assessment [363] 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 (one-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 Parkinson's disease (mean 9.0 on scale of 1–10). (3)

9.1.4 Health economic evidence statements

The RCT [362] 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 £4,050 to £5,860 (£ 1996) and from £3,480 to £5,630 in the control group based on 1,859 people from 438 general practices in nine randomly selected health authority areas of England.

It is not always clear whether PDNS care is substituting some or all of the consultant care or is serving as additional care.[364] By varying the cost-savings of other health professional costs by PDNS care, costs for 1 year of PDNS care range from an additional cost of £3,289 to cost-savings of £4,564. Full details of these analyses are shown in Appendix F.

9.1.5 From evidence to recommendation

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 Parkinson's disease and their carers are further addressed in Chapter 3.

There has only been limited evidence showing improvements in direct measures of outcome.

The evidence indicates the cost-effectiveness of PDNS care is inconclusive.

9.1.6 Recommendations

60. People with Parkinson's disease should have regular access to:

- clinical monitoring and medication adjustment
- a continuing point of contact for support, including home visits when appropriate
- a reliable source of information about clinical and social matters of concern to people with Parkinson's disease and their family members and their carers (as appropriate),

which may be provided by a Parkinson's disease nurse specialist. [2006]

9.2 Physiotherapy and physical activity

What is the effectiveness of physiotherapy (physical activity) compared with usual care in patients with Parkinson's disease?

9.2.1 Introduction

The aim of this review question was to establish the effectiveness of physiotherapy in the management of the following symptoms associated with Parkinson's disease:

- Gait
- Functional mobility and balance
- Falls
- Motor function and mobility

The review focussed on identifying studies that fulfilled the conditions specified in Table 17

Table 17: PICO table for physiotherapy in Parkinson's disease

Population	Patients with a confirmed diagnosis of Parkinson's disease
Interventions	Physiotherapy including (but not restricted to) the following: • Exercise therapy • Tai chi • The Alexander technique • Cueing techniques • Dance • Wii interactive fitness and balance programs • Physical activity • Nordic walking
Comparators	Usual care
Outcomes	• Resource use and cost • Health related quality of life • Freezing • Falls and balance • Speed of gait • Functional mobility (UPDRS) • Depression • Posture • Carer outcomes

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For full details of the review protocol, please see Appendix C. Randomised controlled trials (RCTs) were considered to be the most appropriate study design to derive comparative effectiveness measures, and were therefore considered to be the highest quality within a GRADE framework. All other study designs were excluded from this review, including case–control studies, cohort studies and case reports.

9.2.2 Evidence review

A systematic search was conducted (see appendix I) which identified 4,372 references. The references were screened on their titles and abstracts and full papers of 38 references were obtained and reviewed against the inclusion and exclusion criteria in the review protocol (see appendix C). The 3 studies included in CG35 were also reviewed against the current protocol.

Of the 38 ordered papers, 36 studies were excluded as they did not meet the inclusion criteria specified in the review protocol such as inappropriate study design (cohort study, descriptive narrative, opinion, etc.) or studies which were already included within a Cochrane review (Tomlinson et al., 2012). A detailed list of excluded studies and reasons for their exclusion is provided in appendix G.

One published paper and 1 Cochrane review of 39 RCTs met the inclusion criteria and were included in the analysis. The 3 studies previously included in the original guideline (CG 35) did not meet the current inclusion criteria and were excluded from the analysis. The Cochrane review that was included is an update of the Cochrane review that was included in the previous guideline.

The included studies examined the effectiveness of physiotherapy to improve symptoms associated with Parkinson's disease such as speed of gait, balance, falls and the general mobility and quality of life in patients with idiopathic Parkinson's disease. Studies that compared the effectiveness of physical therapy interventions to other physical therapy interventions were not included within this review as this fell outside the present review protocol.

An additional 92 new papers were identified through rerun searches at the end of the guideline, of which 19 were included and 73 excluded. A total of 21 publications (1 Cochrane review of 39 RCTs and 20 RCTs) were therefore included in the final analysis.

Evidence tables for included studies can be found in Appendix D, with GRADE profiles reported in Appendix E.

9.2.3 Description of included studies

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One Cochrane review of a total of 39 RCTs involving 1,827 participants examined the effectiveness of physiotherapy interventions in comparison with placebo or usual care. Trials were classified into the following interventions: exercise therapy, general physiotherapy, treadmill training, cueing, dance and martial arts. The results of all trials were combined using standard meta-analysis methods to estimate an overall treatment effect for each of the outcomes of interest. Tests for heterogeneity were used to assess for differences in treatment effects across these different physiotherapy interventions. Sample sizes for all studies were small, ranging from 6 to 153 participants. The assessment period ranged from 3 weeks to 12 months. The mean age of participants was 67 years, and 64% were male. The mean Hoehn & Yahr stage was 2.4 and participants had had Parkinson's disease for approximately 6 years. Wide variation between the studies existed in terms of the type, frequency, length, and intensity of intervention, length of time at follow-up assessment and methods of assessment.

Of the additional 20 RCTs, the following comparisons were identified:

- 7 studies comparing exercise therapy with usual care
- 1 study comparing exercise therapy or dance with usual care
- 5 studies comparing general physiotherapy with usual care
- 2 studies comparing treadmill training with usual care
- 4 studies comparing martial arts with usual care
- 1 study comparing physiotherapy and occupational therapy with usual care (PD REHAB)

9.2.4 Health economic evidence

Literature searches were undertaken to find any existing CUAs of physiotherapy interventions for people with Parkinson's disease (see appendix I for the search strategy). In total, 841 articles were returned, of which 1 met the NICE reference case (NICE 2012).

Fletcher et al. (2012) conducted an economic evaluation alongside an RCT (Goodwin et al., 2011) that was included in the Cochrane review. It compared 10-week group exercise classes with usual care for people with Parkinson's disease and a history of falling. The RCT found no significant difference in fall rates but those in the intervention groups experienced superior gains in balance and physical activity. A substantial number of RCT participants (37/130) did not record economic data and the paper tested a number of methods for dealing with missing data but found the methods did not impact the conclusions. Resource-use estimates were taken from administrative data sources, but the authors noted a lack of resource-use data for community NHS services such as physiotherapy. Unit costs were taken from standard administrative sources. Utility data were collected using EQ-5D. No significant differences were found in costs or QALYs at 20-week follow-up. Confidence intervals around costs and QALYs were wide, suggesting the analysis may have been underpowered to detect such differences. Physiotherapy was found to be cheaper and produce more QALYs in over 80% of bootstrapped iterations.

Farag et al. (2016) conducted an economic evaluation alongside an included Australian RCT (Canning et al., 2015) comparing a monthly group exercise class with standard care. The RCT found no difference in falls in its full population, but a significant benefit in the 'low-severity' subgroup (participants with a baseline UPDRS-III at or below the observed median of 26). The CUA drew resource use estimates from data collected alongside RCT, to which it applied unit costs from standard Australian sources. Quality of life was measured using the SF-12 in the RCT; this was converted to the SF-6D to which a UK societal tariff was applied. In the full population, group physiotherapy was likely to be associated with QALY gains, but at an incremental cost that may not justify the benefits (ICER=$AUS338,800); the a probability that the intervention is cost effective was less than 20% at all QALY thresholds up to AUS$100,000. In the low-severity subgroup, the base-case point-estimate was that the intervention may be dominant (providing small QALY gains and very small cost savings); however, this finding was subject to very significant uncertainty in probabilistic analysis, with the probability that the intervention is cost-effective not exceeding 55% at any QALY threshold up to AUS$100,000.

Update 2017

Further details of the 2 included CUAs are provided in economic evidence tables in appendix F.

This question was not prioritised for economic modelling by the GDG

9.2.5 Evidence statements – pairwise meta-analyses

9.2.5.1 Gait outcomes

Two- or 6-minute walk test

Moderate-quality evidence from 10 RCTs indicates that, compared with usual care, physiotherapy (exercise, treadmill, dance, martial arts and Nordic walking) is associated with a significant increase in the distance walked in 2 or 6 minutes.

Ten- or 20-metre walk test

Very low-quality evidence from 6 RCTs could not find any meaningful difference on the 10 or 20 metre walk test between physiotherapy (general physiotherapy, exercise, and treadmill) and usual care.

Speed

Moderate-quality evidence from 24 RCTs indicates that, compared with usual care, physiotherapy (general physiotherapy, exercise, treadmill, cueing, dance and martial arts) is associated with significant increase in gait outcomes of speed.

Cadence

Low-quality evidence from 9 RCTs could not find any meaningful difference in cadence (steps/min) between physiotherapy (general physiotherapy, exercise, treadmill and cueing) and usual care.

Stride length

Moderate-quality evidence from 10 RCTs indicates that, compared with usual care, physiotherapy (general physiotherapy, exercise, treadmill, cueing, dance and martial arts) is associated with significantly improved stride length (m).

Step length

Low-quality evidence from 7 RCTs could not find any meaningful difference in step length (m) between physiotherapy (general physiotherapy, exercise, treadmill, cueing) and usual care.

Freezing of gait questionnaire (FOG)

Low-quality evidence from 4 RCTs indicates that, compared with usual care, physiotherapy (exercise, cueing, and dance) is associated with significantly improved freezing of gait questionnaire score.

9.2.5.2 Functional mobility and balance outcomes

Update 2017

Timed up-and-go test

Very low-quality evidence from 17 RCTs indicates that, compared with usual care, physiotherapy (general physiotherapy, exercise, cueing, dance, martial arts, and Nordic walking) is associated with significantly improved (i.e. reduced) time taken to complete the timed up-and-go test.

Functional reach (cm)

Low-quality evidence from 6 RCTs indicates that, compared with usual care, physiotherapy (exercise, cueing, Nordic walking) is associated with significantly improved functional reach (cm).

Berg balance score

Very low-quality evidence from 11 RCTs indicates that, compared with usual care, physiotherapy (general physiotherapy, exercise, treadmill, dance, martial arts, and Nordic walking) is associated with significantly improved Berg balance score.

Activity specific balance confidence

Low-quality evidence from 3 RCTs could not find any meaningful difference in activity specific balance confidence between physiotherapy (exercise and cueing) and usual care.

Falls efficacy scale (FES)

Very low-quality evidence from 8 RCTs could not find any meaningful difference in the falls efficacy scale between physiotherapy (general physiotherapy, exercise, treadmill, cueing, and martial arts) and usual care.

Number of people falling

Very low-quality evidence from 2 RCTs could not distinguish the risk of falling between physiotherapy (exercise and martial arts) and usual care.

9.2.5.3 Depression

No data were found which examined the effect of physiotherapy on depression in Parkinson disease.

9.2.5.4 Clinician-rated disability

Disease severity

Very low-quality evidence from 7 RCTs indicates that physiotherapy (general physiotherapy, exercise, treadmill, and dance) is associated with significant improvements, compared with usual care, in UPDRS total score, although the mean difference was below the minimal clinically important difference as defined by Schrag et al., 2006.

Mental health

Moderate-quality evidence from 4 RCTs indicates that physiotherapy (general physiotherapy, treadmill, and martial arts) is associated with significant improvements, compared with usual care, in UPDRS mental score.

Activities of daily living (ADL)

Moderate-quality evidence from 7 RCTs indicates that physiotherapy (general physiotherapy, exercise, treadmill, dance, and martial arts) is associated with significant improvements, compared with usual care, in UPDRS ADL score, although the mean difference was below the minimal clinically important difference as defined by Schrag et al., 2006.

Low-quality evidence from an RCT (Clarke et al., 2016) could not differentiate levels of activities of daily living (NEADL) at 3 months or 15 months between people given and not given a programme of physiotherapy and occupational therapy.

Motor symptoms

Very low-quality evidence from 23 RCTs indicates that physiotherapy (general physiotherapy, exercise, treadmill, cueing, dance, martial arts and Nordic walking) is associated with significant improvements, compared with usual care, in UPDRS motor score, although the confidence intervals of the mean difference crossed the line of minimal clinically important difference as defined by Schrag et al., 2006 and Horvath et al., 2015.

9.2.5.5 Parkinson's disease-specific quality of life (PDQ39)

Summary index (PDQ39)

Very low-quality evidence from 14 RCTs indicates that physiotherapy (general physiotherapy, exercise, treadmill, cueing, dance and martial arts) is associated with significant improvements, compared with usual care, in Parkinson's disease-specific quality of life, although the confidence intervals of the mean difference crossed the line of minimal clinically important difference as defined by Peto et al., 2001.

Update 2017

Low- to moderate-quality evidence from 1 RCT (Clarke et al., 2016) could not differentiate levels of Parkinson's disease-specific quality of life (PDQ-39) at 3 months or 15 months between people given and not given a programme of physiotherapy and occupational therapy.

Mobility (PDQ39)

Low-quality evidence from 4 RCTs could not differentiate mobility levels (PDQ-39) between physiotherapy (general physiotherapy, exercise, dance, and martial arts) and usual care.

9.2.5.6 Health-related quality of life

Low- to moderate-quality evidence from 1 RCT (Clarke et al., 2016) found higher levels of health-related quality of life (EQ-5D) at 3 months or 15 months in people given a programme of physiotherapy and occupational therapy compared with those not given the programme.

9.2.5.7 Carer outcomes

Low- to moderate-quality evidence from 1 RCT of 762 people found worse levels of mental health (SF-12) at 3 months in carers of people given a programme of physiotherapy and occupational therapy compared with those not given the programme, but could not differentiate levels at 15 months for mental health or at 3 or 15 months for physical health.

9.2.5.8 Health economics

One partially applicable cost–utility analysis with potentially serious limitations found that group physiotherapy was cost-effective in over 80% of probabilistic iterations compared with standard care. This was based on an RCT that found no significant differences in costs or QALYs.

One partially applicable cost–utility analysis with potentially serious limitations suggested that, across the full population of people with Parkinson's disease who have a history of falls or are at high risk of falling, a 6-month group exercise programme is unlikely to be considered cost effective compared with usual care (ICER=AUS$338,800 / QALY). When the analysis was restricted to people with baseline UPDRS-III scores of 26 or lower, the base-case point-estimate was that the intervention may be dominant (providing small QALY gains and very small cost savings); however, this finding was subject to very significant uncertainty in probabilistic analysis.

Update 2017

9.2.6 Evidence to recommendations

Relative value of different outcomes	The GDG considered the relative value for the different outcomes in the evidence base and agreed that the Berg Balance Scale, UPDRS scores and quality of life were the most highly valued outcome of those presented. Reasons cited for the value of this measure include the following: • The UPDRS is regularly used in clinical practice and within research, and provides a global rating of the many facets of Parkinson's disease-related symptoms and can be used as a surrogate measure of quality of life and mood. • The Berg Balance scale is widely used in clinical practice and is considered important to those with Parkinson's disease, whereas the Falls efficacy scale is seen as subjective and not as widely used in clinical practice, where falls diaries are more widely used. The other outcomes, such as the timed up-and-go, 2- and 6-minute and 10- and 20-metre walk tests, were considered of lesser importance, providing only indirect evidence. The GDG were concerned that there is no clear link between individual-derived objective outcomes and clinical benefit observed at the group level as presented in this review. The translation of statistical benefit to clinically

	meaningful benefit at the individual level was discussed as a further outcome of interest that was not captured accurately in the included literature. The GDG felt that many of the clinically minimally important differences cited in the literature were set too high and that, in their experience, people with Parkinson's disease reported clinically beneficial improvements at the individual level following relatively small improvements in standardised outcome measures such as the Berg balance scale. The freezing of gait (FOG) questionnaire was discussed by the GDG and it was agreed that it is not widely used in physiotherapy clinical practice because of its very low ability to detect clinically meaningful changes.
Trade-off between benefits and harms	The GDG agreed that there were benefits in terms of the objective measures reported in the evidence which could be extrapolated to an overall benefit for some individuals with Parkinson's disease. The GDG also raised the notion that it is likely that some groups of people with Parkinson's disease, such as those in early stages of the disease who may not typically be offered physiotherapy until their symptoms worsen, will benefit from physiotherapy, as well as those with more advanced disease. For example, the GDG agreed that, by engaging in physical therapy prior to the onset of symptoms, the onset of symptoms may be delayed. The GDG agreed that overall the benefits that some people with Parkinson's disease gain from engaging in physiotherapy far outweighs the minimal or null benefit experienced by a minority of people with Parkinson's disease. The GDG agreed strongly that all people with Parkinson's disease should be offered physiotherapy in the knowledge that most will benefit from it, and that those who do not engage with or benefit from a physical therapy intervention are able to discontinue therapy if they wish. The GDG agreed that – for all people with Parkinson's disease, regardless of the stage of the disease – there would be few if any adverse effects associated with physiotherapy. The GDG had specific discussion around the results of the PD REHAB study, as this was deemed to be of particular importance, as it was a large, recent UK based study. They agreed that, despite the trial showing evidence of benefits from physiotherapy (e.g. the improvements in health-related quality of life at both 3 and 15 months), the overall pattern of results was considerably more mixed than for the other studies included in the analysis. This was felt to be down to two key components of the PD REHAB trial. First, the physiotherapy (and occupational therapy) provided was not Parkinson's disease specific, in contrast to that in most of the other trials. Secondly, the intervention provided was of very low intensity (on average people received 263 minutes of therapy across both physiotherapy and occupational therapy). The GDG agreed it was unsurprising that such low-intensity, non-specific physiotherapy was less effective, and felt it important this evidence was reflected in the recommendations. Therefore, both recommendations were written to ensure that people should have contact with a physiotherapist with experience of Parkinson's disease, which is the intervention supported by robust evidence.
Trade-off between net health benefits and resource use	The GDG noted from 1 included study (Amano et al., 2013) that, if an exercise intervention is inexpensive, even a small improvement in quality of life from physiotherapy could be cost-effective. It noted there was a lack of health economic evidence for other forms of physiotherapy intervention, or other studies included in the Cochrane review. The GDG discussed whether the requirement of Parkinson's disease specific physiotherapy was likely to result in higher resource implications than general physiotherapy. It was agreed that whilst there would not be access to Parkinson's disease specific physiotherapists in all areas of the country, it should be possible to access someone with experience of Parkinson's disease, who would be able to provide Parkinson's disease specific physiotherapy. The potentially slightly higher resource implications of this were felt to be less of a risk than providing people with generic physiotherapy, which had the risk both of

	providing lower clinical benefits, and not representing a good use of NHS resources providing ineffective treatment, when an effective treatment is known to exist.
Quality of evidence	The GDG agreed that the overall evidence base was of moderate quality, and that the consistency in findings across studies and different types of physiotherapy increased their confidence in the robustness of the results. On this basis, the GDG did feel confident enough in what was presented to make an "offer" recommendation in people who are experiencing balance problems or problematic motor disability. For people in the earlier stages of Parkinson's disease, whilst the GDG felt benefits were still to be expected, the evidence was felt to be less strong (specifically, because fewer trials have been conducted in this population), and therefore a "consider" recommendation was preferred for people in these earlier stages. Specific discussion was had around the quality of the evidence from the PD REHAB trial, with two specific issues raised which limit the applicability of the results. First, because the intervention in the trial contained both physiotherapy and occupational therapy, it was not possible to separate out the impact of the two interventions. Secondly, the primary outcomes of the trial, the Nottingham Extended ADL scale, is not a Parkinson's' disease specific instrument (it was developed for use post-stroke), and therefore it may not be sensitive to changes in this population.
Other considerations	The GDG agreed that the overall follow-up period presented in the evidence was insufficient to extrapolate any potential long-term gains of physiotherapy. The GDG also agreed that reporting on participant response should include dichotomous outcomes such as the number of participants who responded and those who did not, to enable subgroup analysis to better quantify the benefits of physiotherapy. The GDG agreed that it is widely accepted that physiotherapy may be helpful to many people with Parkinson's disease. However, interventions may not be beneficial to all, and therefore it is essential to offer access to physiotherapy to those who are most likely to benefit, such as those experiencing balance problems or motor disability. The GDG also highlighted that it is very important that the physiotherapist has specialist knowledge in Parkinson's disease because they need to take into account the importance of medication, on and off time, knowledge of common non-motor features (for example, anxiety, depression or fatigue) when they are developing a therapy plan. The Parkinson's disease population presented within the research evidence base was also highlighted as problematic, in that they tended to have quite advanced disease. The GDG agreed that those who received physiotherapy intervention earlier in the course of their disease would benefit, as well as those with advanced disease, and that further research should be done to examine this. The GDG discussed that it was important that referral to a physiotherapist was made early in the course of disease to potentially delay the onset of symptoms, rather than only receiving physiotherapy intervention when problems begin to occur.

9.2.7 Recommendations

61. Consider referring people who are in the early stages of Parkinson's disease to a physiotherapist with experience of Parkinson's disease for assessment, education and advice, including information about physical activity. [new 2017]

62. Offer Parkinson's disease-specific physiotherapy for people who are experiencing balance or motor function problems. [new 2017]

9.2.8 Research recommendation

7. Does physiotherapy started early in the course of Parkinson's disease, as opposed to after motor symptom onset, confer benefits in terms of delaying symptom onset and/or reducing severity?

Why this is important

The GDG felt that physiotherapy was beneficial for those in the earlier course of the disease as it may delay or lessen problems associated with symptoms, as well as for those who have developed symptoms and problems. At present, no substantial evidence exists to support the efficacy of physiotherapy as an early intervention to prevent the onset or reduce severity of motor symptoms, as most of the trials have been conducted in people who have already developed motor symptoms. If physiotherapy was shown to have a beneficial effect in either delaying the onset or decreasing the severity of symptoms, this would have a substantial beneficial impact on the quality of life of people with Parkinson's disease and their family and carers. Relevant trials would not compare physiotherapy with no physiotherapy, but rather early physiotherapy (at the time of diagnosis) with physiotherapy offered at the current standard times in the UK.

Update 2017

9.3 Occupational therapy

What is the effectiveness of occupational therapy (OT) compared with usual care to treat the complications of Parkinson's disease?

9.3.1 Introduction

The aim of this review question was to investigate the effectiveness of OT compared with usual care on complications of Parkinson's disease, including: activities of daily living, recreation and leisure participation, driving, cognition, fatigue and sleep, and anxiety and mood. The review focused on identifying studies that fulfilled the conditions specified in Table 18.

Table 18: PICO table for occupational therapy

Population	Patients with a confirmed diagnosis of Parkinson's disease
Interventions	Occupational therapy intervention
Comparators	Usual care
Outcomes	• Resource use and cost • Health related quality of life: PDQ39 • Functional tasks (e.g. upper limb function) • Workplace adjustments • Activity of daily living • Recreation and leisure and participation • Driving • Cognition • Fatigue • Sleep • Anxiety/ mood

Update 2017

For full details of the review protocol, please see Appendix C. Randomised controlled trials (RCTs) were considered to be the most appropriate study design to derive treatment effect metrics, and were therefore considered to be the highest quality within a GRADE framework. All other study designs were excluded from this review, including case–control studies, cohort studies, and case reports.

9.3.2 Evidence review

A systematic search was conducted (see appendix I) and identified 1,263 references. The references were screened on their titles and abstracts and full papers of 18 references were obtained and reviewed against the inclusion and exclusion criteria in the review protocol (see appendix C).

Overall, 17 studies were excluded as they did not meet the eligibility criteria specified in the review protocol such as inappropriate study design or focused on physical therapy, rather than occupational therapy. A detailed list of excluded studies and reasons for their exclusion is provided in appendix G.

The 1 remaining published paper did meet the eligibility criteria and was included in the analysis. The 2 previously included studies (within a Cochrane review – Deane et al., 2003, re-published at review as Dixon et al., 2007) in the previous guideline (CG35) were reviewed against the current protocol. Both of these studies did not meet the inclusion criteria for the current guideline and were excluded from the present analysis (see table of excluded studies, appendix G). Furthermore, studies that investigated the efficacy of multimodality therapy

interventions, such as combination OT with physiotherapy, were not included within this review as this fell outside the present review protocol.

An additional 3 new papers were identified through rerun searches at the end of the guideline. However, none met the inclusion criteria for this review and were therefore excluded.

The included study examined the effectiveness of occupational therapy to improve activities of daily living and quality of life in people with Parkinson's disease. The overall quality of the evidence was high.

Additionally, the PD REHAB study (Clarke 2016), which was included as part of the review on physiotherapy, was also considered as part of this question. Since the intervention in that study contained both physiotherapy and occupational therapy and it was not possible to separate out the effects of the two interventions, the same evidence was presented for this question as for the physiotherapy question. Please see sections 9.2.5.4, 9.2.5.5 and 9.2.5.6 for the evidence statements coming from the Clarke 2016 paper.

Evidence tables for included studies can be found in Appendix D, with GRADE profiles reported in Appendix E.

9.3.3 Description of included studies

The 1 additional included study (Sturkenboom et al., 2014) was an assessor-blind randomised controlled trial that examined the efficacy of occupational therapy to improve engagement in meaningful activities of daily living and health related quality of life. A total of 162 individuals with Parkinson's disease were randomised to receive individual-tailored occupational therapy (median age = 71 years; mean disease duration=6 years; 63% male) compared with 67 participants who received usual care and no therapy intervention (median age=70 years; mean disease duration=6 years; 61% male).

Update 2017

The intervention consisted of 10 weekly sessions of occupational therapy which was individually tailored to the participant's specific needs and goals of therapy. Sessions lasted approximately 1 hour and were conducted by occupational therapists (median experience=12 years) in the patient's home. Therapists attended a 3-day specialist training course prior to the trial, with a 1-day booster session in the middle of the trial. Control participants received usual medical care with no intervention. A carer for each of the participants in both groups also completed questionnaires relating to their own quality of life and general health. All participants and their carers were assessed by a blind assessor at 3 and 6 months post the intervention.

9.3.4 Health economic evidence

Literature searches were undertaken to find any existing CUAs of occupational therapy interventions for people with Parkinson's disease (see appendix I for the search strategy). In total, 857 articles were returned, of which 1 met the NICE reference case (NICE 2012).

One CUA (Sturkenboom et al., 2015) conducted an economic evaluation alongside a Dutch RCT (Sturkenboom et al., 2014) comparing 10-week, individualised, home-based occupational therapy with usual care for people with Parkinson's disease and their main caregivers. The RCT found the intervention was effective at improving patients' self-perceived performance in daily activity compared with usual care.

The CUA followed people for 6 months and adopted a societal perspective, recording costs and outcomes for people with Parkinson's disease and their carers. Resource-use was recorded via 3 month retrospective questionnaires (administered at 0, 3 and 6 months). Unit costs were taken from standard Dutch administrative sources. Utility data were collected using EQ-5D, valued using the Dutch tariff.

No significant differences were found in costs or QALYs at 6-month follow up for people with Parkinson's disease, their carers, or matched people with Parkinson's disease–carer pairs. Intervention costs tended to be lower for people with Parkinson's disease and their carers; the only category with significant difference in costs was lower institutional care costs for people with Parkinson's disease in the intervention group. However, there were inconsistencies in reporting of costs, with the sum of the cost categories not matching the reported totals.

Utility tended to be higher for all groups in the intervention arm, although the authors noted differences reduced over time and some form of maintenance therapy may be necessary to sustain benefits. Both these findings point towards the need for longer-term follow-up or modelling of this intervention.

Confidence intervals around costs and QALYs were wide, suggesting the analysis may have been underpowered to detect meaningful differences. Cost-effectiveness calculations could not be replicated using the reported costs and QALY differences. No sensitivity analyses were reported.

Around 40% of matched people with Parkinson's disease–carer pairs contained incomplete data; conclusions were not altered by adjusting for these missing data.

Further details of the included CUA are provided in an economic evidence table in appendix F.

This question was not prioritised for de novo economic modelling by the GDG.

9.3.5 Evidence statements

Update 2017

Quality of life

Moderate-quality evidence from 1 study (Sturkenboom et al., 2014) reported no improvement in quality of life in those who received occupational therapy compared with control participants in both a generic measure (EQ-5D; MD=0.03 [95%CI −0.03 to 0.08]) and a Parkinson's disease-specific quality of life measure (PDQ39; MD=−1.7 [95%CI −3.9 to 0.5]).

Functional tasks

No evidence was reported for the outcome of functional tasks.

Workplace adjustments

No evidence was reported for the outcome of workplace adjustment.

Activity of daily living

High-quality evidence from 1 study (Sturkenboom et al., 2014) reported occupational therapy intervention to significantly improve participants' self-perceived participation in meaningful daily activities at both 3 (MD=1.2; 95% CI 0.8 to 1.6) and 6 months (MD=0.9; 95%CI 0.5 to 1.3) post intervention compared with control participants. Occupational therapy was also reported to significantly improve participants' satisfaction with their performance of meaningful daily activities at both 3 (MD=1.1; 95%CI 0. to 1.5) and 6 months post intervention (MD= 0.9; 95%CI: 0.5 to 1.3) compared with those who did not receive the intervention.

Recreation and leisure and participation

Moderate-quality evidence from 1 study (Sturkenboom et al., 2014) reported no improvement in participants' self-perceived competence to cope with difficult situations (Utrecht proactive coping competence scale: MD=0.09: 95%CI −0.02 to 1.21), nor in their satisfaction with participation in

rehab activities (Utrecht evaluation of rehabilitation participation satisfaction scale: MD=3.2; 95%CI −0.6 to 6.8) in those who received occupational therapy compared with control participants.

Driving

No evidence was reported for the outcome of driving.

Cognition

No evidence was reported for the outcome of cognitive function.

Fatigue

Moderate-quality evidence from 1 study (Sturkenboom et al., 2014) reported no improvement in fatigue in those who received occupational therapy compared with control participants (fatigue severity scale: MD=0.1; 95%CI −0.2 to 0.4).

Sleep

No evidence was reported for the outcome of sleep

Anxiety/ mood

Moderate-quality evidence from 1 study (Sturkenboom et al., 2014) reported no improvement in depression in those who received occupational therapy compared with control participants (Beck depression inventory; MD=−1.4; 95%CI −3.0 to 0.3).

Update 2017

Carer quality of life

Moderate-to-high-quality evidence from 1 study (Sturkenboom et al., 2014) reported a small improvement in carer quality of life in the carers of those who received occupational therapy compared with carers of the no intervention control participants at 3 months post intervention (EQ5D; MD=0.06; 95%CI: 0.02 to 0.11); however, this was not sustained at 6-month follow-up (MD=0.04; 95%CI −0.01 to 0.3).

Health economics

One partially applicable cost–utility analysis with very serious limitations reported no significant difference in costs or QALYs at 6 months between people receiving occupational therapy and those receiving usual care.

9.3.6 Evidence to recommendations

Relative value of different outcomes	The GDG recognised ability to engage in activities of daily living and health-related quality of life as the primary outcomes of interest for this review question. Carer quality of life was also regarded as a critical outcome of interest.
Trade-off between benefits and harms	The GDG noted that the therapists in the Sturkenboom trial all had a high level of experience and specialist training in Parkinson's disease. It was noted that there are courses available to OTs for specialist training in Parkinson's disease – these are usually between 1 and 3 days duration. The GDG discussed that, as this evidence shows, the optimal scenario is to refer patients to a therapist who has experience in Parkinson's disease; however it was recognised that some hospitals have access to Parkinson's specific therapists, whereas others have a general neurology-specialist

therapeutic team. It was noted that some hospital services do not offer any specialised OT and that a general service only is available. In this circumstance, the GDG agreed that there would be a member of the multi-disciplinary team (MDT) with a neurology speciality who could direct therapy towards those areas of particular concern in a patient with Parkinson’s disease.

One of issues discussed at length by the GDG was that OT service in Parkinson’s disease can particularly aid with non-motor issues such as anxiety, sleep and fatigue. For this reason it is important to have someone with experience in Parkinson’s disease involved in the therapy plan, as a general OT may not be aware of these issues. The GDG recognised that Parkinson’s disease is a very complex condition, and that all those who are providing care should have some experience and knowledge in Parkinson’s disease to give disease-specific care.

The GDG discussed the clinical relevance of the evidence presented and the notion that patients and their carers set specific, individualised goals for the therapy. Therefore, it is very difficult to define an MID as this will differ for the number and nature of goals that each person has set for their own treatment.

It was noted that therapy is often also dependent on the patient’s age, with elderly patients having more areas in which to improve.

The GDG discussed the mean difference of 1.2 points improvement on the satisfaction of engagement in ADLs between the intervention and no intervention condition. As this scale is based on a 1–10 rating, 1.2 points difference was viewed by the group as very likely to be clinically significant.

The GDG agreed that it is important to note that this rating is for satisfaction and thus is an individual measure based on the person’s own expectations and perceptions of self-efficacy. It is therefore a very subjective measure.

The GDG noted that taking into account the patient’s perspective and individual expectations of what they hope to achieve through engaging in therapy is very important. The measures presented in the evidence are not measuring absolute change, they are measuring individual change and perception of what constitutes success to the individual.

The GDG discussed the inherent problems with relying on a self-reported measure to measure clinical change, where patients may over- or underestimate the effects of OT on their ADL, depending on their own individual expectation. However, it noted that this is true of people in real-world practice, as well, so any intervention that can be shown to improve patients' perception of their functional ability can be assumed to have made a nontrivial contribution to their quality of life.

The GDG noted that the score on ADL measures very much depends on how many goals the patients has set at the beginning of therapy, where the more goals that are set, the more likely it is that a meaningful change is observed. The GDG also discussed that if a patient is more satisfied on how they are doing on a day-to-day basis, they will be more likely to engage in ADLs.

It was noted that such a heterogeneous population requires heterogeneous interventions, where it is almost impossible to measure an overall benefit of OT when this is so individually-based.

The GDG agreed that the major problem in this area is that rating scales are insensitive to change. It was noted that the PDQ-39 is known to be very insensitive to measuring small changes. However, although the PDQ39 is largely insensitive to change, the point estimate was in favour of OT in improving quality of life. A small change in the right direction was also observed for the EQ-5D improvement in participants. It was discussed as very difficult to observe change in these scales, so even a small change in this scale was viewed as very important. Furthermore, the GDG agreed that it is important to note that carers did show a significant improvement in EQ-5D at 3 months, and this is in line with group members' expectation and experience that interventions that increase the independence of people living with Parkinson's disease should

	reduce the burden on their carers (although this benefit was not sustained at 6 months). The GDG discussed that a standard OT intervention lasts 6–10 weeks. Often a programme will run over 6 weeks and then follow up with the patient at 3 months. It was noted as common for patients to get a referral to an OT on diagnosis so that patients receive 1−2 sessions, where these sessions are mainly information and education based. Patients will most often need re-assessment as their condition deteriorates. The intervention presented in the Sturkenboom paper was home-based. The GDG discussed that patients can benefit from group-based therapy, and that a group-based therapy intervention may show greater clinical benefit to patients in light of the social and emotional benefits of interacting with others with the same condition. The GDG noted that the patients in the study presented had Parkinson's disease for an average of 6 years, and were already experiencing problem with ADLs. It was noted that often in UK practice patients are only referred to OT when they are experiencing problems with ADLs. However, the clinical experience of the group was that patients benefit significantly from OT at an earlier stage of the disease – ideally, at diagnosis. There is often a high non-motor burden to patients and carers at diagnosis, such as anxiety, depression, and fatigue – this early population could benefit greatly from OT input. These early sessions at diagnosis may include information and education about the condition. The GDG reiterated that it is very important that the OT has specialist knowledge in Parkinson's disease because they need to take into account important medication, on and off time, knowledge of salient non-motor features i.e. anxiety, depression, fatigue when they are developing a therapy plan. The GDG felt strongly that people with Parkinson's disease should be offered OT if they are experiencing difficulty in ADLs. The evidence for OT intervention presented did show significant benefit to patient's perception of engagement in ADLs and their satisfaction with their engagement. This was viewed as very important to patients by both lay and clinical members of the GDG. The GDG had specific discussion around the results of the PD REHAB study, as this was deemed to be of particular importance, as it was a large, recent UK based study. They agreed that, despite the trial showing evidence of benefits from occupational therapy (e.g. the improvements in health-related quality of life at both 3 and 15 months), the overall pattern of results was considerably more mixed than for the other studies included in the analysis. This was felt to be down to two key components of the PD REHAB trial. First, the occupational therapy (and physiotherapy) provided was not Parkinson's disease specific. Secondly, the intervention provided was of very low intensity (on average people received 263 minutes of therapy across both physiotherapy and occupational therapy). The GDG agreed it was unsurprising that such low-intensity, non-specific occupational therapy was less effective, and felt it important this evidence was reflected in the recommendations. Therefore, both recommendations were written to ensure that people should have contact with an occupational therapist with experience of Parkinson's disease, which is the intervention supported by robust evidence.
Trade-off between net health benefits and resource use	The GDG considered the included economic evaluation, with the caveat that it took a societal perspective, including work absence, informal care and travel costs. Whilst costs were reported broken down by category, reporting of median costs meant it was not possible to establish costs from an NHS and PSS perspective. The cost effectiveness of the intervention compared with no intervention was also hard to assess due to reporting inconsistencies. Reported net monetary benefit calculations were not replicable. There were no significant differences in costs or QALYs, and the group noted the RCT was not powered to detect such

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	differences. This did not necessarily signal a cost-neutral intervention. The point estimate was in favour of the intervention improving quality of life but the impact appeared to reduce between 3 and 6 months. The short time-horizon limited the economic evaluation and the group were unable to assess whether benefits would be sustained and whether any future cost savings may be outweighed by the cost of further interventions. The GDG noted a significant difference in institutional care costs (including inpatient, outpatient and residential care) was observed between the intervention and control arms. It was not possible to ascertain the numbers of participants incurring such costs. This cost difference needed to be traded off against the cost of the delivering the intervention and it was not possible to assess the overall cost difference between arms. The group agreed that, if this benefit were real, it would be very important – not just in terms of costs saved but also as regards the increased independence a lower use of care resources would denote. However, it acknowledged that it is difficult to have any confidence that the trial had detected a genuine, replicable effect. Costs for an NHS based intervention may also vary from those reported if different grades or experience of OTs were employed. The GDG agreed the economic evidence presented did not exclude the possibility that an occupational therapy intervention could be cost-effective in an NHS setting.
Quality of evidence	The GDG recognised the overall quality of evidence was high; however the GDG also recognised a shortcoming in the evidence base that the instruments used to assess change are insensitive to reflect a benefit in the individual patient that has subjectively set their own goals and have their own expectations from therapy. Specific discussion was had around the quality of the evidence from the PD REHAB trial, with two specific issues raised which limit the applicability of the results. First, because the intervention in the trial contained both physiotherapy and occupational therapy, it was not possible to separate out the impact of the two interventions. Secondly, the primary outcomes of the trial, the Nottingham Extended ADL scale, is not a Parkinson's' disease specific instrument (it was developed for use post-stroke), and therefore it may not be sensitive to changes in this population.

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9.3.7 Recommendations

63. Consider referring people who are in the early stages of Parkinson's disease to an occupational therapist with experience of Parkinson's disease for assessment, education and advice on motor and non-motor symptoms. [new 2017]

64. Offer Parkinson's disease-specific occupational therapy for people who are having difficulties with daily living activities. [new 2017]

9.4 Speech and language therapy

a) What is the effectiveness of speech and language therapy (SLT) compared with usual care to manage speech and communication difficulty in people with Parkinson's disease?
b) What is the effectiveness of SLT compared with usual care to manage swallowing difficulty in persons with Parkinson's disease?

9.4.1 Introduction

The aim of this review question was to ascertain the usefulness of SLT in the management of speech and communication, and swallowing complications of Parkinson's disease. The review focused on identifying studies that fulfilled the conditions specified in Table 19.

Table 19: PICO table for SLT in Parkinson's disease

Population	People with a confirmed diagnosis of Parkinson's disease
Interventions	• Vocal training • Speech control training • Breathing control training • Auditory feedback alteration therapy • Singing training • Swallowing or dysphagia therapy
Comparators	Usual care

Outcomes	• Intelligibility of speech:
	  ○ Vocal loudness
	  ○ Monotonicity
	  ○ Articulation
	• Resource use and cost
	• Disease severity
	• Health related quality of life
	• Voice handicap
	• Swallowing efficiency
	• Swallowing outcomes:
	  ○ Drooling
	  ○ Choking
	  ○ Aspiration
	  ○ Penetration of foodstuffs into larynx
	• Nutrition
	• Carer health related quality of life

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For full details of the review protocol, please see Appendix C. Randomised controlled trials (RCTs) were considered to be the most appropriate study design to derive mean change (MC) from baseline, and mean difference (MD) metrics, and were therefore considered to be the highest quality within a GRADE framework. All other study designs (e.g. case–control studies, cohort studies and case reports) were excluded from this review.

9.4.2 Evidence review

A systematic search was conducted (see appendix I) which identified 735 references. The references were screened on their titles and abstracts and full papers of 11 references were obtained and reviewed against the inclusion and exclusion criteria in the review protocol (see appendix C).

Overall, 9 studies were excluded as they did not meet the eligibility criteria such as inappropriate study design or population. Studies that examined the effectiveness of one SLT intervention compared with another were also not included within this review, as this fell outside of the present review protocol. A detailed list of excluded studies and reasons for their exclusion is provided in appendix G.

Two remaining published papers did meet eligibility criteria and were included in the analysis. One of these was a primary study (Troche et al., 2010), and the other a recently updated Cochrane review (Herd et al., 2014) which replaced a previous Cochrane review that was included in the previous Parkinson's disease guideline CG35 (Deane et al., 2001). Each of the studies included varied in terms of the type, frequency, length and intensity of intervention, length of time at follow-up assessment, and methods of assessment. An additional 6 new papers were identified through rerun searches at the end of the guideline. However, none met the inclusion criteria for this review and therefore all were excluded.

The included studies examined the effectiveness of SLT to improve speech, communication, and swallowing difficulties associated with Parkinson's disease, and quality of life in people with Parkinson's disease.

Evidence tables for included studies can be found in Appendix D, with GRADE profiles reported in Appendix E.

9.4.3 Description of included studies

9.4.3.1 Speech and communication

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One Cochrane review (Herd et al., 2012) of 3 RCTs involving an aggregate of 63 participants) examined the effectiveness of SLT interventions in comparison with placebo or usual care in patients with Parkinson's disease. The methods of SLT differed in each of the trials. Johnson (1990) gave the patients therapy with an emphasis on prosodic features of pitch and volume. Therapy was reinforced with the use of a number of visual feedback systems. The therapy in the second study (Ramig et al., 2001) aimed to maximize phonatory effort and loudness during speech with improved vocal fold adduction and overall laryngeal muscle activation, and was carried out on an individual basis. This method was referred to as Lee Silverman Voice Therapy (LSVT). The results of 2 of the trials (Johnson et al., 1990; Ramig et al., 2001; N=41) were combined using standard meta-analysis methods to estimate an overall treatment effect for each of the outcomes of interest; however the third study (Robertson et al., 1984) was unable to be incorporated into quantitative meta-analysis due to no raw data being provided. This study was therefore dropped from all analyses. Sample sizes for all studies were small, ranging from 12 to 29 participants. The assessment period was short, with a maximum follow up period of 12 weeks. The mean age of participants was 63.2 years, and more than 75% were male. Disease severity was assessed in only 1 study and was reported as moderate in all patients

9.4.3.2 Swallowing

One primary RCT of 68 participants was included in the analysis of intervention for swallowing (Troche et al., 2010). Participants were randomised to complete either 5 sets of 5 repetitions of expiratory muscle strength training (EMST) 5 times per week for 4 weeks, or the same intensity and frequency using a sham device. The mean age of participants in the EMST group was 66 years (SD 8.9) and 68.5 years (SD 10.3) in the sham group. The mean duration of disease was not reported. Pre intervention, the mean UPDRS motor score in the EMST training group was 39.4 (SD 9.2) and 40 (SD 8.5) in the sham group.

9.4.4 Evidence statements

Voice handicap

Low-quality evidence from 1 RCT reported that total impairment measured with the Frenchay dysarthria assessment improved in the intervention group compared with placebo, indicating an overall improvement in the dysarthria score of 29 points (95%CI: 13.66 to 44.34).

Vocal loudness

Very low-to-low quality evidence from 2 studies (Johnson et al., 1990; Ramig et al., 2001) examined vocal loudness when reading a monologue and reported an overall improvement in vocal loudness with therapy compared with no therapy of 6.17dB (95%CI: 3.57 to 8.77). Ramig and colleagues (2001) followed this up at 6 months post therapy and reported that the improvement in objective loudness had reduced to 3.5dB (95%CI: 0.9 to 6.1), however this was still a significant increase compared with those who did not receive therapy.

Very low-to-low quality evidence from 2 studies (Johnson et al., 1990; Ramig et al., 2001) examined vocal loudness when reading a standard passage and reported an overall improvement in vocal loudness with therapy compared with no therapy of 7.18dB (95%CI: 4.65 to 9.71). Ramig and colleagues (2001) followed this up at 6 months post therapy and reported that the improvement in objective loudness was mostly maintained (4.5dB; 95%CI: 1.9 to 7.1).

Low-quality evidence from 1 study (Ramig et al., 2001) also measured the mean objective loudness of a prolonged 'ah' and reported an improvement of 12.1 dB (95% CI: 8.9 to 15.4), which was maintained at 6-month follow-up (9.4 dB; 95% CI: 6.2 to 12.6).

Low-quality evidence from 1 study (Johnson et al., 1990) reported that maximum volume range was significantly improved by 23.7dB in those that received therapy compared with those that did not (95% CI: 9.3 to 38.1).

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Monotonicity

Very low-quality evidence from 1 study (Johnson et al., 1990) reported that maximum pitch range improved by 66Hz after therapy (95% CI: −4.4 to 136.6), however this change was not significant.

Swallow safety: penetration-aspiration scale

High-quality evidence from 1 study (Troche et al., 2010) reported an improvement in mean PA scores from baseline (MC=0.61, 95% CI: 0.10 to 1.11) in the EMST group. No such improvement was reported in the sham group (MC=−0.43, 95% CI: −0.82 to −0.04).

Measure of swallow mechanism: duration of hyoid elevation

Moderate-quality evidence from 1 study (Troche et al., 2010) reported no significant change in duration of hyoid elevation over time in the EMST group compared with the sham group.

Health related quality of life

Low-quality evidence from 1 study (Troche et al., 2010) reported a significant improvement in swallowing quality of life secondary to treatment independent of intervention allocation.

9.4.5 Health economic evidence

No health economic evidence was identified for this question.

9.4.6 Evidence to recommendations

Relative value of different outcomes	The GDG highlighted the critically important outcome for this review question to be swallowing safety and risk of penetration or aspiration. Aspiration pneumonia is one of the most common causes of hospital admission and the primary cause of death in people with Parkinson's disease.
Trade-off between benefits and harms	The GDG discussed the nature of Lee Silverman Voice Therapy (LSVT) to be very intensive – people need to attend 4 days per week, plus continuing the exercises at home. This can feel too great a commitment for both patient and carer. The organisation of services was also agreed to be potentially problematic – LSVT combines time in intensive care clinics and domiciliary care, which can present a barrier to implementation, in SLT services that are not able to offer this flexibility. Expiratory muscle strength training and LSVT are both types of attention-to-effort training. LSVT is based on an attention to effort framework. Attention to effort has been a well-known SLT principle since 1960s. The efficacy of this framework is well established in SLT. LSVT is one commercial version of attention-to-effort training. Attention-to-effort therapies work by encouraging participants to pay attention to their outputs – that is, speak as loudly as you can, focus on your swallowing, focus on the effort and be deliberate in your chewing and swallowing – and be more attentive to the actions they are undertaking. RCTs were highlighted as potentially difficult in this population as those with the most swallowing problems may not meet the stated inclusion criteria (for example, not mobile enough to attend appointments or not at MMSE inclusion levels specified in many of the existing studies). Treatment may be given to people with Parkinson's disease at either an early stage or later when they are having swallowing difficulties. The GDG discussed that there may be no point in offering SLT to people who are asymptomatic in as far as they are not experiencing speech difficulty. For this reason, any recommendation should reflect referral to SLT for people with Parkinson's disease who are experiencing problems. Anecdotal evidence was discussed by the GDG to suggest that patients do report consciously changing the way they communicate, even if they are not experiencing overt problems (for example, using a quiet voice). It was discussed that SLT may benefit these people. A further possible benefit for SLT discussed by the GDG was that, in discussing the broader implications of a Parkinson's disease diagnosis on speech, communication, swallowing, and social interaction with a therapist, both the patient and carer can gain an increased understanding of the way in which having a diagnosis of Parkinson's disease may affect these areas of their life. The potential for SLT to have a significant impact on a person's quality of life by improving social interactions was discussed. Often people don't have an awareness of the loudness of their speech and importance of this to allow communication. This can become more pronounced in Parkinson's disease and can be addressed by SLT. A key priority is to teach people skills and techniques that can then be used throughout the course of their disease or whenever communication or swallowing difficulties are experienced. Attention-to-effort training, such as EMST or LSVT may aid patients in encouraging their peers to engage with them (that is, notify them if they aren't speaking loud enough). There was no evidence for technologies to support communication in Parkinson's disease; however the GDG felt that it was important to acknowledge that many technologies such as apps to promote communication can be important for patients. This kind of technology is being used more and more to

	aid those with communication problems by providing therapeutic mechanisms, as well as enabling supplementation of verbal output with pictorial or digital communication strategies. The GDG discussed and agreed that such technologies were potentially more useful in people as adjuncts to SLT or when training is no longer sufficient.
Trade-off between net health benefits and resource use	No economic evidence was identified for this review question, and health economic modelling was not prioritised. In the absence of formal economic evaluation of the costs, benefits and harms of SLT, the GDG could not estimate the cost effectiveness of SLT in cost-per-QALY terms. However, it was confident that the benefits identified in the evidence would be associated with nontrivial QALY gains – not only by improving the day-to-day health-related quality of life of people with Parkinson's disease (by improving their ability to communicate and maintain independence) but also through a potentially critical positive impact on life expectancy (by reducing the risk of aspiration pneumonia, which is the leading cause of death in Parkinson's disease). The costs incurred to achieve these gains are uncertain; however, the GDG took care to make its recommendations flexible and generic, to enable local health systems to deliver effective therapy in an efficient way. In particular, it was not convinced that the intensive, proprietary Lee SIlverman approach provided distinctive benefits that would justify the additional costs that would be incurred if all speech and language therapists were asked to adopt it for people with Parkinson's disease. The GDG also noted that referral for speech and language therapy is common in current practice for people with Parkinson's disease, and therefore the recommendations would be unlikely to add substantial additional costs to the NHS.
Quality of evidence	The GDG discussed the very low quality of some of the evidence and the limited confidence it had in the outcomes reported. It was, however, noted that high quality evidence was found for swallowing safety (the outcomes prioritised as the most important), and there was a consistent pattern of benefits with SLT across a range of outcome measures. This gave the GDG sufficient confidence to make an "offer" recommendation for people who have developed swallowing or communication difficulties.

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9.4.7 Recommendations

65. Offer speech and language therapy for people with Parkinson's disease who are experiencing problems with communication, swallowing or saliva. This should include:

- strategies to improve the safety and efficiency of swallowing to minimise the risk of aspiration, such as expiratory muscle strength training (EMST)
- strategies to improve speech and communication, such as attention to effort therapies. [new 2017]

66. Consider referring people for alternative and augmentative communication equipment that meets their communication needs as Parkinson's disease progresses and their needs change. [new 2017]

9.5 Nutrition

What is the effectiveness of nutritional support compared with usual care?

9.5.1 Introduction

The aim of this review question was to establish the comparative effectiveness of nutritional interventions to treat Parkinson's disease; this may include complications of Parkinson's disease such as weight loss, postural hypotension and constipation. The review focused on identifying studies that fulfilled the conditions specified in Table 20.

Table 20: PICO table for nutrition in Parkinson's disease

Population	Patients with a confirmed diagnosis of Parkinson's disease
Interventions	Nutritional support and diet supplements
Comparators	Usual care
Outcomes	• Resource use and cost • Health related quality of life • UPDRS • Depression or anxiety • Social interaction • Cognitive function • Weight outcomes (including MUST scores, BMI or other indicators of malnutrition/weight gain) • protein distribution and absorption of dopamine medication; • Energy expenditure due to dyskinesia • Carer outcomes

Update 2017

The dietetic interventions considered within this review were:

- Low-protein, protein redistribution and other diets for the augmentation of dopamine therapy
- Dietetic intervention for the treatment of constipation
- Dietetic intervention for the treatment of postural hypotension
- Dietetic intervention for the treatment of weight loss or weight gain
- Referral to a dietitian
- Information and advice
- Nutritional supplements

Randomised controlled trials (RCTs) were considered to be the most appropriate study design to derive comparative effectiveness, mean difference, odds ratio or risk ratio measures, and were therefore considered to be the highest quality within a GRADE framework. When RCT data were not sufficient, cohort study evidence could be used. All other study designs were excluded from this review, including case–control studies, and case reports.

9.5.2 Evidence review

A systematic search was conducted (see appendix I) which identified 2,894 references. The references were screened on their titles and abstracts and full papers of 42 references were obtained and reviewed against the inclusion and exclusion criteria in the review protocol (see appendix C). This review question was not considered in the previous Parkinson's disease guideline (CG35), no further studies were therefore identified.

Overall, 30 studies were excluded as they did not meet the eligibility criteria such as inappropriate study design (prospective cohort study, descriptive narrative, opinion, etc.) or studies in which the population was not those with Parkinson's disease. A detailed list of excluded studies and reasons for their exclusion is provided in appendix G.

The 12 remaining published papers did meet eligibility criteria and were included. An additional 8 papers were identified through rerun searches at the end of the guideline, of which 2 were included and 6 excluded. One was an RCT and 1 was a systematic review and meta-analysis that included 5 RCTs, of which 1 was already included from the initial literature search. Therefore, a total of 13 papers were included in the final analysis.

The included studies examined the effectiveness of: low-protein diet, fasting diet and high-fibre supplementation on the absorption of dopaminergic medication; coenzyme Q10 supplementation; vitamin D supplementation; creatine supplementation; and extract of trigonella foenum-graecum seeds as adjunct to levodopa treatment. No studies were identified which examined the nutritional treatment of postural hypotension, constipation, weight gain and weight loss.

Evidence tables for included studies can be found in Appendix D, with GRADE profiles reported in Appendix E.

9.5.3 Description of included studies

- 4 crossover RCTs examining the effectiveness ofdifferent types protein diets on the absorption of levodopa in Parkinson's disease;
  - 1 comparing a redistributed low-protein diet on special low protein products originally designed for renal patients versus a balanced low protein diet achieved by diminishing the consumption of protein rich foods (Barichella et al., 2006)
  - 1 comparing a low protein redistribution diet (minimal protein intake during the day, with the balance of protein in the evening) versus a high protein diet (distributed evently throughout the day) (Tsui et al., 1989)
  - 1 comparing a low protein diet (unclear distribution) versus a normal diet (Crozson et al., 1991)1 comparing a diet on a special low protein product originally designed for renal patients versus a low protein diet achieved by diminishing the consumption of protein rich foods (Barichella et al., 2007)
- 1 crossover RCT examining the effectiveness of fibre supplement on the absorption of levodopa in Parkinson's disease (Fernandez-Martinez et al., 2014)
- 1 crossover RCT examining the effectiveness of fasting diet on the absorption of a dopamine agonist (ropinirole) in Parkinson's disease (Brefel et al., 1998)
- 1 double-blind RCT examining the effectiveness of vitamin D supplementation in Parkinson's disease (Suzuki 2013)
- 2 blinded RCTs examining the effect of creatine supplementation and creatine with resistance training in Parkinson's disease (Bender 2006, Hass 2007)
- 1 double-blind pilot RCT examining the effect of amino acid supplementation in levodopa-treated and protein-restricted Parkinson's disease (Cucca 2015)
- 1 double-blind RCT examining the use of trigonella foenum-gracum l seed supplementation in Parkinson's disease (Nathan 2014)
- 1 systematic review and meta-analysis and 1 double-blind RCT examining the effect of co-enzyme Q10 supplementation in Parkinson's disease (Negida 2016, Storch 2007)

Update 2017

9.5.4 Evidence statements

9.5.4.1 Low-protein redistribution diet vs low-protein diet

Very low-to-low quality evidence from 1 crossover RCT, with 18 participants, found an improvement in total on-time but not post prandial on-time following the use of a redistributed low-protein diet. (MD=114.00 [95% CI: 19.92 to 208.08] and MD=30.00 [95% CI: −17.04 to 77.04], respectively).

Very low-to-low quality evidence from 1 crossover RCT, with 18 participants, found an improvement in total off-time but not post prandial off-time following the use of a redistributed low-protein diet. (MD=−107.00 [95% CI: −212.53 to −1.47] and MD=−30.00 [95% CI: −77.37 to 17.37], respectively).

9.5.4.2 Low-protein redistribution diet vs high-protein diet

Very low quality evidence from 1 crossover RCT, with 10 participants, found an improvement in percentage of on-hours when taking the low protein redistributed diet but this did not reach significance (MD=10.65; 95% CI: −4.28 to 25.58).

Very low quality evidence from 1 crossover RCT, with 10 participants, found an improvement in modified Columbia scores when taking the low-protein redistributed diet but this did not reach significance. (MD=−3.98; 95% CI: −14.82 to 6.86).

9.5.4.3 Low-protein diet (unclear distribution) vs usual diet

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Low quality evidence from 1 crossover RCT, with 8 participants, found no significant improvement in total off-hours in the group taking the low-protein diet (MD=−0.81; 95% CI: −6.23 to 4.61).

9.5.4.4 Low-protein diet vs low-protein diet

Very low quality evidence from 1 crossover RCT, with 6 participants, found no significant difference between those who received a low-protein diet product marketed for renal patients and those who received a low-protein natural diet with non-special food for the outcomes of time spent in physical activity and patient global improvement scores.

Very low quality evidence from 1 crossover RCTwith 6 participants, found no significant difference between those who received a low-protein diet product marketed for renal patients and those who received a low-protein natural diet with non-special food for the outcome of energy expenditure.

9.5.4.5 High-fibre supplement

Low quality evidence from 1 crossover RCT, with 18 participants, found no significant difference between those who received plantago ovata husk supplements and those who did not for the outcomes of area under the curve, peak plasma concentration and time to reach peak plasma concentration of levodopa.

9.5.4.6 Fasting diet

Very low quality evidence from 1 cross-over RCT, with 12 participants, found no significant difference between those who received a fasting diet and those who did not for the outcomes of area under the curve and peak plasma concentration. Time to peak plasma concentration was significantly shorter in the group receiving the fasting diet (MD=−2.12; 95% CI: −2.81 to −1.43).

9.5.4.7 Vitamin D supplementation vs placebo (usual care)

UPDRS (and other disease activity measures)

Moderate quality evidence from 1 RCT, with 112 participants found a significant improvement in UPDRS scores (total and ADL) and Hoehn and Yahr scores from baseline for people receiving vitamin D supplementation compared with those receiving usual care. However, the mean difference in UPDRS total score was reported to be below the minimal clinically important difference and the confidence intervals around the mean difference for UPDRS ADL crossed the line of the minimal clinically important difference as defined by Schrag et al., 2006. No meaningful differences were noted between groups for UPDRS motor, complications, mentation, behaviour and mood subscales or PDQ-39 outcomes.

Cognitive function

Moderate quality evidence from 1 RCT, with 112 participants, found no significant difference between people receiving vitamin D supplementation and those receiving usual care for MMSE change from baseline.

Health-related quality of life

Moderate quality evidence from 1 RCT, with 112 participants, found no significant differences between people receiving vitamin D supplementation and those receiving usual care for EQ-5D outcomes.

9.5.4.8 Creatine supplementation vs placebo (usual care)

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Health-related quality of life

Very low quality evidence from 1 RCT, with 60 participants, found a significant benefit in SF-36 scores for 'emotional role limitation' and 'general mental health' (MD=21.00 [95% CI: 5.29 to 36.7] and MD=8.00; [95% CI: 0.03 to 15.97], respectively). There were no significant findings for the outcomes of general health perception, vitality, social functioning, bodily pain, role limitations and physical functioning scores between groups.

UPDRS (and other disease activity measures)

Very low quality evidence from 1 RCT, with 60 participants, found a significant benefit for people receiving a creatine supplement compared with usual care in only 1 domain of the UPDRS – 'mentation behaviour and mood' (UPDRS-I) (MD=−1.1; 95% CI: −2.01 to −0.19). There were no meaningful differences between groups for total UPDRS score, UPDRS-II, UPDRS-III or UPDRS-IV.

Very low quality evidence from 1 RCT, with 60 participants, found a smaller increase in dopamine agonist dose over the 2 years following the use of a creatine supplement compared with usual care (MD=−132; 95% CI: −195.75 to −68.25). There were no significant findings for the outcomes of change in levodopa dose.

9.5.4.9 Creatine supplementation and resistance training vs placebo (usual care)

UPDRS (and other disease activity measures)

Low quality evidence from 1 RCT, with 20 participants, found a significant difference in Hoehn and Yahr score but no meaningful difference in UPDRS scores between people receiving creatine supplementation and resistance training and those receiving usual care.

Weight outcomes

Low quality evidence from 1 RCT, with 20 participants, found no significant difference for increase in mass from baseline between people receiving creatine supplementation and resistance training and those receiving usual care.

9.5.4.10 Amino acid supplementation vs placebo (usual care)

UPDRS III (motor)

Low quality evidence from 1 RCT, with 14 participants on a protein-restricted diet, found no meaningful difference between amino acid supplementation and placebo in UPDRS motor score.

Weight outcomes

Low quality evidence from 1 RCT, with 14 participants on a protein-restricted diet, found no significant difference in body weight between amino acid supplementation and placebo.

9.5.4.11 Co-enzyme Q10 supplementation vs placebo (usual care)

UPDRS (and other disease activity measures)

Low-to-high quality evidence from a meta-analysis of 4 RCTs found no meaningful difference between people receiving co-enzyme Q10 supplementation and those receiving placebo for the outcomes of UPDRS scores (total, UPDRS-I, UPDRS-II or UPDRS-III) or Schwab and England modified score 'for examiner' (ADL).

Moderate quality evidence from 1 additional RCT with 131 participants, found no significant difference between people receiving co-enzyme Q10 supplementation and those receiving placebo in combined UPDRS motor and ADL scores.

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9.5.4.12 Trigonella foenum-gracum l seeds supplementation vs placebo (usual care)

UPDRS (and other disease activity measures)

Moderate quality evidence from 1 RCT, with 42 participants, found no meaningful difference in Hoehn and Yahr or UPDRS scores between people receiving trigonella foenum-gracum l seeds and those receiving usual care.

Resource use and cost

No evidence was identified which examined the impact of nutritional intervention on resource use and cost outcomes.

Depression or anxiety

No evidence was identified which examined the impact of nutritional intervention on depression or anxiety in Parkinson's disease.

Social Interaction

No evidence was identified which examined the impact of nutritional intervention on social interaction in Parkinson's disease

Carer burden

No evidence was identified which examined the impact of nutritional intervention on carer quality of life.

9.5.5 Health economic evidence

No health economic evidence was identified for this review question.

9.5.6 Evidence to recommendations

Relative value of different outcomes	This review assessed the benefit of different nutritional interventions for the treatment of Parkinson's disease on the outcomes of resource use and cost, health-related quality of life, UPDRS, depression or anxiety, social interaction, cognitive function, weight outcomes (including MUST scores, BMI or other indicators of malnutrition/weight gain), protein distribution and absorption of dopamine medication, energy expenditure due to dyskinesia and carer outcomes. The GDG discussed the fact that dyskinesia is an important outcome. However there was no reporting of this. Other outcomes that were not reported in any study included: resource use and cost, depression and anxiety, social interaction and carer burden. When discussing the study reporting on protein redistribution diet, on- and off-time were the primary outcomes indirectly showing how the benefit of dopamine absorption varied between groups. The GDG agreed that on- and off-times were important, but noted that the recording of these outcomes can be rather subjective. The method of reporting is self-reporting via diary, and some patients have difficulties in accurately reporting their states. The diaries only allowed patients to identify as either 'on' or 'off', which the group recognised as problematic because real-life experience is not as clear as this. It was also raised that this missed out on other important symptoms the patient could have been experiencing, for instance dyskinesia. The GDG also emphasised that one should not ascribe benefit to a treatment twice over by considering on- and off-time as independent outcomes. If a patient is experiencing a significant improvement in on-time, it follows that he or she is also experiencing a significant reduction in his off-time, since the two are mutually exclusive. Though none of the outcomes requested in the protocol were identified, the GDG expressed an interest in whether any of the studies on modified-protein diet had reported worsened adverse events. The studies reporting on use of low-protein or redistributed protein diets did not report adverse events which could be important, especially with the possibility of worsening a patient's weight loss. The group agreed that, even if a low protein diet had shown evidence of benefit, they would be wary of recommending any diet that could have detrimental effects on a patient's weight. For dietary supplements, the GDG agreed it was important to assess the benefits in terms of a reduction in the risk of falling (vitamin D deficiency) and improved bone health, although neither of these outcomes was reported in the study presented. The study did however show interesting benefits in the areas of UPDRS and Hoehn and Yahr scores. Since these were overall measures of disease activity it was agreed that these were important outcomes of interest. Drug absorption graphs were useful but limited as they did not necessarily link drug absorption to a patient's clinical outcomes.
Trade-off between benefits and harms	The GDG felt that the potential benefits of any good nutritional intervention should be first and foremost clinical effectiveness and whether the intervention would actually offer any meaningful benefit to the person's mental or physical condition and/or the progression of the disease. Impeding disease progression or improving the person's symptoms would have the benefit of improving the

person's quality of life for longer and reducing the reliance on expensive medications. Introducing a diet that could lengthen or amplify the experience of benefit of a drug could delay the time taken to reach a state of reduced or non-effect. This could help a patient to remain independent for as long as possible and avoid other complications, such as falls, that could result in lengthy inpatient stays and an increased rate of hospital admissions with greater resource use/cost.

The harms associated with nutritional interventions could involve an increase in the burden for the patient who would have one more intervention to remember to adhere to. Patients may find it difficult to adhere to the intervention and the diet could fail to provide benefit. Worse than this, further potential harms include the potential for the patient to develop obsessive eating behaviours and consider all protein to be 'bad'. If poorly managed this could lead to increased weight loss. The GDG note that this would be less true for supplements which would simply have to be taken with the rest of the medication.

Low-protein diets were discussed, and it was agreed the evidence did not show any clear benefit. The GDG did not want to recommend a reduced-protein diet for people with Parkinson's disease, due to the risk of malnutrition, which this group is more prone to. There is a big difference between redistribution of protein diets and reducing protein intake (low-protein diets) and the two should not be confused.

The GDG agreed that protein-redistribution diets have a role for the individual patient where there is a significant differentiation between on- and off-time. For people where fluctuations become a problem, this may require more individualised assessment where, according to the evidence, the person may have to try low protein during the day and have 85% of total protein in the evening. Consuming 85% protein at night could be very difficult practically and it is unclear whether this diet would work if a little more protein were permitted during the day. For patients taking multiple tablets throughout the day, managing protein intake around this can be very difficult. Concerns were raised that some patients may develop an unhealthy fear of protein or obsessively over-diet and the intervention would have to be well explained before starting. The GDG did not want patients to limit their protein intake to the extent that they became underweight or malnourished. For this reason, the recommendation was made that people should avoid a reduction in the total daily protein consumption and that some people may benefit from specialist advice from a dietitian. The strength of recommendation of this diet was lowered to a 'discuss' in light of the fact that there will likely be a very heterogeneous response: some patients will respond well and others may find the diet difficult to adhere to or experience no response. Therefore, it was recommended that healthcare professionals should discuss the potential for a protein redistribution diet with people who are beginning to fluctuate in their response to dopaminergic medication, as they may benefit. The GDG noted it would not necessarily be worthwhile for all patients.

During discussion of protein-redistribution diets, the GDG noted that protein redistribution might not be entirely benign; and that the mechanisms by which this may influence levodopa absorption and action, are unclear. It could be related to levodopa metabolism competition or more simply due to stomach-emptying gastroparesis. GDG members also added that observational evidence that was not included in this review has shown that high-protein diets had a negative effect on overall function and on/off-time.

In these studies there was no reporting on dyskinesia levels – it is important to consider this and know whether patients are experiencing more or less dyskinesia. This would give a better idea of the benefits and harms found within these interventions.

The GDG noted that any recommendation made has to recognise that it is based on extrapolating evidence found in small studies and that the quality of evidence was poor. Therefore the GDG specified that any protein distribution

	diet should only be attempted in the specific circumstances outlined in the recommendation. Concerning the evidence on low-protein products and marketed nutritional supplements in place of food, the GDG agreed that these are not ideal and the dietary implications are not trivial. Replacing well balanced meals with a food product or supplement can result in losing out on key nutrients, vitamins and minerals found in natural food sources. The GDG therefore agreed that it is important to explain to people with Parkinson's disease that they should not take any over-the-counter dietary supplements without first consulting their pharmacist or other healthcare professionals. The GDG also noted the poor quality of the 1 crossover trial composed of only 6 participants. The GDG discussed the benefits for general health of making sure that the vitamin D is at the correct level for people with Parkinson's disease. NICE guidance supports supplementing vitamin D in anyone over 65 who is deficient and the GDG didn't feel it should go beyond the existing guidance with regard to vitamin D supplementation as the evidence presented around vitamin D supplementation was in a population who were already depleted of vitamin D. For this reason the GDG were unclear if the evidence would be transferable to a general population of people with Parkinson's disease, who may not be depleted of vitamin D.. However the GDG wanted to use the recommendations to encourage practitioners to think about vitamin D levels in people with Parkinson's disease as they are more likely to be sedentary and more likely to be at an increased risk of osteoporosis and increased risk of falling. Therefore it was recommended to be aware that people with Parkinson's disease are at high risk of vitamin D deficiency and to recommend vitamin D supplementation for people with Parkinson's disease. However, it was noted that vitamin D is not entirely innocuous. There is a cost associated with vitamin D supplementation, it may enhance the risk of vascular disease and it cannot be assumed to be completely harmless. It was also noted that the supplements used should not contain calcium, as this had the potential for higher adverse events (such as cardiovascular disease) without any evidence of additional benefit.
Trade-off between net health benefits and resource use	For the NHS, the option of using an intervention as potentially cheap and cost-saving as a dietetic intervention could prove useful. The point was made that, in a patient with fluctuating disease on levodopa therapy and dopamine agonists, the alternative to changing the diet could be the use of higher doses of levodopa or more expensive alternative drugs, both of which could result in greater resource use and more severe side effects. Attempting a protein redistribution diet as an alternative to additional pharmacological management could be beneficial in people with Parkinson's disease. The GDG noted that this is more likely to be beneficial where the diet is relatively non-intrusive and the patient can adapt to it well. Likewise it was noted that the benefits of vitamin D supplementation could be significant and relatively cheap. Vitamin D can have an effect on calcium absorption and may decrease osteoporotic risks in reducing fracture risk as a result of falls in Parkinson's disease. The GDG considered whether to make an "offer" recommendation for vitamin D supplementation. However, they felt that the list of prescribable vitamin D supplements was limited, and came with a much higher cost than those available over the counter. Therefore, it was felt to be more appropriate on average to advise people to take supplements than make them available via prescription. The evidence for creatine supplementation was of low quality; but there was some benefit shown in the study presented and the GDG agreed that it could be useful to draft a research recommendation on this area since there are signs that it could prove useful in other neurological conditions such as motor neurone disease.
Quality of	The overall quality of evidence was low for the protein diets and the GDG

Update 2017

evidence	recognised that the strength of the recommendations should reflect this. There was also a potential issue of indirectness in the evidence discussed for vitamin D. The dose given to participants was higher than that normally given in general practice to restore a patient's levels of vitamin D. The GDG queried whether this means that we would not necessarily expect the same benefit shown in the study when the dose given to patients in clinical practice would not be as high. However, the GDG agreed that at least restoring a patients vitamin D levels to normal should not cause harm and that clinicians should at least be thinking about their patient's vitamin D levels in people with Parkinson's disease who are at high risk of both osteoporosis and falls.

9.5.7 Recommendations

67. Discuss a diet in which most of the protein is eaten in the final main meal of the day (a protein redistribution diet) for people with Parkinson's disease on levodopa who experience motor fluctuations. [new 2017]

68. Advise people with Parkinson's disease to avoid a reduction in their total daily protein consumption. [new 2017]

69. Consider referring people with Parkinson's disease to a dietitian for specialist advice. [new 2017]

70. Advise people with Parkinson's disease to take a vitamin D supplement. See the NICE guideline on vitamin D for recommendations on vitamin D testing, and the NICE guidelines on falls in older people and osteoporosis. [new 2017]

71. Advise people with Parkinson's disease not to take over-the-counter dietary supplements without first consulting their pharmacist or other healthcare professional. [new 2017]

Update 2017

9.5.8 Research recommendation

8. How effective is long term creatine supplementation on clinical outcomes in Parkinson's Disease?

Why this is important

The evidence surrounding creatine supplementation for those with Parkinson's disease was limited. However it may be beneficial in other neurological conditions such as Motor neurone disease, and therefore research in this area is justified. It is proposed that a blinded randomised controlled trial is undertaken to explore this question. The proposed study would monitor UPDRS, Hoehn and Yahr, and health related quality of life scores, whilst also considering other important outcomes such as cost of therapy, levels of dyskinesia, depression or anxiety, social interaction and cognitive function.

9.6 Neuroprotection

Neuroprotection is a process in which a treatment beneficially affects the underlying patho-physiology of Parkinson's disease (Figure 6.1). This definition is preferred 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 that delay the onset of motor complications in Parkinson's disease, 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.[93,94]

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 (Figure 6.1).[93,94]

Neurorestoration refers to increasing the numbers of dopaminergic neurones by techniques such as cell implantation and nerve growth factor infusion (Figure 6.1). Such surgical techniques are discussed but not reviewed in the chapter on 'Surgery for Parkinson's disease'.[93,94]

Neuromodulation has been used by some to refer to deep brain stimulation (DBS) procedures in Parkinson's disease such as bilateral subthalamic stimulation.[93,94]

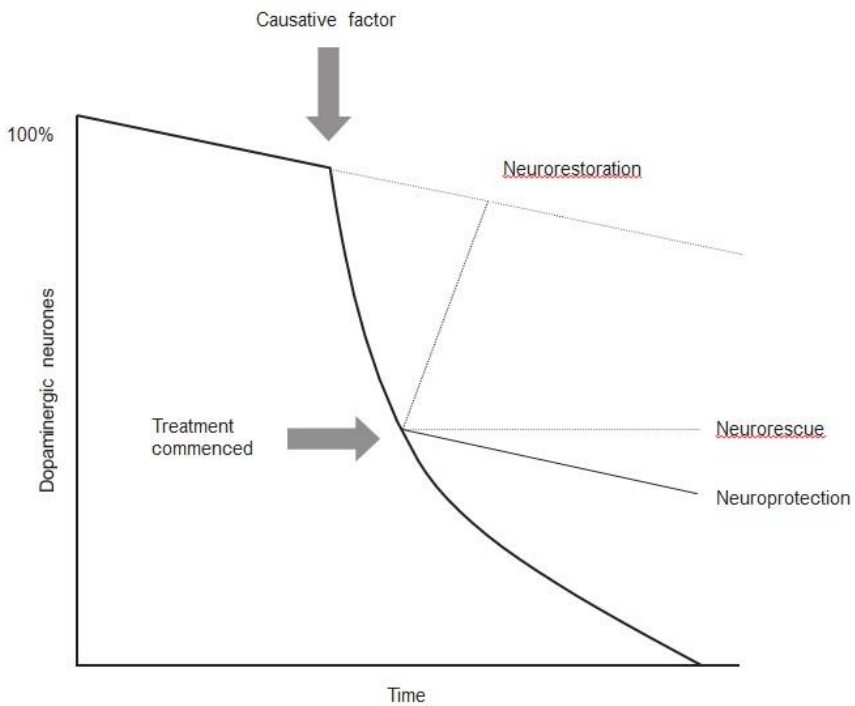

Figure 6.1 Schematic representation of neuroprotective processes[95]
(reproduced with permission from the authors)

9.6.1 Pathogenesis of disease modification

Detailed discussion of this topic is beyond the scope of this guideline.[96] 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)

9.6.2 Measuring disease progression

Considerable debate surrounds how to measure the rate of progression of Parkinson's disease in clinical trials of neuroprotective therapies.[93,97] The measures used to date are detailed in Table 6.1 along with a summary of their potential benefits and drawbacks.

Table 6.1 Outcome measures used in neuroprotection trials in Parkinson's disease

Outcome measures	Benefits	Problems
Quality of life	Patient-related so more meaningful to them	Open to symptomatic effects of therapy. Likely to have low sensitivity unless agent has large treatment effect
Clinical rating scales	Standard method used for many years	Open to symptomatic effect of therapy unless evaluated after drug withdrawal
Mortality	Has direct relevance to people with PD	Open to symptomatic effects of therapy. Studies need to be large or long term to have adequate power.
SPECT and PET imaging	Intuitively a good biomarker for the disease. May improve diagnostic accuracy at the start of trials. May be more sensitive than clinical outcomes	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.
Delaying motor complications	Has direct relevance to people with PD	More likely to be a pharmacokinetic or dynamic effect than neuroprotection.

Adapted from Refs [97,98]

The majority of previous neuroprotection trials have been of 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 Parkinson's disease given placebo.[99] With this technique one group is randomised to active treatment from the outset but one or more other groups are randomised to start the active drug after a period on placebo (Figure 6.2). 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.

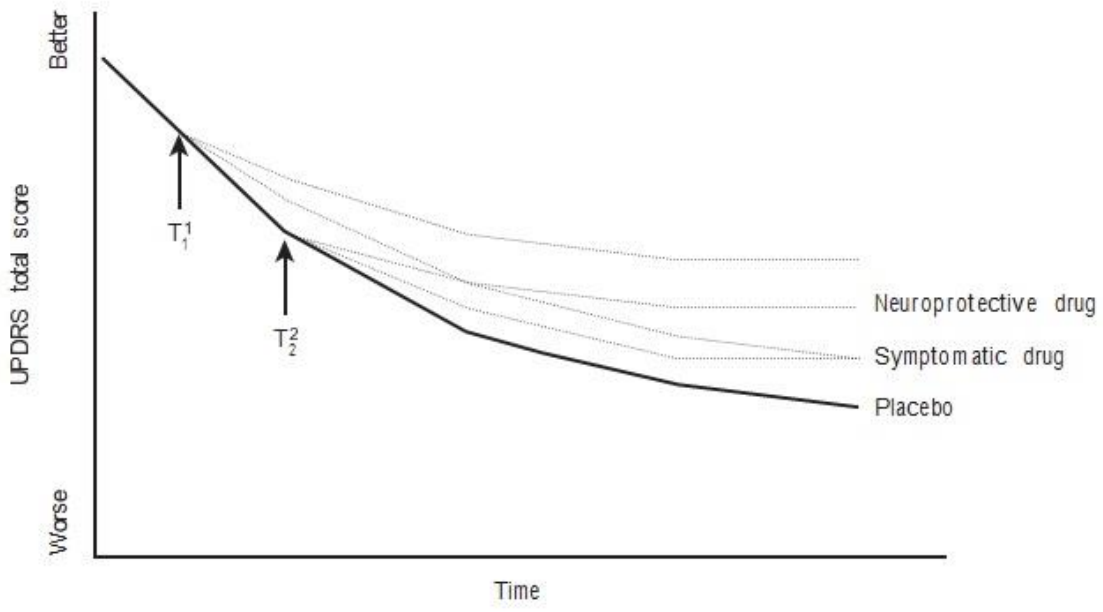

Figure 6.2 Schematic representation of delayed-start design trial.[94]

At time points T_1 and T_2 people with Parkinson's disease 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.[94]

9.6.3 Methodological limitations of neuroprotective studies

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 documentation of allocation concealment methods comparability of results from different centres in multi-site studies drug regimen varied between trials (drug, dose, frequency).

9.6.4 Potential neuroprotective agents

Many agents suggested to have neuroprotective properties have undergone systematic review by the National Institute for Neurologic Disorders and Stroke (NINDS).[100] They developed a shortlist of 12 candidate drugs for neuroprotection trials, which are listed in Table 6.2. In addition, vitamin E has been examined for neuroprotective potential.

On the basis of the evidence available, the GDG chose to review the four classes of potential neuroprotective drugs for Parkinson's disease based on the human studies:

- vitamins
- co-enzyme Q_{10}
- dopamine agonists
- monoamine oxidase type B (MAOB) inhibitors.

Table 6.2 Candidate neuroprotective drugs for Parkinson's disease selected by NINDS[100]

Caffeine	Minocycline
Co-enzyme Q_{10}	Nicotine
Creatine	Oestrogen
GM-1 ganglioside	Monoamine oxidase type B inhibitors (rasagiline and selegiline)
GPi-1485	Dopamine agonists (ropinirole and pramipexole)

9.6.5 Vitamin E

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

Does vitamin E have neuroprotective properties in Parkinson's disease?

9.6.6 Methodology

Three papers[101–103] were found, which analysed data from the same cohort recruited into the DATATOP study.[104] 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 Parkinson's disease.

9.6.7 Evidence statements

All of the studies[101–103] failed to demonstrate a significant benefit of vitamin E in slowing the progression of Parkinson's disease. **(1++)**

One report[101] examined 24 months' follow-up data and showed the following:

The probability of reaching the endpoint (onset of disability prompting administration of levodopa) was not reduced in people with Parkinson's disease receiving tocopherol.

There was no significant change in UPDRS variables for the tocopherol treatment groups. There was no evidence of any beneficial effect of -tocopherol (2000 IU per day) in either slowing functional decline or ameliorating the clinical features of Parkinson's disease. **(1++)**

Another report[103] looked at 24 months' follow-up data and showed:

- no significant benefit of tocopherol in reducing the likelihood of reaching the endpoint (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 (ADL) scale, neuropsychological testing, Hamilton depression scale). **(1++)**

A third report[102] 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. **(1+)**

9.6.8 From evidence to recommendation

The DATATOP evidence shows that vitamin E taken as 2000 IU of tocopherol daily is not neuroprotective in Parkinson's disease.

9.6.9 Recommendations

72. Do not use vitamin E as a neuroprotective therapy for people with Parkinson's disease. [2006, amended 2017]

Co-enzyme Q_{10}

Mitochondrial complex I activity is reduced in post-mortem substantia nigra and in the platelets of people with Parkinson's disease.[105,106] Co-enzyme Q_{10} is the electron acceptor for complexes I and

II and as a result is a potent anti-oxidant. The level of co-enzyme Q_{10} is reduced in platelet mitochondria in Parkinson's disease.[107] Oral supplementation with co-enzyme Q_{10} reduced dopaminergic neurone loss in MPTP-treated mice.[108]

In view of this positive pre-clinical work, is there any clinical trial evidence that co-enzyme Q_{10} has neuroprotective properties in Parkinson's disease?

9.6.10 Methodology

Two studies[109,110] examined the effectiveness of co-enzyme Q_{10} in reducing the rate of progression of Parkinson's disease. The methodological limitations included a lack of detail concerning randomisation and allocation concealment in one study,[109] and a small sample size without power calculations in both studies.[109,110]

9.6.11 Evidence statements

The two studies[109,110] used validated clinical rating scales as the outcome measures to assess benefit from co-enzyme Q_{10}.

One trial[110] (N=80) compared three different doses (300 mg/d, 600 mg/d and 1,200 mg/d) of co-enzyme Q_{10} with 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 Q_{10}. 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 1,200 mg/d group had a significant effect compared with placebo (p=0.04). **(1++)**

This trial[110] also found the following:

People with Parkinson's disease taking co-enzyme Q_{10} 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 Q_{10} did not have a significant effect on the scores for the Hoehn and Yahr scale or the timed tapping task. **(1++)**

Another trial[109] (N=28) compared a low dose (360 mg/day) of co-enzyme Q_{10} with placebo and showed:

- the UPDRS total score was in favour of co-enzyme Q_{10} treatment (p=0.012)
- a benefit of co-enzyme Q_{10} supplementation on the Visual Function Test (p=0.008) measured with the Farnsworth–Munsell 100 Hue Test. **(1+)**

9.6.12 From evidence to recommendation

The small neuroprotection trials performed with co-enzyme Q_{10} in Parkinson's disease so far have been encouraging, but further evidence is required before it can be recommended routinely.

9.6.13 Recommendations

73. Do not use co-enzyme Q10 as a neuroprotective therapy for people with Parkinson's disease, except in the context of clinical trials. [2006, amended 2017]

9.6.14 Dopamine agonists

A considerable body of pre-clinical work has suggested that dopamine agonists are neuro-protective in cell culture and various animal models of Parkinson's disease.[111,112]

What clinical evidence is there that dopamine agonists have neuroprotective properties in Parkinson's disease?

9.6.15 Methodology

Eight studies[42,61,113–118] were found which addressed the neuroprotective effects of dopamine agonists versus levodopa therapy in Parkinson's disease.

One trial[114] 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.

GDG members found a related abstract[119] on pergolide therapy, but this abstract was excluded, as the results have not been published in a full paper.

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.[42,117,115]

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 Parkinson's disease had normal scans.[61] Another study did not include a washout period in order to distinguish between the symptomatic and neuroprotective effects of the drugs administered.[113]

9.6.16 Evidence statements

With respect to clinical rating scales, the ropinirole REAL-PET (N=162) study found UPDRS motor score during treatment at 2 years was superior with levodopa compared with ropinirole (a score increase of 0.70 in the ropinirole group and a decrease of 5.64 in the levodopa group, 95% CI 3.54 to 9.14).[61] **(1++)**

Non-significant results reported by the studies included:

CALM-PD[113] (pramipexole) (N=82) mean total and mean motor UPDRS **(1++)** REAL-PET[61] (ropinirole) Clinical Global Impression (CGI) improvement scale **(1++)** UK-PDRG study[42] (bromocriptine) (N=782) mean Webster disability scores **(1+)** cabergoline study[118] UPDRS part III (motor) (N=412) and part II (ADL). **(1+)**

With respect to mortality, the following results were found:

The PRADO study[115] (N=587) was terminated when 18 deaths were reported in the levodopa group versus eight deaths in the levodopa/bromocriptine group (p=0.07; adjusted for age and sex p=0.02). The risk ratio of death in the levodopa group compared with the levodopa/bromocriptine group was 2.7, a reduction of 63%. **(1+)**

All three of the bromocriptine studies[53,116,117] found no significant differences between treatment groups. **(1+)**

The cabergoline study[118] found no significant difference between treatment groups. **(1+)**

With respect to imaging, several analytical measures found benefit of ropinirole and pramipexole over levodopa; these are summarised in Table 6.3.

Table 6.3 Rate of decline in tracer uptake (1++)

Variable	% Change dopamine agonist	% Change levodopa	Significance
Ropinirole (REAL-PET)[61]	**(SE)**	**(SE)**	
Region-of-interest analysis (reduction in putamen Ki over 2 years)	13.4% (2.14)	20.3% (2.35)	RD 34% (95% CI 0.65 to 13.06, p=0.022)
Statistical parametric mapping (reduction in putamen)	14.1% (1.58)	22.9% (1.70)	RD 38% (95% CI 4.24 to 13.3, p<0.005)
Amplitudes of change (substantia nigra)	4.3 % (3.67)	–7.5 % (3.94)	MD 11.9 (95% CI 1.3 to 22.4, p=0.025)
Pramipexole (CALM-PD)[113]	**(SD)**	**(SD)**	
Striatal ^{123}I- -CIT (rate of decline) at 22 months	–7.1 (9.0)	–13.5 (9.6)	p=0.004
At 34 months	–10.9 (11.8)	–19.6 (12.4)	p=0.009
At 46 months	–16.0 (13.3)	–25.5 (14.1)	p=0.01

RD = relative difference; Ki = influx constant; SE= standard error; MD= mean difference.

With respect to motor complications:

the REAL-PET study[61] found:

- development of dyskinesia favoured ropinirole (odds ratio (OR) 0.09, 95% CI 0.02 to 0.29, p<0.001)
- time to develop dyskinesias favoured ropinirole (hazard ratio 8.28, 95% CI 2.46 to 27.93, p<0.001) **(1++)**

the PRADO study[115] found the incidence of dyskinesias favoured bromocriptine (rate ratio: 0.73, 95% CI 0.57 to 0.93). **(1+)**

The cabergoline versus levodopa study[118] 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 with levodopa
- cabergoline-treated people requiring levodopa were at the same risk of developing motor complications as those on a stable levodopa dose. **(1+)**

9.6.17 From evidence to recommendation

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 Table 6.1).[97] Clinical motor rating scales were better in levodopa-treated individuals with Parkinson's disease or no different in these trials. The delaying of motor complications by the agonists may be due to a pharmacokinetic or pharmacodynamic effect rather than slowing of disease progression.

9.6.18 Recommendations

74. Do not use dopamine agonists as neuroprotective therapies for people with Parkinson's disease except in the context of clinical trials. [2006, amended 2017]

9.6.19 Monoamine oxidase type B inhibitors

The propargylamines selegiline and rasagiline are monoamine oxidase type B (MAOB) inhibitors, thereby reducing the turnover of dopamine and hopefully reducing free radical generation.[96] However, they may also have an anti-apoptotic effect.[100]

What *in vivo* evidence is there that MAOB inhibitors are neuroprotective in Parkinson's disease?

9.6.20 Methodology

Two meta-analyses[120,121] and an RCT[99] were found, which addressed the effectiveness of MAOB inhibitors in reducing the rate of progression of Parkinson's disease.

One meta-analysis included 3,525 people with Parkinson's disease 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 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. The other meta-analysis[121] was a Cochrane review with a similar authorship. This included 2,422 people with Parkinson's disease from 10 trials where treatment duration or follow-up was 1 year or longer. Nine trials were on selegiline and one was on lazabemide. Several trials were included in both meta-analyses.

The RCT[99] consisted of 404 people with Parkinson's disease randomised to rasagiline or placebo-delayed rasagiline therapy. The delayed-start design (see Figure 6.2) consisted of randomising them to one of three groups:

- rasagiline 1 mg/d for 1 year
- rasagiline 2 mg/d for 1 year
- placebo for 6 months, followed by rasagiline 2 mg/d for 6 months.

9.6.21 Evidence statements

A meta-analysis[120] 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 3 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=0.0004)
- activities of daily living scores: 0.9 points (95% CI 0.5 to 1.4, p=0.00007).

The Cochrane review[121] also found significantly improved scores in favour of MAOB inhibitors from baseline to 1 year on treatment. **(1++)**

Although the large DATATOP study accounted for over 79% of people with Parkinson's disease in a MAOB inhibitors versus placebo comparison, the combined results from the other studies were consistent with those from DATATOP (p=0.004).[120] **(1++)**

The rasagiline trial[99] showed:

Total UPDRS score for rasagiline 1 mg/d for 1 year versus delayed-start rasagiline 2 mg/d for 6 months was significant –1.82 (95% CI 3.64 to 0.001, p=0.05) in favour of longer treatment.

Rasagiline 2 mg/d for 1 year versus delayed-start rasagiline 2 mg/d for 6 months was significant –2.29 (95% CI –4.11 to –0.48, p=0.01) in favour of longer treatment. ADL score for rasagiline 2 mg/d for 1 year versus delayed-start rasagiline 2 mg/d for 6 months significantly favoured the longer treatment (p=0.005).

The comparisons of other UPDRS subscales were not significant. **(1++)**

A meta-analysis[120] 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 MAOB inhibitor-treated individuals with Parkinson's disease and controls (p=0.8)
- in the UK-PDRG study there were significantly more deaths in the selegiline arm versus the levodopa arm (OR=1.57, 95% CI 1.09 to 2.30, p=0.015)
- by taking all available data, 20% of deaths occurred in the MAOB inhibitor group compared with 21% in the controls (p=0.2)
- no significant heterogeneity was found between trials (p=0.6), even including the UK-PDRG study
- the Cochrane review[121] found a non-significant increase in deaths among patients treated with MAOB inhibitors compared with controls. **(1++)**

A meta-analysis[120] found five trials, which reported data on motor complications. The combined results showed:

- a 25% reduction in motor fluctuations in MAOB 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 with non-MAOB inhibitor group.

The Cochrane review[121] found very similar results. However, with regard to motor fluctuations, they found that the result was dependent on the adjusted results of one study (the UK-PDRG study) and if the unadjusted figures were used the overall result became insignificant. Additionally, results were not reported for a number of patients in these studies and a modified worst-case sensitivity analysis also made the results non-significant. **(1++)**

9.6.22 From evidence to recommendation

The benefits of MAOB 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 MAOB inhibitors. The delayed onset of motor fluctuations with MAOB 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.

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.

Further large trials with longer-term follow-up are required to assess whether the MAOB inhibitors have neuroprotective properties in Parkinson's disease.

9.6.23 Recommendations

75. Do not use MAO-B inhibitors as neuroprotective therapies for people with Parkinson's disease, except in the context of clinical trials. [2006, amended 2017]

10 Advanced therapies: deep brain stimulation and levodopa–carbidopa intestinal gel

Parkinson's disease is invariably treated initially with medication, but advanced therapies may be considered in those with poor response to drugs, intolerable adverse effects or severe fluctuations in response.

Advanced therapies include neurosurgery (deep brain stimulation; DBS), levodopa–carbidopa intestinal gel (LCIG) and continuous subcutaneous apomorphine infusion. Surgery involves the insertion of electrodes, usually bilaterally, into deep nuclei within the brain. These are connected to a battery-powered generator via leads that are tunnelled beneath the skin. The battery has a finite lifespan and requires replacement once depleted, though rechargeable systems with a longer lifespan are now available. There is currently a recent trend towards implantation earlier in the course of the disease.

Surgery is usually undertaken with the patient awake to allow response to be monitored, though some centres carry out the procedure under general anaesthetic.

LCIG treatment involves constant infusion of levodopa gel into the jejunum via a jejunostomy, using a proprietary kit (Duodopa®). Whilst an effective long term treatment for Parkinson's disease, treatment costs are high at present, and the patients need continuing support for fashioning and managing the jejunostomy.

Subcutaneous apomorphine infusion is also an effective treatment for Parkinson's disease. Also usually provided by using a proprietary kit, the infusion can be associated with improved control of symptoms compared with best oral medication, but adverse effects of the infusion, including injection site reactions, are common. The cost of subcutaneous apomorphine is considerably less than the other two advanced therapies.

Update 2017

10.1 Call for evidence

The guidelines manual (NICE 2012) allows a call for evidence where it is believed 'there is relevant evidence in addition to that identified by the searches'.

Preliminary scrutiny of the literature reviews (see below) showed that follow-up was relatively limited in all included trials and not all outcomes in which the GDG were interested were reported (for example, there was no information on rates of people entering full-time care). The GDG thought it was possible that some of these data may have been collected in some trials, and knew that some RCTs had collected data for more than the reported follow-up period.

Therefore a call for evidence was issued. The primary focus was on unpublished RCT data, but 2 additional types of evidence were sought: cost–utility analyses and, for the purpose of informing the original health economic model undertaken for this guideline (see 10.3.5.2), longer-term observational data for all interventions. Appendix M provides a copy of the call for evidence.

A total of 10 stakeholders and other data-holders made submissions in response to the call for evidence. These were considered against the eligibility criteria for the review questions and the additional criteria specified in the call for evidence. Most submitted data were excluded. Full details are provided in appendix M.

Three submissions contained evidence that met the eligibility criteria:

- The University of Birmingham made patient-level data available from the PDSURG RCT (see below), including follow-up extending beyond the published RCT's 1-year data. These data were used to derive estimates of effectiveness for the review questions focusing on advanced Parkinson's (see 10.3.4) and early Parkinson's (see 10.4.4) and also to inform the original cost–utility model (see 10.3.5.2).
- The University of Marburg, Germany, provided a draft cost–utility analysis that was considered as part of the review of economic evidence on DBS for early Parkinson's (see 10.4.5.1).
- Medtronic supplied drafts of 2 relevant cost–utility analyses that were considered as part of the review of economic evidence on DBS for early Parkinson's (see 10.4.5.1).

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10.2 Expert witnesses

Before reviewing the evidence and making recommendations on these questions, the GDG were assisted by the attendance of 2 expert witnesses – Professor Adrian Williams and Dr Caroline Rick – who had been involved in the design and conduct of PDSURG – a large, UK-based RCT of DBS compared with BMT (see below). The experts answered GDG questions about the design and conduct of the trial, and provided insight into its strengths and limitations. No papers were submitted for consideration. The expert witnesses were not present when the evidence (including PDSURG) was reviewed and recommendations were made.

10.3 Deep brain stimulation, levodopa–carbidopa intestinal gel and best medical treatment for advanced Parkinson's disease

10.3.1 Review questions

- In people with advanced PD for whom deep brain stimulation (DBS) and levodopa–carbidopa intestinal gel (LCIG) are treatment options, what is the comparative effectiveness of DBS, LCIG and best medical treatment (BMT)?

  In people who are contraindicated for DBS, what is the effectiveness of LCIG plus BMT, compared with LCIG alone in people with Parkinson's disease?
- In people who are contraindicated for LCIG, what is the effectiveness of DBS plus BMT, compared with BMT alone in people with Parkinson's disease?

10.3.2 Introduction

The aim of these review questions was, firstly, to determine the comparative effectiveness of DBS, LCIG and BMT in people with advanced Parkinson's disease for whom DBS and LCIG are both treatment options and, secondly, to assess whether there is a place for DBS or LCIG in people with advanced Parkinson's disease for whom the other surgical option is contraindicated.

A separate review question sought to assess the effectiveness of DBS at an earlier stage of disease (see 10.4).

This review updates the DBS review question and chapter on surgical intervention from the 2008 guideline for Parkinson's disease (CG35). This updated review incorporates studies that were included in the previous guideline together with newly published evidence.

The review focused on identifying studies that fulfilled the conditions specified in Table 21.

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Table 21: PICO table for the effectiveness of DBS and LCIG in people with PD who are suitable candidates for both treatments

Populations	Patients with a confirmed diagnosis of Parkinson's disease who are • suitable candidates for both LCIG and DBS , **or** • suitable candidates for LCIG but contraindicated for DBS, **or** • suitable candidates for DBS but contraindicated for LCIG
Interventions	• DBS surgery of: ○ STN ○ GPI ○ Thalamus ○ Pedunculopontine nucleus ○ Zona incerta + best medical treatment • LCIG + best medical treatment
Comparators	• Each other • Best medical treatment
Outcomes	• Adverse events – perioperative • Adverse events – long-term complications (including falls) • Symptom severity: ○ UPDRS ○ dyskinesia ○ 'on' and 'off' time

- Disease progression: Hoehn & Yahr score
- Neuropsychiatric non-motor features:
  - Cognitive impairment
  - Sleep disorder
  - Suicidal ideation
- Health-related quality of life – patient
- Health-related quality of life – carer
- Information to inform decision making
- Resource use and cost (including medication load)
- Time to full time institutional care

For full details of the review protocols, please see Appendix C. Randomised controlled trials (RCTs) were considered to be the most appropriate study design to derive treatment effect metrics, and were therefore considered to be the highest quality within a GRADE framework. All other study designs were excluded from this review, including case–control studies, cohort studies and case reports.

10.3.3 Evidence review

A single systematic search was conducted (see appendix I) for all 4 of the surgical review questions which identified 12,011 references. The references were screened on their titles and abstracts and full papers of 56 references were obtained and reviewed against the inclusion and exclusion criteria in the review protocol (see appendix C).

Overall, 50 studies were excluded as they did not meet the eligibility criteria such as not being a randomised-control design, or inappropriate intervention, such as pallidotomy. A detailed list of excluded studies and reasons for their exclusion is provided in appendix G.

The 6 remaining published papers did meet eligibility criteria and were included in the analysis. Evidence tables for included studies can be found in Appendix D, with GRADE profiles reported in Appendix E.

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10.3.4 Description of included studies

None of the included studies focused on a population that could be considered contraindicated for DBS or LCIG. Therefore, all evidence was considered relevant for the 3-way comparison of DBS -v- LCIG -v- BMT. The evidence on LCIG -v- BMT and DBS -v- BMT was also considered relevant for the questions focusing on LCIG for people who cannot have DBS and DBS for people who cannot have LCIG, respectively. Although the RCTs were not confined to people with particular contraindications, they compared the viable options for people whose choice of therapies is limited.

None of the included studies were considered for the previous NICE guideline as all postdate its publication.

DBS -v- BMT

A total of 4 studies, reported in 5 publications, (Deuschl et al., 2006 [secondary publication: Witt et al., 2008]; Weaver et al., 2009; Williams et al., 2010; Okun et al., 2012) examined the effectiveness of DBS compared with BMT. Investigators of the PDSURG trial (primary publication: Williams et al. 2010) made patient-level data available to the guideline developers. The GDG was aware that PDSURG recruited participants with a broad range of disease severity at baseline; therefore, the group requested that – for these review questions, which focus on treatment of advanced PD – subgroup analysis based on

participants with Hoehn and Yahr status 3 or greater (HY≥3) should be used, where available. Analyses based on this population were derived by the developers. Participants with a Hoehn and Yahr score lower than 3 were analysed as part of the early DBS review question (see 10.4).

When the PDSURG HY≥3 population had been extracted and combined with the other published RCTs, a pooled population was derived comprising 666 patients with advanced Parkinson's disease (mean age=60.9; mean disease duration=12.2 years; mean Hoehn & Yahr stage=3.3; mean PDQ-39 single index=42.7; mean motor [UPDRS-III] score [on]=21.5; mean anti-Parkinson's medication dose equivalent to 1270 mg of levodopa per day).

For adverse event data and neuropsychological outcomes, outcomes stratified by severity were not available in the patient-level data for PDSURG; therefore, results from the full population (as published in Williams et al. 2010) were included.

In 3 of the studies, electrodes were implanted bilaterally into the subthalamic nucleus (STN). In Weaver et al. (2009), half of the intervention group received bilateral STN surgery, and the other half received bilateral globus pallidus interna (GPI) surgery. Four participants in PDSURG also received GPI surgery. Follow-up periods within the studies ranged from 3 to 12 months. Only 1 study (Okun et al., 2012) controlled for implantation effect: all patients underwent the surgical procedure but the control group's devices were not activated during the period of randomisation. However, participants were aware of their treatment allocation. In the other 3 RCTs, participants were not blinded to treatment allocation, though some outcome assessors were.

GRADE tables summarising the findings of the included evidence and its susceptibility to bias, along with details of quantitative synthesis, are provided in appendix E. Full evidence tables are in appendix D.

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LCIG -v- BMT

One RCT (Olanow et al., 2014) investigated the effectiveness of continuous intrajejunal infusion of levodopa-carbidopa intestinal gel (LCIG) compared with BMT in 66 individuals with advanced Parkinson's disease (mean age=64.4; mean disease duration 10.4 years; mean PDQ-39 single index=36.8; mean motor [UPDRS-III] score [on]=20.2; mean levodopa dose 1062 mg/day). The trial had a randomised, controlled, double-blind, double-dummy design. All participants underwent jejunal placement of a percutaneous gastrojejunostomy tube, and were then randomised to receive immediate-release oral levodopa–carbidopa plus a placebo intestinal gel, or an oral placebo plus levodopa–carbidopa intestinal gel. Patients were followed up for 12 weeks.

A GRADE table summarising the findings of the included RCT and its susceptibility to bias is provided in appendix E. A full evidence table is in appendix D.

Indirect comparison

An indirect comparison between DBS and LCIG was performed using 1-year data from PDSURG and 12-week data from Olanow et al. (2014), assessed via a common comparator of BMT. The approach was based on standard indirect comparison methods (Bucher et al., 1997), but was modified to account for increased uncertainty inherent in the shorter follow-up of the LCIG trial. For full details of methods, see appendix F

A GRADE table summarising the results of the indirect comparison is provided in appendix E.

10.3.5 Health economic evidence

10.3.5.1 Review of published cost–utility analyses

Literature searches were conducted to identify existing CUAs comparing DBS, LCIG and BMT for people with advanced Parkinson's disease (see appendix I for the search strategies). A total of 2,910 articles were returned, of which 15 were ordered and 7 were included. In addition, 3 CUAs were identified in the rerun search at the end of guideline development (including 1 that had been made available to us in draft by the authors as part of the call for evidence – see 0). Finally, the CUA that had been performed for the previous NICE guideline was also considered as evidence, giving a total of 11 included analyses.

Relevant details of the included studies are summarised in economic evidence profiles in appendix F.

DBS -v- LCIG -v- apomorphine -v- BMT

One study (funded by manufacturers of apomorphine) with very serious limitations compared DBS, LCIG, continuous subcutaneous apomorphine infusion (CSAI) and BMT (without apomorphine). Walter and Odin (2015) found CSAI to be cost effective compared with BMT (ICER £6440 per QALY), with DBS dominated and LCIG much more expensive (ICER £244,700 per QALY). The authors used a range of non-synthesised clinical evidence and a range of assumptions (including health state utilities).

LCIG -v- BMT

Two studies (both funded by the manufacturers of LCIG) with potentially serious and very serious limitations compared LCIG and BMT. Kristiansen et al. (2009) used a 2-year decision tree to find LCIG was not cost-effective compared with BMT (ICER SEK6,100,000 per QALY). The intervention effect was assumed to remain for 2 years and utilities were not measured using EQ-5D. Lowin et al. (2011) used a Markov model and found LCIG was not cost effective compared with BMT (ICER £36,000 per QALY), despite favourable assumptions and an underlying assumption that modelled effects (Hoehn and Yahr stage and off time) were independent.

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DBS -v- BMT

Eight studies compared DBS with BMT. The only directly applicable study was a UK RCT-based CUA with 5-year and 10-year extrapolations (McIntosh et al., 2016), but this still had potentially serious limitations. It found DBS was not cost effective compared with BMT (5-year ICER £45,200 per QALY, 10-year ICER £70,600 per QALY) and had methodological differences to modelled analyses and assumptions that may not reflect current clinical care in the UK.

Dams et al. (2013), Eggington et al. (2014; funded by makers of DBS equipment) and Kawamoto et al. (2016) used similar structures to Lowin et al. (2011), with similar independence assumptions and potentially serious limitations. They found that, compared with BMT, DBS was associated with ICERs ranging from €6700 to US$70,200 per QALY. Transitions, assumptions about intervention effects and included costs, utilities and discount rates differed between the 3 papers. The previous NICE clinical guideline (NICE, 2006) found DBS to be cost effective compared with BMT (ICER £19,500 per QALY) but was a simplified cost–benefit analysis with very serious limitations. Using a residence-based model, Tomaszewski and Holloway (2001; potentially serious limitations) found DBS to confer additional QALYs at an ICER of $49,200 per QALY, compared with BMT. Valldeoriola et al. (2007) reported outcomes from a partially applicable 1-year Spanish prospective, open study and found, with very serious limitations, DBS to be reasonably cost effective compared with BMT (ICER €34,400 per QALY). Zhu et al. (2014) report a rudimentary before-and-after

analysis of a very small (n=13) population of people undergoing DBS, estimating an ICER of US$62,846 per QALY gained with DBS compared with previous care over a 2-year time horizon.

Summary

There was limited consistency in the results of the included CUAs. Both CUAs comparing LCIG with BMT (Kristiansen et al. 2009, Lowin et al. 2011) and the most directly applicable CUA comparing DBS with BMT (McIntosh et al., 2016) found ICERs above commonly accepted willingness-to-pay thresholds for the interventions. The multiple comparison between DBS, LCIG, CSAI and BMT (Walter and Odin, 2015) suggested neither DBS nor LCIG are cost effective compared with BMT, but CSAI is. Model-based CUAs found DBS is cost effective compared with BMT (Dams et al, 2013, Eggington et al. 2014, NICE 2006, Tomaszewski and Holloway 2001) but generally with ICERs very close to accepted thresholds. A non-randomised trial-based CUA found DBS to be reasonably cost effective compared with BMT (Valldeoriola et al. 2007). However, all studies had potentially serious or very serious limitations.

As no directly applicable studies with only minor limitations were found that covered all the comparators under consideration, an original health economic analysis was undertaken.

10.3.5.2 Original cost–utility analysis

10.3.5.2.1 *Methods*

An original health economic analysis was constructed to compare DBS, LCIG and BMT (which may include apomorphine) for people with advanced Parkinson's disease (see Appendix F for a full description of the model and its results). A cohort-level state-transition model was developed, structured around the occurrence of 2 critical events – requirement for full-time care and death (Figure 1).

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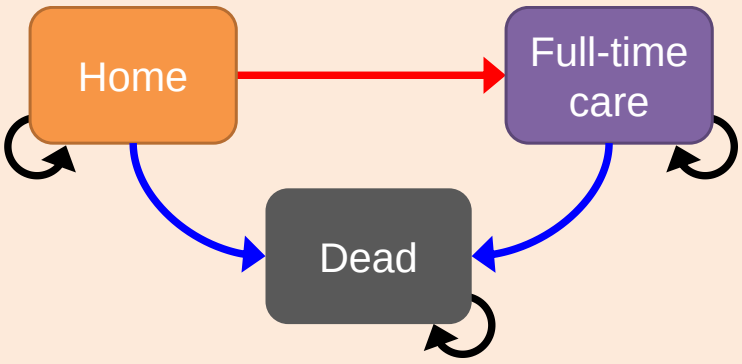

Red arrow indicates transition that depends on time-to-event model for entry to care
Blue arrows indicate transitions that depend on time-to-event model for death

Figure 1: Original cost–utility model: basic structure

Transitions were estimated using UK individual-level longitudinal data (PINE and PDSURG datasets) to quantify a surrogate relationship between treatment effects (as observed in included RCTs) and the events of interest. Variables considered were UPDRS-III (on), UPDRS-II (on), off-time, EQ-5D and PDQ-39. Cox proportional hazards models were estimated using these variables as time-varying covariates. Because UPDRS-III appeared to be the strongest predictor of both time to care and time to death, univariable versions of each

model were also developed, in which transitions were estimated as functions of UPDRS-III effect alone.

The proportional hazards models were applied to baseline functions estimated from the same datasets.

The short-term effectiveness of the interventions – in terms of UPDRS II, UPDRS III, off-time, PDQ-39 and EQ-5D – was modelled using data from included RCTs (see 10.3.3).

- For DBS, particular reliance was placed on PDSURG, not only because it was a UK-based trial that provided the longest follow-up in the assembled evidence but also because patient-level data were available to the developers, which enabled the estimation of treatment effects in participants of direct relevance to the question. For these reasons, 1-year DBS effectiveness was estimated using the PDSURG HY≥3 analyses alone, although the model was also configured to optionally use data from the other included RCTs with shorter follow-up to estimate effectiveness over the first year following surgery.
- For LCIG, only 1 RCT was available (Olanow et al., 2014), and this was limited to 12 weeks' follow-up. In order to estimate 1-year treatment effects, these 12-week data were supplemented by 12–52 week 'drift' rates, using the observed 12–52-week effects from Fernandez et al. (2015). This did not result in any change to the expected treatment effect; however, it appropriately reduced the precision of the 1-year estimate.

The GDG advised on the most plausible assumptions for extrapolating 1-year treatment effects to the lifetime horizon of the model. The group agreed that different assumptions should be adopted for the different variables. It felt that, for motor symptoms – UPDRS-III and off-time – it was reasonable to assume that the benefit of DBS and LCIG over BMT that was observed in the RCTs would persist indefinitely. However, in other domains – activities of daily living (UPDRS-II) and quality of life (PDQ-39 and EQ-5D) – an attenuation of benefit over time was a more realistic assumption. This reflects group members' experience (particularly of DBS) that, while the motor effect of treatment does not diminish, its contribution to overall quality of life is gradually reduced by the development of non-motor symptoms over time. In the base case, it was assumed that these outcomes would gradually revert to the same level as modelled in the BMT arm over a period of 7 years.

The absolute rates of progress over time to which these relative effects were applied were estimated from patient-level data (PINE or PDSURG).

Although relative and absolute functions to project EQ-5D over time were developed, an alternative approach to estimating health-related quality of life was adopted in the base case. Using patient-level data, models to estimate EQ-5D as a function of the other clinical variables were developed.

The GDG estimated quality-of-life decrements associated with undergoing DBS or percutaneous endoscopic gastro-jejunostomy (PEG-J) insertion surgery, or the complications that may arise with them, on the basis of their experience.

DBS battery replacements were modelled using device-level data from PDSURG.

The use of continuous subcutaneous apomorphine infusion was part of best medical treatment in PDSURG, and the RCT suggested that DBS may reduce the need for apomorphine, thereby reducing significant costs. To account for this in the model, data were extracted from the PDSURG dataset for, with DBS and BMT, the proportion of participants using apomorphine at baseline who discontinued it during year 1 and, similarly, the proportion not using apomorphine at baseline who commenced using it during the same period. For people who had been randomised to DBS, it was also possible to calculate subsequent rates of discontinuing or commencing apomorphine for years 2–3, and >3. In the base case, it was assumed that the transition matrix implied by these probabilities would continue to apply beyond the observed periods (meaning a simple Markov model could be calculated to estimate the proportion of people requiring apomorphine at any one time). No

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analogous data were available for LCIG, so it was assumed that LCIG has a 100% apomorphine-sparing effect.

Other intervention resource use and unit costs were taken from standard sources and agreed by the GDG. Concomitant medication costs and other healthcare usage costs were taken from PDSURG. All costs were adjusted to 2014 prices.

All costs and effects were discounted at 3.5% per annum.

10.3.5.2.2 *Results*

Both DBS and LCIG are predicted to confer gains in quality-adjusted life expectation, when compared with BMT. DBS is associated with a little under three-quarters of a QALY gained, and LCIG around one-fifth of a QALY. People receiving DBS are predicted to spend a smaller proportion of their lives in full-time care than those receiving LCIG or BMT. Figure 2 shows predicted full-time-care-free survival.

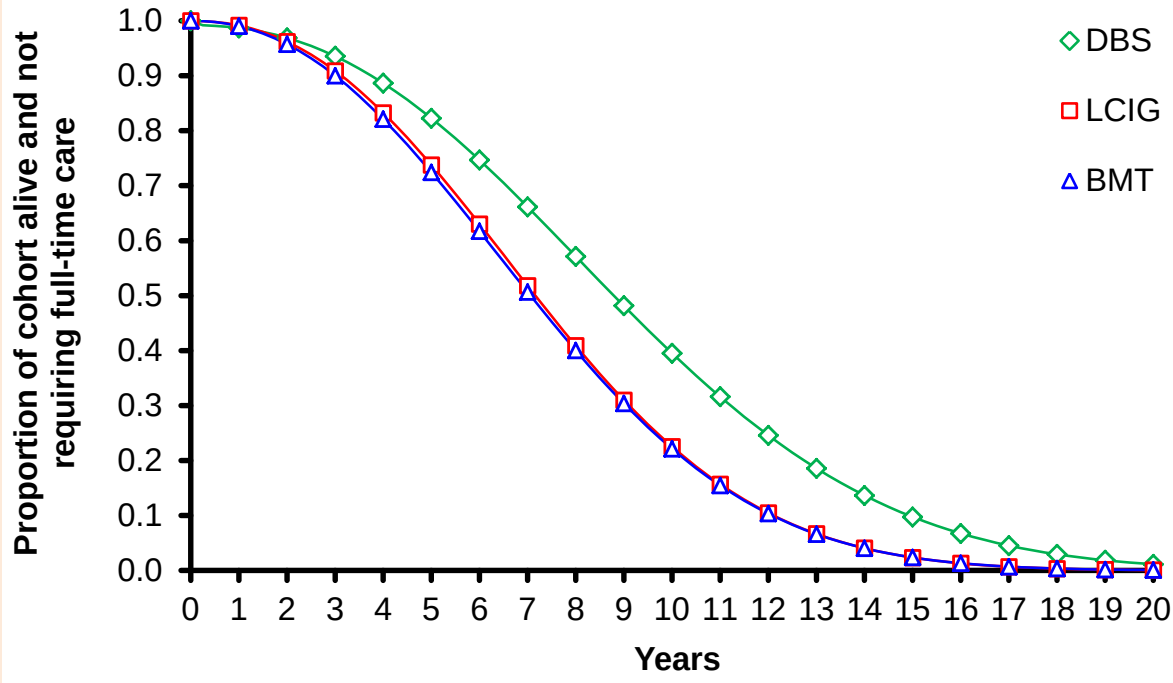

Figure 2: Original cost–utility model: predicted full-time-care-free survival (using PINE LOCF models for time to full-time care and time to death)

The lifetime costs of initial DBS surgery, AEs and device replacements amount to around £40,000 for the average patient. Some of this money is offset by reductions in apomorphine and full-time care costs; however, the net estimate is that DBS costs a little under £25,000 more than BMT, in the typical case. LCIG surgery costs much less than DBS, and substantial savings over BMT could be expected as the need for other medication is reduced and the need for apomorphine is removed. However, these amounts are dwarfed by the very high costs of LCIG itself. It is estimated that the average patient's lifetime LCIG cost would be over £150,000 (over £33,500 per year).

When cost and QALY data are combined (Table 22), DBS is associated with an ICER of around £33,500 per QALY gained. LCIG is dominated by DBS (that is, it is predicted to cost more and confer less benefit).

Table 22: Original cost–utility model: incremental cost–utility results

	Costs	Effects	Incremental

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	(£)	(QALYs)	Costs (£)	Effects (QALYs)	ICER (£/QALY)
BMT	£105,156	2.346			
DBS	£129,642	3.075	£24,485	0.729	£33,603
LCIG	£225,386	2.568	£95,744	-0.507	dominated

In probabilistic analysis, DBS provided best value in 26.7% of iterations and LCIG in 0%, if QALYs are valued at £20,000 each.

In one-way sensitivity analyses, the ICER for DBS compared with BMT was found to be most sensitive to:

- Device lifespan – if batteries last a mean of 20 years, the ICER falls below £20,000/QALY
- Effect of DBS on EQ-5D – if the upper 95%CI (a mean difference of 0.225, compared with BMT) is adopted, the ICER falls below £20,000/QALY
- Coefficients for time-to-care and time-to-death models, especially off-time and UPDRS-III

When LCIG was compared with BMT alone, the extra QALYs conferred by LCIG were found to come at a cost of £542,012 each. In sensitivity analysis, no plausible variations to parameters resulted in an ICER lower than £200,000 per QALY. Even when all effectiveness parameters are set to the favourable bound of their 95% confidence intervals and all effects are assumed to last indefinitely, LCIG is associated with an ICER in the region of £80,000 per QALY when compared with BMT. The only circumstance under which LCIG would have an ICER lower than £20,000 per QALY, compared with BMT, is if it is assumed that cassettes cost £20 or less (and the current assumption that the pump and its maintenance are provided without charge to the NHS can be maintained).

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10.3.6 Evidence statements

10.3.6.1 Adverse events – perioperative

DBS

Moderate-quality evidence from 4 RCTs reported exposure to DBS to more than double the likelihood of experiencing a serious adverse event compared with BMT only (RR=2.26, 95%CI: 1.57 to 3.23).

Very low-quality evidence from 4 RCTs could not differentiate the rate of falls in people receiving DBS and BMT: at a 95% confidence level, data were consistent with appreciable benefit or appreciable harm.

LCIG

Adverse events were very common in people receiving both active and placebo intestinal infusions, with around 90% of participants experiencing at least 1 device complication. However, the RCT provided very low-quality evidence on the relative incidence of AEs, so it was not possible to establish whether administration of active LCIG increased or decreased complications.

Very low-quality evidence from 1 RCT could not differentiate the rate of falls in people receiving LCIG and BMT: at a 95% confidence level, data were consistent with appreciable benefit or appreciable harm.

10.3.6.2 Symptom severity: Hoehn and Yahr score, UPDRS, dyskinesia, 'on' and 'off' time

DBS

Moderate-quality evidence from 3 RCTs showed that Hoehn and Yahr score decreases by a greater amount in people receiving DBS than in those who receive BMT only (MD=−0.66; 95%CI: −0.82 to −0.50).

Low-quality evidence from 2 RCTs showed that mean daily 'on' time without troublesome dyskinesias is considerably higher in people receiving DBS compared with those who receive BMT only (MD=3.66 hours; 95%CI: 1.62 to 5.71).

Low-quality evidence from 2 RCTs showed that mean daily 'off' time is considerably reduced in people receiving DBS compared with those who receive BMT only (MD=−2.48 hours; 95%CI: −3.10 to −1.86).

Moderate-quality evidence from 4 RCTs did not identify meaningful differences in mentation (as measured by UPDRS part I) between people receiving DBS and those who receive BMT only.

Moderate-quality evidence from 4 RCTs showed that activities of daily living (as measured by UPDRS part II) are less impaired in people receiving DBS compared with those who receive BMT only (MD=−2.98; 95%CI: −4.50 to −1.46).

Low-quality evidence from 4 RCTs showed that motor function (as measured by UPDRS part III) is better in people receiving DBS compared with those who receive BMT only (MD=−4.93; 95%CI: −7.52 to −2.34).

Low-quality evidence from 3 RCTs showed that complications of therapy (as measured by UPDRS part IV) are less prevalent in people receiving DBS compared with those who receive BMT only (MD=−4.05; 95%CI: −5.83 to −2.28).

LCIG

High-quality evidence from 1 RCT showed that mean daily 'on' time without troublesome dyskinesias is considerably higher in people receiving LCIG compared with those who receive BMT only (MD=2.28 hours; 95%CI: 0.4 to 4.09).

High-quality evidence from 1 RCT showed that mean daily 'off' time is considerably reduced in people receiving LCIG compared with those who receive BMT only (MD=−1.91 hours; 95%CI: −3.03 to −0.79).

High-quality evidence from 1 RCT showed that activities of daily living (as measured by UPDRS part II) are less impaired in people receiving LCIG compared with those who receive BMT only (MD=−3.00; 95%CI: −5.16 to −0.84).

Moderate-quality evidence from 1 RCT did not identify meaningful differences in motor function (as measured by UPDRS part III) between people receiving LCIG and those who received BMT only (MD=1.40; 95%CI: −2.72 to 5.52).

High-quality evidence from 1 RCT showed that LCIG improves clinical global impression of change score compared with BMT only (MD=−0.7; 95%CI: −1.4 to −0.1).

Indirect comparison

Low- and very low-quality indirect comparisons based on 2 RCTs did not identify meaningful differences in activities of daily living (as measured by UPDRS part II) and mean daily 'off' time between people undergoing DBS and those receiving LCIG.

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A moderate-quality indirect comparison based on 2 RCTs showed that motor function (as measured by UPDRS part III) is better in people undergoing DBS compared with those who receive LCIG (MD=−7.88; 95%CI: −13.63 to −2.14).

10.3.6.3 Neuropsychiatric non-motor features: cognition, depression

DBS

Moderate-quality evidence from 3 RCTs showed that DBS is associated with a moderate-sized deficit in phonemic fluency, when compared with BMT alone (SMD=−0.52; 95% CI: −0.71 to −0.33).

In other domains of cognitive function and depression, low- and very low-quality evidence from 3–4 RCTs showed that DBS may be associated with small deficits, when compared with BMT alone; however, at a 95% confidence level, data are also consistent with no meaningful difference.

LCIG

No evidence for the effect of LCIG on any neuropsychiatric features was reported.

10.3.6.4 Health-related quality of life – patient

DBS

Moderate-quality evidence from 3 RCTs showed a considerable improvement in Parkinson's disease-related quality of life, as assessed by the PDQ-39, in people undergoing DBS compared with those receiving BMT only (MD=−8.28; 95%CI: −10.27 to −6.30).

Moderate-quality evidence from 1 RCT showed a considerable improvement in health-related quality of life, as assessed by the EQ-5D, in people undergoing DBS compared with those receiving BMT alone (MD=0.12; 95%CI: 0.02 to 0.22).

LCIG

Moderate-quality evidence from 1 RCT showed a considerable improvement in Parkinson's disease-related quality of life, as assessed by the PDQ-39, in people receiving LCIG compared with those receiving BMT only (MD=−7.00; 95%CI: −12.49 to −1.51).

Moderate-quality evidence from 1 RCT was suggestive of a considerable improvement in health-related quality of life, as assessed by the EQ-5D, in people receiving LCIG compared with those receiving BMT only; however, at a 95% confidence level, data are also consistent with no difference (MD=0.07; 95%CI: −0.01 to 0.15).

Indirect comparison

Low-quality indirect comparisons based on 2 RCTs did not identify meaningful differences in PDQ-39 or EQ-5D between people undergoing DBS and those receiving LCIG.

10.3.6.5 Health-related quality of life – carer

DBS

No evidence was reported for the effect of DBS on carer quality of life.

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LCIG

High-quality evidence from 1 RCT showed that, compared with best medical therapy, LCIG may decrease level of carer burden as assessed by the Zarit interview; however, at a 95% confidence level, data are also consistent with no difference (MD=−4.50, 95%CI: −10.58 to 1.58).

10.3.6.6 Medication load

DBS

Moderate-quality evidence from 3 RCTs showed a considerable reduction in anti-Parkinson's medication in people undergoing DBS compared with those who receiving BMT only (MD=−381 mg levodopa-equivalent; 95%CI: −468 to −295).

LCIG

Moderate-quality evidence from 1 RCT showed that LCIG may reduce requirement for levodopa compared with BMT only; however, at a 95% confidence level, data are also consistent with no difference (MD=−158 mg; 95%CI: −324.5 to 8.5).

10.3.6.7 Health economic evidence statements

Original cost–utility analysis

One directly applicable original health economic model with potentially serious limitations found that, when compared with BMT, DBS confers around 0.75 QALYs at an additional cost of approximately £25,000, leading to an ICER of £33,500 per QALY gained. LCIG is more costly and less effective than DBS and has no probability of providing good value for money compared with BMT.

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DBS

Nine studies with potentially or very serious limitations found a range of ICERs for DBS compared with BMT. One directly applicable study with potentially serious limitations and 1 partially applicable study with very serious limitations found DBS was not cost effective compared with BMT (ICERs of £70,500 per QALY and ICER US$62,800 per QALY, respectively); 1 partially applicable study with very serious limitations found DBS was dominated by continuous apomorphine infusion. Six partially applicable studies with potentially serious or very serious limitations found DBS to produce additional QALYs compared with BMT, but at ICER values close to commonly accepted thresholds in their respective countries.

LCIG

Three partially applicable studies with potentially serious or very serious limitations found that LCIG is associated with ICERs above usual thresholds, when compared with BMT (£36,000 per QALY; SEK6.1m per QALY) or CSAI (£244,700 per QALY).

10.3.7 Evidence to recommendations

Relative value of different outcomes	The GDG did not prioritise symptom-based outcomes above person-reported outcomes or adverse events. The group felt it was important to consider both the benefits and harms of interventions, and to consider a wide perspective of benefits. Most of the outcomes of interest for this question are measured on a continuous scale (usually in terms of change from baseline). Minimally

	clinically important differences (MCID) were discussed. The GDG was aware of attempts to quantify MCIDs for some outcomes in the research literature. It agreed the following as reasonable. • PDQ39 single index: 1.6 points (Peto et al., 2001) • UPDRS-II (activities of daily living): 3 points (Schrag et al., 2006) • UPDRS-III (motor): between 3.25 (Horváth et al., 2015) and 5 points (Schrag et al., 2006) For some outcomes (EQ-5D, Zarit carer burden interview, on time and off time), the GDG agreed that any statistically significant differences in changes from baseline would also be clinically meaningful. The GDG agreed that it was not sensible to attempt to define a population-level MCID for changes in HY stage: individuals can only move by whole or half-points on the scale (and any such changes are reflective of obviously meaningful deterioration/improvement), but a population-level mean change of a fraction of a point is more difficult to interpret. Therefore, the GDG decided it was reasonable to conclude that any treatments that result in measurable, statistically significant differences in mean Hoehn and Yahr score must have affected a nontrivial proportion of people by a nontrivial amount.
Trade-off between benefits and harms	UPDRS outcomes were all measured in the on-medication state. The GDG noted a potential multiplicative effect where people were having more on time and their UPDRS outcomes were better in that longer time. Whilst both interventions (DBS and LCIG) generally provided benefits over best medical treatment (BMT), the indirect comparison showed the interventions themselves were only significantly different for UPDRS-III (motor score). Other outcomes all indicated a trend towards DBS being more effective than LCIG, but these differences were non-significant. The GDG agreed that these findings had clinical face validity. The GDG noted that the benefits of DBS clearly outweighed potential harms and DBS provided greater levels of benefits than LCIG, which in turn provided greater benefits than BMT. The blinding strategy in the LCIG RCT (Olanow et al., 2014) meant the evidence showed non-significant adverse event outcomes (because all participants underwent insertion of a PEG tube). However, the GDG noted that virtually every participant in both arms experienced adverse events as well as device complications. The GDG noted some evidence that DBS may have a negative effect on cognition. The included trials showed that phonemic fluency decreases to a greater degree in participants receiving DBS than in people receiving medication alone, with an effect size that would conventionally be thought of as moderate. There was also a significant difference in semantic fluency, although the effect size was small. The GDG noted that these findings were consistent with members' clinical experience, though the group also found it credible that the magnitude of any impact is small (that is, cognitive changes, where noticeable, are invariably relatively minor, and outweighed by larger benefits in other domains). The GDG had identified incidence of falls as a potentially important outcome. These showed a heterogeneous picture with fairly low event rates. The GDG postulated it could be argued that both increases (due to improved mobility and more opportunities to fall) and decreases (due to improved control over mobility) in falls could be consistent with positive outcomes. The GDG concluded that, clinically, if DBS and LCIG were both options, then DBS should be preferred to LCIG.
Trade-off between net health benefits and resource use	The original health economic model found DBS showed QALY benefits over LCIG (and both did over BMT) and the GDG agreed that this was consistent with the clinical evidence. The GDG agreed that the most important evidence for resource use with DBS compared with BMT came from the PDSURG trial, and noted that there have been some changes in practice since that trial was initiated (see

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'Quality of evidence', below). However, the GDG was aware that, in the original model, DBS costs were based, so far as possible, on current NHS practice and costings and, therefore, should not be unduly biased by any unrepresentativeness in PDSURG costs.

The GDG chose to model the most applicable and long-term DBS data (PDSURG HY≥3 population), rather than the published PDSURG data or meta-analysed outcomes over a variety of time points, as the group agreed that this most accurately reflected the population in the decision space. It noted that, of the available clinical data, this population showed the greatest benefit levels.

The GDG gave advice on the most plausible assumptions for extrapolating 1-year treatment effects to the lifetime horizon of the model. The group agreed that different assumptions should be adopted for the different variables. It felt that, for motor symptoms – UPDRS-III and off-time – it was reasonable to assume that the benefit of DBS and LCIG over BMT that was observed in the RCTs would persist indefinitely. However, in other domains – activities of daily living (UPDRS-II) and quality of life (PDQ-39 and EQ-5D) – an attenuation of benefit over time was a more realistic assumption. This reflects group members' experience (particularly of DBS) that, while the motor effect of treatment does not diminish, its contribution to overall quality of life is gradually reduced by the development of non-motor symptoms over time. In the base case, it was assumed that these outcomes would gradually revert to the same level as modelled in the BMT arm over a period of 7 years.

No long-term (beyond 1 year) randomised data exist measuring the intervention effect length, or the shape of the progression over time (for example, tapered, sustained benefit followed by quicker tapering). The group debated the potential to use non-randomised data but noted the lack of a counterfactual (that is, a comparator arm estimating how people's disease might have progressed without intervention) made it impossible to draw meaningful conclusions from the experience of people receiving DBS over time. However, in support of its base-case expectation of 7 years' effect, the GDG highlighted non-randomised, case series evidence supporting sustained benefit at 5 years (Volkmann et al., 2009), but not at 8–9 years (Fasano et al., 2010; Zibetti et al., 2011).

Sensitivity analyses indicated that, if 100% of the benefit at 1 year were sustained over all patients' lifetimes, the ICER for DBS versus BMT fell to £20,000 per QALY, which is closely comparable with the results of existing economic evaluation making similar assumptions.

There was support within the GDG for assuming DBS had a greater sustained impact than LCIG, where the impact was felt to taper more quickly. However, in its base case, the GDG chose to keep the assumptions the same for both interventions.

Device lifespan was also a key parameter. Whilst the actual operation is relatively cheap and has only a small quality of life impact, device replacement equipment is costly (around £10,500). Device lifespan estimates were taken from individual level PDSURG data, giving a mean of 5.7 years. Noting many of the PDSURG operations were undertaken over a decade ago and technology may have improved, the GDG felt it was possible that current battery-life may be greater. However, sensitivity analysis demonstrated that batteries would need to last an average of 20 years before the ICER for DBS -v- BMT fell below £20,000 / QALY. It was noted that DBS could not be recommended without funding device replacements, as an intervention could not be stopped in this manner.

Rechargeable devices are becoming available and the GDG pre-specified a scenario analysis using the unit costs of rechargeable devices (higher up-front cost than replaceable devices, but no ongoing costs). Whilst costs for rechargeable devices were available, no data on their efficacy, or the quality of life impact of recharging the device, were included. The GDG felt there could be a quality of life impact from the recharging process associated with

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rechargeable devices and this had not yet been explored in the literature. The GDG also noted that assuming replacement costs of zero is likely to underestimate the true maintenance costs of rechargeable devices. For these reasons, whilst a scenario using rechargeable devices resulted in ICER that was essentially identical to the base-case result assuming periodic replacements, the GDG saw this as providing a 'best-case' estimate.

The GDG saw no circumstance under which LCIG would be recommended compared with either DBS and BMT (dominated by DBS) or BMT alone (ICER £540,000 per QALY). The model captured quality of life and off-time gains from LCIG, but the results were driven primarily by lack of effect on UPDRS-III score and the very substantial costs of LCIG itself (estimated to be over £150,000 over an average person's lifetime). Because all results for LCIG were substantially above any plausible cost-effectiveness threshold (compared with DBS and BMT), the GDG concluded it should make a negative recommendation (that is, state that LCIG should not be offered to people with advanced PD).

The GDG understood that it was not straightforward to select a single deterministic ICER from the original model as representing a best estimate of the cost effectiveness of DBS compared with BMT, because various scenarios are possible with different inputs, especially when it comes to the choice of models estimating the effect of clinical variables on time to care and time to death. Averaging probabilistically across the most plausible scenarios (while also accounting for parameter uncertainty) resulted in an ICER of around £33,500 / QALY. The GDG noted that this is somewhat higher than the thresholds defined as representing an effective use of NHS resources in NICE's methods for developing guidelines. However, the GDG emphasised that there is currently a single commissioner for all complex neurosurgery – including DBS – in NHS England's arrangements for specialised services. As existing DBS services are well established and there is only one commissioner responsible for these, it could be reasonable that NHS England might choose to continue to fund DBS, even though the ICER is likely to be higher than usual thresholds for NICE clinical guidelines. Given the commissioning context, it is not clear that funding bears the same opportunity costs as treatments commissioned by local NHS commissioning bodies – in other words, the particular funding stream available for specialised commissioning is used to fund a variety of expensive interventions, and it is not clear that any disinvestment from DBS would release funds for the rest of the NHS to make use of. Therefore, the GDG chose to make a recommendation that DBS should be considered for people with advanced Parkinson's disease, in the knowledge that it would only be available for use if the body that commissions it considers it a reasonable use of NHS resources. This funding arrangement has the additional benefit of ensuring that DBS can only be made available in appropriately experienced and equipped centres.

The GDG noted that subcutaneous apomorphine infusion is provided fairly commonly for people with advanced Parkinson's disease in the NHS. In line with this, it understood that subcutaneous apomorphine was a potential component of the BMT to which DBS was compared in PDSURG. As a result, the original model had to assume that it was available as part of BMT. However, it is unclear how clinically effective and cost effective apomorphine is, and it is not possible to predict what outcomes would have been observed in PDSURG had it not been available. In the original model, DBS and LCIG derive some cost benefit from reducing the need for apomorphine. It is possible that BMT would provide better value for money if there were no possibility of subcutaneous apomorphine. In comparison with such an approach, DBS and LCIG would lose some cost benefit and appear somewhat less cost effective. The GDG noted this anomaly, and expressed the view that the ideal trial would have 4 arms – comparing DBS with no apomorphine, BMT with no apomorphine, DBS ± apomorphine and BMT ± apomorphine. However, in the absence of such evidence, it is not possible to

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	speculate how much value apomorphine contributes to BMT. Moreover, the GDG noted that it would not be possible to recommend future research adopts such a design, as the clear benefits of DBS would make it difficult to recruit participants ethically. The GDG noted that the original health economic model suggests DBS provides somewhat better value for money than the published economic evaluation of PDSURG, even though the original model is predominantly based on evidence from PDSURG. It understood that there were multiple reasons for this: the PDSURG analysis is based on the whole RCT population, whereas the original model uses data on the HY≥3 subgroup (in whom the greatest effects were seen); the original model estimates ongoing cost benefits from apomorphine-sparing effects of DBS (which is not accounted for beyond 1 year in the PDSURG analysis) and from reduced time in full-time care (which is not considered at all); the method for estimating device replacement costs was also believed to be more precise in the original model than in PDSURG. The GDG also explored the substantial differences between the new modelling and that presented in the previous clinical guideline, where DBS was recommended with an ICER of £19,500 per QALY compared with BMT. The GDG was confident the new modelling provided a substantially more robust assessment of the cost effectiveness of DBS in people with advanced Parkinson's disease. Nevertheless, published, model-based economic evaluations (all with potentially or very serious limitations) tended to produce ICERs somewhat nearer common cost-effectiveness thresholds. The GDG agreed the original health economic model had addressed many of the identified limitations including: • Model structures reliant on assumed independent transitions across 2 measures from non-advanced PD populations • Lack of appropriately synthesised, randomised intervention effects • Assumed quality of life gains • A failure to model critical resource impacts explicitly (full-time care and use of apomorphine)
Quality of evidence	Best medical treatment (BMT) was noted to be country specific; in particular, not all countries advocate the use of apomorphine, whereas its use is comparatively common in the UK. This could make the intervention effect magnitude appear greater in RCTs from countries where apomorphine is not part of BMT. This may also impact multi-centre studies in the UK, with some centres using apomorphine more routinely than others. Additionally, people in the BMT arm of PDSURG (Williams et al., 2010) – knowing they could receive DBS at the end of the 12-month randomisation period – may have been less willing to maximise apomorphine use in the randomised period. RCT populations, whilst similar to each other, were felt to be younger than typical Parkinson's disease populations. Typical diagnosis would be aged 60+, whereas the included RCTs had an average age of around 60 with a decade of Parkinson's disease duration. The single RCT for LCIG versus BMT was the only blinded RCT. All people received a PEG-tube which meant any reported adverse event differences should be related to the drug rather than the device. However, adverse event rates were high in both arms. The GDG felt it was inappropriate to downgrade DBS RCTs for a lack of blinding due to ethical and practical considerations when trying to design a blinded DBS RCT. The GDG noted the included RCTs were likely to be the highest quality that could be achieved for DBS. This lack of blinding may lead to an overestimate of the intervention effect, but other factors may lead to underestimates (for example, participants who know they have been randomised to surgery may have unrealistic expectations of the procedure, which may impact on patient-reported outcomes following surgery).

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Measuring change over time in quality of life may be impacted by a person's expectations of therapy. Also, the level to which a person has previously adapted to their limitations may impact both their baseline valuation and valuation of any subsequent change. The GDG felt these issues had been shown in previous research in people with advanced Parkinson's disease and may result in lower than expected quality of life gains. It also felt, whilst the EQ-5D has been proven to be sensitive for people with Parkinson's disease in general (Schrag et al., 2000), this may not be the case in people with advanced Parkinson's disease and it may be more difficult to achieve improvement across the 3 levels of the 5 EQ-5D domains.

Virtually all outcomes were downgraded for indirectness as, apart from the PDSurg HY≥3 population, all RCTs contained people who did not have advanced Parkinson's disease (as defined for this review question).

UPDRS-II was not downgraded for inconsistency as, although there was evidence of statistical heterogeneity between RCTs, that was plausibly explained by duration of follow-up (that is, the effect improves over time). However, UPDRS-III and UPDRS-IV were downgraded for inconsistency as their shape is less clear over time.

Perioperative adverse event data could not be analysed for the PDSURG HY≥3 population. The GDG felt perioperative adverse event data for this population would not be unduly different to that for the full population. Age may impact adverse event rates, but this population had a similar mean age to the full population.

Before reviewing published evidence for these questions, the GDG had the benefit of a presentation from – and subsequent discussion with – 2 expert witnesses who had been investigators on the PDSURG RCT.

The GDG explored the contribution of the expert witnesses, particularly regarding the age of the PDSURG RCT (other RCTs – apart from Okun et al., 2012 – were conducted in a similar period of the 1990s and 2000s). It felt DBS may have become more effective and less expensive in recent years with changes including:

- Shorter operating times and inpatient stays and fewer outpatient appointment resources used
- Changes in intra-operative imaging requiring less operative time and staff
- Some expensive equipment no longer used (for example, robotic arms)
- Improvements in hardware such as connectors, cables, electrodes reducing the need for subsequent surgeries and revisions
- Battery lifespan has improved meaning fewer replacements needed; the replacement operation is now done as a day case under local anaesthetic

The GDG noted the high ongoing cost and impact of LCIG and queried whether treatment and evidence would be better considered on a 'responder' basis (that is, a test response period for all people, with only those showing some defined level of response continuing treatment beyond the test response period). It was noted that sometimes a naso-jejunal test was undertaken, but this was not universal. The included RCT did not involve a naso-testing period.

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10.3.8 Recommendations

76. Offer people in the later stages of Parkinson's disease best medical therapy, which may include continuous subcutaneous apomorphine infusion. [new 2017]

77. Do not offer deep brain stimulation to people whose Parkinson's disease is controlled by best medical therapy. [new 2017]

78. Consider deep brain stimulation for people in the later stages of Parkinson's disease whose symptoms are not controlled by best medical therapy. [new 2017]

79. Do not offer levodopa–carbidopa intestinal gel at any stage of Parkinson's disease. [new 2017]

10.4 Deep brain stimulation compared with best medical treatment for earlier Parkinson's disease

10.4.1 Review questions

- Is there a benefit in receiving DBS in earlier, rather than later, stages of Parkinson's disease compared with usual care?

10.4.2 Introduction

The aim of this review question was to assess whether there is a benefit in receiving DBS earlier in the course of Parkinson's disease (before all medical options have been exhausted), compared with usual care. The ideal study design to answer the question explicitly posed in the scope for this guideline would have been an extended longitudinal study that randomised people to DBS at a relatively early stage in disease progression or to a conventional approach with DBS reserved for advanced-stage disease. However, it was recognised, from the outset, that such evidence is extremely unlikely to exist; therefore, it was considered reasonable to review evidence on the effectiveness of DBS, compared with BMT alone, in patients at an earlier stage of disease.

Separate review questions sought to assess the effectiveness of DBS at a later stage of disease (see 10.3).

The review focused on identifying studies that fulfilled the conditions specified in Table 23.

Table 23: PICO table for the effectiveness of DBS in people with early PD

Populations	Patients with a confirmed diagnosis of Parkinson's disease who are: • Within 5 years of developing motor complications, **or** • Hoehn & Yahr stage <3
Interventions	Early intervention DBS + BMT
Comparators	BMT

Outcomes	• Adverse events – perioperative
	• Adverse events – long-term complications (including falls)
	• Symptom severity:
	  ○ UPDRS
	  ○ dyskinesia
	  ○ 'on' and 'off' time
	• Disease progression: Hoehn & Yahr score
	• Neuropsychiatric non-motor features:
	  ○ Cognitive impairment
	  ○ Sleep disorder
	  ○ Suicidal ideation
	• Health-related quality of life – patient
	• Health-related quality of life – carer
	• Information to inform decision making
	• Resource use and cost (including medication load)
	• Time to full time institutional care

For full details of the review protocols, please see Appendix C. Randomised controlled trials (RCTs) were considered to be the most appropriate study design to derive treatment effect

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metrics, and were therefore considered to be the highest quality within a GRADE framework. All other study designs were excluded from this review, including case–control studies, cohort studies and case reports.

10.4.3 Evidence review

Evidence for this question was identified via the same search that was undertaken for section 10.3; see 10.3.3 for a description.

3 published RCTs and a subgroup analysis of patient-level data from a fourth RCT were considered relevant to this question.

Evidence tables for included studies can be found in Appendix D, with GRADE profiles reported in Appendix E.

10.4.4 Description of included studies

A total of 4 RCTs (Charles et al., 2014; Schüpbach et al., 2007; Schüpbach et al., 2013; Williams et al., 2010) examined the effectiveness of DBS compared with BMT.

The 2 publications by Schüpbach and colleagues report a pilot (2007) and then a larger RCT (2013; 'EARLYSTIM') that followed similar protocols. Patients assigned to neurostimulation underwent bilateral stereotactic surgery of the subthalamic nucleus (StN). Final follow-up assessment was conducted at 18 months (pilot, 2007) and 24 months (full RCT, 2013) post baseline assessment. Participants and investigators were not blinded to treatment allocation; however, a repeat assessment of motor scores by blinded assessors was undertaken as a sensitivity analysis.

The small pilot RCT reported by Charles et al. (2014) randomised participants to DBS or BMT at an early stage in their disease course (age 50–75; 6–48 months' history of medication; no motor fluctuations or dyskinesias). The authors report 2 years' follow up. The primary outcome – UPDRS III – was assessed on video by an assessor who was unaware of the participants' treatment allocation; all other outcomes were collected in an unblinded fashion.

Investigators of the PDSURG trial (primary publication: Williams et al. 2010) made patient-level data available to the guideline developers. The GDG was aware that PDSURG recruited participants with a broad range of disease severity at baseline; therefore, the group requested that – for this review question, which focuses on treatment of moderate PD – subgroup analysis based on participants with Hoehn and Yahr scores lower than 3 at baseline should be used, where available. Analyses based on this population were derived by the developers. As a sensitivity analysis, results were also derived for participants from PDSURG who met the – somewhat narrower – eligibility criteria for the EARLYSTIM trial; it was not possible to specify a cohort that precisely matched these criteria, due to different baseline measurements, but the critical inclusion requirements could all be replicated: age 18–60; disease duration ≥4 years; Hoehn and Yahr <3; improvement of 50% or more with dopaminergic medication on UPDRS-III. PDSURG participants with a Hoehn and Yahr score of 3 or greater were analysed as part of the advanced PD review questions (see 10.3).

When the PDSURG HY<3 population had been extracted and combined with the other published RCTs, a pooled population was derived comprising 548 patients with earlier Parkinson's disease (mean age=55.7; mean disease duration=9.2 years; mean PDQ-39 single index=32.3; mean motor [UPDRS-III] score [on]=14.2; mean anti-Parkinson's medication dose equivalent to 899 mg of levodopa per day).

For adverse event data and neuropsychological outcomes, outcomes stratified by severity were not available in the patient-level data for PDSURG; therefore, no data are reported in

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this question – results from the full population (as published in Williams et al. 2010) were used in section 10.3.

In PDSURG, electrodes were implanted bilaterally into the StN; 4 participants also received GPI surgery. Participants were followed up for 12 months. Participants and outcome assessors were not blinded to treatment allocation.

10.4.5 Health economic evidence

10.4.5.1 Review of published cost–utility analyses

A single literature searches was conducted to identify existing CUAs for this question and for those comparing DBS, LCIG and BMT for people with advanced Parkinson's disease (see appendix I for the search strategies). A total of 2,910 articles were returned, of which 15 were ordered and none were included. However, 3 CUAs comparing early DBS with BMT were submitted as part of the call for evidence (see 0); 1 was subsequently published in a journal (Fundament et al., 2016). Relevant details of the included studies are summarised in economic evidence profiles in appendix F.

Using their previously published model (see 10.3.5.1) and updating inputs where necessary, Dams et al. (2016) submitted a partially applicable study with very serious limitations which modelled the EARLYSTIM RCT. They found early DBS to be cost effective compared with BMT (ICER €22,700 per QALY), assuming a lifetime treatment effect. Medtronic (AIC) submitted a partially applicable study with potentially serious limitations that used a simplified version of their previous economic model (Eggington et al. 2014) to also model the EARLYSTIM RCT. They found early DBS increased QALYs compared with BMT at an ICER of €48,900 per QALY, but this ICER was highly sensitive to a number of key inputs. In probabilistic sensitivity analysis, DBS conferred additional QALYs to BMT at an incremental cost of €50,000 or less in 57% of iterations.

Fundament et al. (2016; funded by a manufacturer of DBS equipment) undertook a directly applicable study with potentially serious limitations, modelling the EARLYSTIM RCT from a UK NHS perspective. The model projected 2-year data from the RCT to a 15-year time horizon, assuming that benefits would remain constant in all domains except motor complications (UPDRS-IV), for which it was assumed that the gap between DBS and BMT would widen over an 8-year period. Mortality, fall probability and extrapolated quality of life all depended on projected UPDRS profiles. The model assumed device replacements take place at 4.5-year intervals. Apomorphine and LCIG arms were also modelled, but these are not relevant to this population. This study found early DBS increased QALYs compared with BMT at an ICER of £19,887 per QALY. In probabilistic sensitivity analysis, DBS conferred additional QALYs to BMT at an incremental cost of £20,000 or less in 51% of iterations.

10.4.6 Evidence statements

Adverse events

Moderate-quality evidence from 1 RCT could not differentiate the rate of serious adverse events or falls in people receiving DBS and BMT: at a 95% confidence level, data were consistent with appreciable benefit or appreciable harm.

Symptom severity: Hoehn and Yahr score, UPDRS, dyskinesia, 'on' and 'off' time

High-quality evidence from 1 RCT showed that Hoehn and Yahr score decreases by a greater amount in people receiving DBS than in those who receive BMT only (MD=−0.32; 95%CI: −0.56 to −0.09).

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High-quality evidence from 1 RCT showed that mean daily 'on' time without troublesome dyskinesias is higher in people receiving DBS compared with those who receive BMT only (MD=1.90 hours; 95%CI: 0.51 to 3.29).

High-quality evidence from 2 RCTs showed that mean daily 'off' time is considerably reduced in people receiving DBS compared with those who receive BMT only (MD=−1.70 hours; 95%CI: −2.35 to −1.06).

Moderate-quality evidence from 3 RCTs did not identify meaningful differences in mentation (as measured by UPDRS part I) between people receiving DBS and those who receive BMT only.

Moderate-quality evidence from 4 RCTs did not identify meaningful differences in activities of daily living (as measured by UPDRS part II) between people receiving DBS and those who receive BMT only.

High-quality evidence from 4 RCTs showed motor function (as measured by UPDRS part III) is better in people receiving DBS compared with those who receive BMT only (MD=−3.21; 95%CI: −4.49 to −1.93).

High-quality evidence from 4 RCTs showed that complications of therapy (as measured by UPDRS part IV) are less prevalent in people receiving DBS compared with those who receive BMT only (MD=−4.68; 95%CI: −6.75 to −2.61).

Neuropsychiatric non-motor features: cognition, depression

High-quality evidence from 2 RCTs showed that DBS improves symptoms of depression, as assessed by the Montgomery–Åsberg depression rating scale, compared with BMT alone (MD=−2.66; 95%CI: −4.11 to −1.20).

Moderate-quality evidence from 2 RCTs did not identify meaningful differences in dementia (as measured by the Mattis Dementia Rating) between people receiving DBS and those who receive BMT only.

Health-related quality of life – patient

High-quality evidence from 4 RCTs showed an improvement in Parkinson's disease-related quality of life, as assessed by the PDQ-39, in people undergoing DBS compared with those receiving BMT only (MD=−5.96; 95%CI: −8.27 to −3.65).

Low-quality evidence from 1 RCT did not identify meaningful differences in health-related quality of life, as assessed by the EQ-5D, in people undergoing DBS compared with those receiving BMT only. At a 95% confidence level, data are consistent with considerable benefit and considerable harm.

Health-related quality of life – carer

No evidence was reported for the effect of DBS on carer quality of life.

Medication load

Moderate-quality evidence from 3 RCTs showed a considerable reduction in anti-Parkinson's medication in people undergoing DBS compared with those receiving BMT only (MD=−469 mg levodopa-equivalent; 95%CI: −765 to −173).

Health economic evidence statements

One partially applicable study with very serious limitations found early DBS to produce additional QALYs, compared with BMT, at an ICER €22,700 per QALY. Another partially

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applicable study with potentially serious limitations found early DBS to produce additional QALYs, compared with BMT, at an ICER of €48,900 per QALY. One directly applicable study with very serious limitations found early DBS increased QALYs, compared with BMT, at an ICER of £20,000 per QALY. In probabilistic sensitivity analysis, DBS conferred additional QALYs to BMT at an incremental cost of £20,000 or less in 51% of iterations

10.4.7 Evidence to recommendations

Relative value of different outcomes	The GDG did not prioritise symptom-based outcomes above person reported outcomes or adverse events. It felt it was important to consider both the benefits and harms of interventions, and to consider a wide perspective of benefits. Minimally clinically important differences (MCID) were discussed and agreed for some outcomes in the review questions for people with advanced disease (see 10.3.7).
Trade-off between benefits and harms	The considerations from the previous review question on DBS versus LCIG versus BMT regarding multiplicative outcomes, non-motor outcomes and falls outcomes were felt also to be relevant to this evidence (see 10.3.7). The GDG felt the 2 main RCTs (EARLYSTIM and PDSURG) were set up to answer different research questions. It felt that the EARLYSTIM cohort was very specific and unlike people with Parkinson's disease that are commonly seen in UK practice. Also, BMT in the EARLYSTIM trial was thought likely to be considerably different to that in the UK. The GDG's experience of operating DBS on people with less advanced Parkinson's disease was that these people did find benefits, but not to the same magnitude as those with advanced Parkinson's disease. This experience was in keeping with the evidence presented for this review question compared with results seen in the advanced population (see 10.3). It felt that a difference of 2.6 points on the Montgomery–Åsberg depression scale may not represent a clinically meaningful change. The GDG also noted the lack of EQ-5D benefit shown in the PDSURG subset. Overall, the GDG noted no evidence was presented suggesting that the short-term benefit of DBS for people with earlier Parkinson's disease is greater than it is for those with advanced disease. The GDG felt DBS was being offered to increasingly younger people in the UK. To explore the clinical effectiveness and cost effectiveness of such practice, a trial comparing DBS in people who have just begun to develop motor complications/dyskinesias with DBS at its current advanced Parkinson's disease indication (using UK-based BMT) would be useful. The point at which early DBS should be offered was felt to be when people would currently offer adjuvant therapy to initial levodopa.
Trade-off between net health benefits and resource use	The economic evidence review question on DBS for people with advanced Parkinson's disease found DBS was not cost effective compared with BMT at commonly accepted cost-effectiveness thresholds. The original health economic modelling was sensitive to the intervention effect duration and magnitude (particularly for EQ-5D) and the device lifespan. The GDG noted the clinical evidence presented for this review question showed smaller gains for EQ-5D (and for UPDRSIII (on) and PDQ-39) compared with those that had been identified in the advanced Parkinson's disease population. Given the smaller effect, and that there was no available evidence on device lifespan for this population, but assuming that a longer duration of therapy would incur more device replacements, the GDG felt it was highly unlikely any original health economic modelling would produce an ICER within commonly accepted thresholds for this review question. The GDG discussed the UK-focused CUA that had been submitted by a manufacturer of DBS equipment via the call for evidence (and was subsequently published; Fundament et al., 2016). It noted the critical assumptions that all benefits observed in the 2-year EARLYSTIM RCT of

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	DBS, compared with BMT, would persist indefinitely, and the benefit in motor complications (UPDRS-IV) would continue to grow over a period of 8 years. The GDG agreed that, although it could see why the clinical experts advising the developers of this model had emphasised the important effect that DBS has on motor complications (dyskinesias in particular), it was also true that these symptoms normally respond well to the kind of optimised second-line pharmacological management to which early DBS should be compared. Therefore, the GDG did not believe it was plausible that the benefit of DBS would increase over time. The GDG also noted that the other 2 published economic studies identified for this review question were each based on essentially unchanged models that had previously been used to estimate the cost effectiveness of DBS for the advanced Parkinson's disease population. Both generated higher ICERs for the earlier population.
Quality of evidence	The considerations from the previous review question on DBS versus LCIG versus BMT regarding BMT, blinding and downgrading of outcomes, RCT quality, quality of life outcomes and changes since PDSURG were felt also to be relevant to this evidence (see 10.3.7). Additionally, the GDG questioned whether dopamine agonists were used in a different manner in EARLYSTIM (Germany and France) to how they would be used in the UK. It was noted that, despite a bespoke individual level analysis, the PDSURG dataset used for this analysis portrayed an older population with longer disease duration than in the other included studies. This suggests that, in each of the included RCTs, there may have been selection effects over and above the explicitly stated eligibility criteria.

10.4.8 Recommendations

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See section 10.3.8 for recommendations on deep brain stimulation

10.4.9 Research recommendations

9. What is the effectiveness and cost effectiveness of early DBS compared with intensified medical management (with DBS delayed until conventional indications develop)?

Why this is important

There is a growing trend towards DBS surgery being undertaken at earlier stages of Parkinson's disease (before all other medical options have been exhausted). This has the potential to provide symptomatic benefit earlier in the disease course, but also possible downsides, including the development of DBS-related complications and a tapering of the treatment benefit at an earlier stage. Currently, the question of early versus late DBS can only be addressed indirectly, through trials that compare early DBS versus no DBS, and trials that compare late DBS versus no DBS. The evidence base could be improved with a specific RCT comparison of early DBS versus DBS at the standard times it is currently used. Such a trial would have the additional advantage of being easier to recruit to (since everyone will be offered DBS) than a trial of DBS versus nothing, which is likely to be impractical to perform now DBS has become such a commonly available procedure.

11 Managing and monitoring impulse control disorder as an adverse effect of dopaminergic treatment

Impulse control disorders (ICDs) are a group of psychiatric conditions linked by their repetitive reward-based behaviours. Their core feature is the failure to resist an impulse, drive, or temptation to perform an act harmful to either self or others. ICDs are a recognised feature of Parkinson's disease (PD) with reviews reporting their prevalence as between 14 and 24% in treated patients. Evidence suggests an association with both dopamine agonists and levodopa. The most frequently reported behaviours include pathological gambling, hypersexuality, compulsive shopping, hobbyism and overeating.

ICDs in Parkinson's disease are postulated to result from inappropriate activation of dopamine receptors. Dopaminergic ventral tegmental projections to the ventral striatum are involved in motivation and reward prediction. One hypothesis is that the neurodegenerative process in PD mainly affects the substantia nigra, whereas the ventral tegmental area can be relatively spared, potentially leading to differential stimulation following administration of dopaminergic medication.

The presence of ICDs can lead to severe distress for patients and carers, as well as financial difficulties and even criminal convictions. It is important to recognise that ICDs may be covert, with patients taking steps to conceal their behaviour from carers and family. It is essential to counsel patients about the possibility of developing ICDs before commencing dopamine replacement therapy. This will hopefully enable early diagnosis and treatment. Typically the first pharmacologic management is to reduce the oral dopamine agonists, reflecting their role in producing ICDs. The act of withdrawing of the dopamine agonist is often sufficient. In some patients dose reduction without withdrawal can be effective, however it is not clear why some patients respond to simple dose reduction while and others require drug cessation. Dopamine agonist reduction or withdrawal is sometimes complicated by two distinct negative clinical consequences, namely worsening of motor function and the dopamine agonist withdrawal syndrome. There have also been trials of other non-pharmacological and pharmacological treatments.

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11.1 Predictors for the development of impulse control disorders

What factors should healthcare professionals consider as potential predictors for the development of impulse control behaviours as an adverse effect of dopaminergic treatment?

11.1.1 Introduction

The aim of this review question was to determine potential predictors for the development of impulse control disorders.

The review focussed on identifying studies that fulfilled the conditions specified in Table 24.

Table 24: PICO table for predictive factors for Impulse control disorders (ICD) in Parkinson's disease

Population	Patients with a confirmed diagnosis of Parkinson's disease currently on dopaminergic medication
Interventions	Dopaminergic medication: • Prolonged release dopamine agonists • Immediate release dopamine agonists • Transdermal dopamine agonists • Levodopa • Apomorphine
Predictive factors	• Sex • Age • Previous history and family history of ICD • Disease duration • Disease severity • Dosage of dopaminergic medication

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For full details of the review protocol, please see Appendix C. Retrospective or prospective case studies, cohort studies, and case–control studies were considered to be the most appropriate study design to derive predictive metrics, such as odd's ratios (OR) and were therefore considered to be the highest quality within a modified-GRADE framework. Case-report studies were excluded from this review.

11.1.2 Evidence review

An overarching systematic search was conducted to inform review questions 8, 9, and 10 (see appendix I), which identified 3,423 references. The references were screened on their titles and abstracts and full papers of 60 references were obtained and reviewed against the inclusion and exclusion criteria in the review protocol (see appendix C). This review question was not considered in the previous Parkinson's disease guideline (CG35), no further studies were therefore identified.

Overall, 44 studies were excluded as they did not meet the eligibility criteria such as inappropriate study design, narrative review with no primary data, or populations other than Parkinson's disease. A detailed list of excluded studies and reasons for their exclusion is provided in appendix G.

The 16 remaining published papers did meet eligibility criteria and were included.

The quality of the evidence from these 16 published papers ranged from very low to high, with overall quality of the evidence being moderate.

Of the 16 included studies, 11 were utilised within the present review question. An additional 8 new papers were identified through rerun searches at the end of the guideline, of which 2 were included in the current review and 5 excluded. Therefore, a total of 13 studies were included in the final analysis. The included studies examined the incidence of impulse control disorders (ICD) in Parkinson's disease and the potential predictive factors for the development of ICD. Studies that examined factors such as personality correlates of ICD's were not included within this review as this fell outside the present review protocol and could not be utilised to inform predictive factors.

Evidence tables for included studies can be found in Appendix D, with GRADE profiles reported in Appendix E.

11.1.3 Description of included studies

A total of 13 studies with 6,631 participants examined the incidence and potential predictive factors for the development of impulse control disorders in Parkinson's disease. Of the total study population, 678 participants were found to meet criteria for 1 or more ICD's (total study prevalence=10.2%). The included studies were both retrospective and prospective cohort studies, and the primary ICD's of interest examined were: pathological gambling, compulsive buying/shopping, compulsive sexual behaviour, and compulsive eating behaviour. There was inconsistency between the studies in terms of diagnostic criteria used to define each of the aforementioned ICD's. The majority of the included studies utilised a structured interview with both the patient and carer, as well as behavioural questionnaires and criteria for assessment such as the Parkinson's disease impulsive compulsive disorders questionnaire (QUIP) and the Diagnostic and Statistical Manual of mental disorders (DSM-IV).

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Dopamine Agonist use

Low-quality evidence from 2 studies reported dopamine agonist use to be an important predictor for the development of ICD in people with Parkinson's disease. High-quality evidence from 2 studies reported dopamine agonist use to be an important predictive factor of the development of ICD after controlling for age, Parkinson's disease duration, male gender, and longer duration of treatment with DA's.Low-quality evidence from 3 studies reported that the use of pramipexole is an important predictive factor to the development of ICD.

Dopamine agonist (DA) levodopa equivalent daily dosage (LEDD) and total levodopa equivalent daily dosage (TLED)

Low- to moderate-quality evidence from 2 studies reported an association between DA LEDD and development of an ICD after adjusting for age at Parkinson's disease onset, duration of Parkinson's disease, gender, marital status, and smoking, for dose of DA LEDD, between 60–160 mg/day, >160 mg /day, and a small increased likelihood for DA LEDD between 540–750 mg/day . However, no meaningful association between dopamine agonist dosage and the development of ICD was found or a DA dosage of >750mg/day.

Moderate-quality evidence from 1 study did not find DA LEDD or TLED to be independent risk factors for the development of ICD.

Duration of treatment with DA

Very low-to-low-quality evidence from 1 study reported no association between duration of treatment with a DA for < 2 years, between 3 and 5 years, and > 6 years compared with no treatment, after controlling for age of Parkinson's disease onset and male gender.

Levodopa use

Very low-quality evidence from 1 study reported no meaningful relationship between levodopa use and the development of ICD in people with Parkinson's disease.

High-quality evidence from 1 study did find a small and non-statistically significant relationship between taking levodopa and the potential for development of ICD after controlling for age at Parkinson's disease onset, gender, DA use, family history of gambling, marital and smoking status.

Moderate-quality evidence from 1 study did not find the dosage of levodopa to be an independent risk factor for the development of ICD.

Combination therapy

Very low-quality evidence from 1 study reported a small non-significant relationship between combination therapy of levodopa and pramipexole and the development of ICD in people with Parkinson's disease.

Amantadine

Moderate-quality evidence from 2 studies reported amantadine use to be a potential predictor for the development of ICD in people with Parkinson's disease.

High-quality evidence from 2 studies reported no evidence to indicate amantadine to be an important predictor for the development of ICD after controlling for age, Parkinson's disease duration, male gender, and longer duration of treatment with DA's.

Entacapone

Low-quality evidence from 1 study reported no evidence for entacapone to be a significant predictor for the development of impulse control disorder.)

Rasagiline/selegiline

Low-quality evidence from 1 study reported no evidence for rasagiline to be a predictor for the development of impulse control disorder.

No evidence was found for selegiline.

Short- and long-acting dopamine agonist

Moderate-quality evidence from 1 study suggested that rotigotine patches and prolonged release pramipexole were associated with significantly lower ICD rates in comparison with other DA formulations (immediate release pramipexole, immediate- and extended release ropinirole).

Marital status

Moderate-quality evidence from 1 study reported evidence for being unmarried to be an important predictor for the development of impulse control disorder.

Alcohol intake

Moderate-quality evidence from 1 study reported evidence for high alcohol intake to be an important predictor for the development of impulse control disorder.

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Smoking status

Low-quality evidence from 1 study reported evidence for smoking to be an important predictor for the development of impulse control disorder.

Younger age of Parkinson's disease onset

Low-quality evidence from 4 studies did not report younger age at Parkinson's disease onset to be a predictive factor for the development of ICD when duration of disease, total LEDD for DA and levodopa, DA use, amantadine use, and prior history of ICD were taken into account.

Male gender

Moderate-quality evidence from 1 study reported male gender to be an important predictor for the development of ICD in people with Parkinson's disease.

Low-quality evidence from a further 2 studies reported male gender not to be a predictive factor for the development of ICD when duration of disease, total LEDD for DA and levodopa, DA use, amantadine use, and prior history of ICD were taken into account.

Moderate-quality evidence from 1 study did not find gender to be an independent risk factor for the development of ICD.

Comorbid anxiety or depression

Very low-quality evidence from 1 study reported comorbid anxiety and/or depression to be a potential predictor for the development of ICD in people with Parkinson's disease, however this was not statistically supported.

High-quality evidence from 1 study reported that an increase from baseline to follow-up in the Beck's depression inventory (BDI) was not a predictor for the development of ICD in people with Parkinson's disease after adjusting for age at Parkinson's disease onset, duration of Parkinson's disease, gender, and DA LEDD mg/d.

Moderate-quality evidence from 1 study reported the presence of comorbid anxiety or depression to be an important predictive factor for the development of ICD after controlling for age of onset of Parkinson's disease and dose of DA /100mg.

Prior ICD symptoms

High-quality evidence from 1 study reported the presence of prior ICD symptoms to be an important predictor for the development of ICD in people with Parkinson's disease after adjusting for age at onset of Parkinson's disease, male gender, duration of DA therapy, amantadine use, and total LEDD.

Family history of alcohol or gambling abuse

High-quality evidence from 1 study reported the presence of positive family history of alcohol abuse to be a potential predictor for the development of ICD in people with Parkinson's disease after adjusting for age at onset of Parkinson's disease, DA treatment, levodopa treatment, marriage status, living in US, and smoking.

Moderate-quality evidence from 1 study reported the presence of positive family history of alcohol or gambling abuse to be a potential predictor for the development of ICD in people with Parkinson's disease.

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11.1.5 Health economic evidence

No health economic evidence was identified for this review question.

11.1.6 Evidence to recommendations

Relative value of different outcomes	The GDG agreed that the most important outcomes of interest were those that were found to be significant predictors for the development of impulse control disorders.
Trade-off between benefits and harms	The GDG noted that it may be important to consider that there may be gender differences in the development of different types of ICDs e.g. hypersexuality is reported to be more prevalent in men. The GDG discussed the potential problems for the availability and accuracy of data in people with Parkinson's disease who live alone, as they are potentially less likely to have ICDs diagnosed when there is no one is watching out for ICD changes. The GDG discussed the levodopa equivalent daily dose (LEDD) evidence and agreed it was not very useful for clinical management purposes, as a high dose LEDD may represent a high dose of levodopa, with less DAs. This was not clear from the evidence presented, and may explain the otherwise unexpected finding that high LEDD values are associated with lower rates of ICDs. The GDG discussed the evidence linking duration of treatment to ICD development and noted that the evidence fits with the common clinical observation, whereby if someone with Parkinson's disease is going to develop an ICD, then this will occur regardless of the duration if dopamine agonist therapy. If an ICD develops later in the disease course, it is often because of increased dopaminergic medication dosage. The GDG discussed retrospective and prospective evidence and noted that both are likely to present different evidence, with prospective studies being more informative. The GDG discussed that once a clinician or researcher has started looking for signs of ICD, they are more likely to find patients who meet ICD criteria. Retrospectively, these signs may not have been mentioned in the notes of people in whom clinicians were not actively looking for an ICD. For this reason, retrospective evidence is less appropriate as one can't control for many potentially important factors, especially recording whether dopaminergic medication has been altered in an attempt to address ICD behaviours or not. It was also noted by the GDG that a dose-response relationship wouldn't be demonstrated in a retrospective study that recruits from a clinically monitored population: these patients will already have had dosages adjusted if they had issues relating to ICDs. It was further noted that the ICDs recognised first, historically, were the ones that are more common in men; as experience has developed, clinicians are becoming more likely to spot those that may be more common in women. This was highlighted as a still-evolving field. The GDG discussed the evidence for depression and noted that in their clinical experience, the presence of anxiety and depression is common in Parkinson's disease, and is not likely to be more common in those with ICD. The GDG also agreed that the evidence which reported a 1 point difference on the Beck's depression inventory is not clinically meaningful. Finally, the GDG discussed the difference between using the term impulse control disorders (ICDs) and impulse control behaviours. It was recognised that there exists a spectrum of behaviours and that some of these behaviours may be problematic, but not necessarily meet the criteria for a diagnosis for ICD in e.g. DSM IV. The GDG agreed the term disorders was the correct one to use in recommendations, as not all behaviours are harmful, and it is those that are harmful we are interest in.
Trade-off between net health benefits	No economic evidence was identified for this review question.

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and resource use	
Quality of evidence	The GDG agreed that the majority of evidence was low quality. The GDG also discussed the retrospective compared with prospective evidence. It was agreed that there exists a need for more evidence from prospective studies with a clear account of dopaminergic medication for patients, and using well-validated scales for the recognition of ICD.

11.1.7 Recommendations

80. Recognise that impulse control disorders can develop in a person with Parkinson's disease who is on any dopaminergic therapy at any stage in the disease course. [new 2017]

81. Recognise that the following are associated with an increased risk of developing impulse control disorders:

- Dopamine agonist therapy.
- A history of previous impulsive behaviours.
- A history of high alcohol consumption and/or smoking. **[new 2017]**

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11.2 Managing dopaminergic treatment in people who have developed impulse control disorder

How should dopaminergic treatment be managed in people who have developed impulse control disorder as an adverse effect of dopaminergic treatment?

11.2.1 Introduction

The aim of this review question was to determine optimal management strategies for ICD's that have developed as an adverse effect of dopaminergic treatment. Management strategies were defined to include either adjuvant pharmacological or behavioural therapies, or direct management of a person's current dopaminergic medication.

The review focussed on identifying studies that fulfilled the conditions specified in Table 25.

Table 25: PICO table for management of impulse control disorders in Parkinson's disease

Population	Patients with a confirmed diagnosis of Parkinson's disease who are currently taking dopaminergic medication and have a diagnosis of impulse control disorder
Interventions	• Titration of dopaminergic therapy at different levels of reduction • Change in dopaminergic therapy • Behaviour management strategy • Adjunctive pharmacotherapy
Comparators	• Usual care • Titration of dopaminergic therapy at different levels of reduction • Change in type of dopaminergic therapy • Adjunctive pharmacotherapy • Psychological intervention
Outcomes	• Clinical/patient improvement • Adverse effects • Resource use and cost • Disease severity • Patient health related quality of life • Measure of ICD e.g. QUIP • Nutrition and overeating • Carer health related quality of life

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A post-hoc decision was made by the GDG to additionally search for evidence of ICD symptom management strategies that are adjuvant to the modification of dopaminergic medication. These could include both behavioural and pharmacological interventions. For full details of the review protocol, please see Appendix C.

Randomised controlled trials (RCTs) were considered to be the most appropriate study design to derive treatment effect metrics for adjunctive pharmacological or behavioural management interventions and were therefore considered to be the highest quality within a GRADE framework for these interventions. For titration of current dopaminergic medication, cohort studies were considered the most appropriate study design, and therefore considered the highest quality within a GRADE framework. All other study designs were excluded from this review, including case–control studies, qualitative studies, and case reports.

11.2.2 Evidence review

An overarching systematic search was conducted to inform review questions 8, 9, and 10 (see appendix I), which identified 3,423 references. The references were screened on their titles and abstracts and full papers of 60 references were obtained and reviewed against the inclusion and exclusion criteria in the review protocol (see appendix C). This review question was not considered in the previous Parkinson's disease guideline (CG35), no further studies were therefore identified.

Overall, 44 studies were excluded as they did not meet the eligibility criteria such as inappropriate study design, narrative review with no primary data, or populations other than Parkinson's disease. A detailed list of excluded studies and reasons for their exclusion is provided in appendix G.

The 16 remaining published papers did meet eligibility criteria and were included.

A total of 4 studies from these 16 published papers examined the management of ICD's and were included within the present review question. An additional 8 new papers were identified through rerun searches at the end of the guideline, of which none were included for the present review.

The overall quality of the evidence from the 4 included studies ranged from low to high.

The included studies examined the effectiveness of strategies to manage symptoms associated with Impulse control disorders (ICD's) in patients with Parkinson's disease and quality of life in patients with Parkinson's disease.

Evidence tables for included studies can be found in Appendix D, with GRADE profiles reported in Appendix E.

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11.2.3 Evidence statements

Management of dopaminergic medication

Resolution of ICD symptoms

Low-quality evidence from 1 study reported the resolution of symptoms of ICD in 13/18 (72.2%) patients with Parkinson's disease and ICD: 10/10 (100%) of patients who discontinued DA usage, 3/5 (60%) who reduced DA dosage, and 0/3 (0%) of people who continued the same dosage experienced a resolution of ICD symptoms.

Adverse effects

Low-quality evidence from 1 study (Bastiaens et al., 2013) reported the development of dopamine agonist withdrawal syndrome (DAWS) in 4/10 (40%) of those who discontinued DA therapy, 1/5 (20%) of those who reduced dosage, and 1 patient who was unable to decrease DA dose because of the severity of DAWS symptoms. No information was given as to how DA therapy was reduced or discontinued, i.e. whether therapy was abruptly ceased or gradually tapered.

The same study reported 4/5 (80%) of those with DAWS to develop dopamine dysregulation syndrome (DDS) as they adjusted levodopa in unsuccessful attempts to alleviate their DAWS symptoms.

Adjuvant cognitive behavioural therapy (CBT)

Resolution of ICD symptoms

High-quality evidence from 1 study with 44 participants reported CBT to considerably reduce ICD behaviours, as measured by the impulse control behavioural scale (MD=−4.7, 95%CI: −5.8 to −2.5)

Depression and general health

Moderate-to-high quality evidence from 1 study with 44 participants reported CBT to considerably improve CGIC score (MD=−0.8; 95%CI: −5.6 to −0.3), as well as general health, as measured by the general health questionnaire (MD= −3.8; 95%CI: −5.6 to −2.0) and mental health (MD= −4.7; 95%CI −9.1 to −0.3), as measured by the neuropsychiatric inventory (NPI). A significant improvement in work social adjustment was also reported in favour of CBT (MC=−3.6; 95%CI: −6 to −1.3). An improvement in depression and anxiety was reported in favour of the treatment group, however this was not statistically supported for depression (MC=−3.5; 95%CI: −6.6 to 0.4), or anxiety (MD=−1.8; 95%CI: −5.4 to 1.8).

Carer health

Moderate-quality evidence from 1 study with 44 participants reported no treatment effect for CBT on carers perception of the quality of their relationship with their partner (GRIMS marital state; MD=−2.3; 95%CI: −5.7 to 1.3), or in their own general health (GHQ; MD=−1.5; 95%CI: −3.2 to 0.1).

Adverse effects

No adverse effects of receiving CBT were reported.

Adjuvant naltrexone therapy

Resolution of ICD symptoms

High-quality evidence from 1 study with 50 participants reported a meaningful decrease in ICD behaviour, as measured by the QUIP, as a consequence of naltrexone therapy compared with placebo (MD=7.37; 95%CI: 2.45 to 12.66).

Clinical symptoms

Moderate-quality evidence from 1 study with 50 participants reported no treatment effect of naltrexone on clinical global impression of change score (OR=1.57; 95%CI: 0.47 to 5.23), or on UPDRS motor score (MD=−3.70, 95%CI: −9.24 to 1.84).

Adverse effects

Low-quality evidence from 1 study with 50 participants reported adverse events in 48 patients in both the naltrexone and placebo groups.

- New onset nausea was common in the naltrexone group (29.2% vs 0%). This was reported as mild-to-moderate intensity in all cases and was not associated with vomiting, nor did it lead to study discontinuation in any participants.
- 5 participants discontinued treatment (n= 4 naltrexone, n=1 placebo). None of these patients reported nausea or experienced any other adverse event likely to be due to study treatment.
- Other adverse events that occurred in >5% of patients that were more common in naltrexone group were dizziness (16.7% vs 4.2%) and headaches (20.8% vs 16.7%)

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- A change (increase or decrease) in blood pressure was reported as more common in the placebo group compared with the naltrexone group (41.7% vs 25%).

Adjuvant amantadine therapy

Resolution of PG symptoms

Low-quality evidence from 1 crossover RCT with 17 participants reported a meaningful improvement in obsessive-compulsive behaviour in those that received amantadine compared with those exposed to placebo, as assessed by the Yale-Brown obsessive compulsive scale (Y-BOCS; MD=−9.17, 95%CI: −11.1 to −10.3) and the symptom assessment scale (SAS; MD=−9.6, 95%CI: −10.12 to −9.08).

Resolution of PG spending behaviour

Low-quality evidence from 1 crossover RCT with 17 participants reported a considerable decrease in the percentage of daily salary spent on gambling in those that received amantadine compared with those exposed to placebo (MD=−16.40, 95%CI: −18.73 to −14.27).

Adverse effects

Low-quality evidence from 1 crossover RCT with 17 participants reported 5 patients to drop out of the amantadine intervention group due to adverse events. Adverse effects included confusion (n=1), orthostatic hypotension (n=1), insomnia (n=2), and visual hallucinations (n=1).

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11.2.4 Health economic evidence

No health economic evidence was identified for this review question.

11.2.5 Evidence to recommendations

Relative value of different outcomes	The GDG discussed improvement of ICD symptoms to be the most valued outcome of interest in this review. The improvement of these symptoms must be weighed against the control of motor and non-motor symptoms of Parkinson's disease, which also significantly impact upon quality of life for both the patient and carer.
Trade-off between benefits and harms	The GDG discussed the key trade-off between benefit and harm to be balancing the clinical benefit of dopaminergic treatment with ICD side effects. There is an important need to control Parkinson's disease symptoms, but reduce the risk of ICD, as well as avoid withdrawal symptoms of medication. **Cognitive behavioural therapy (CBT):** • The GDG discussed the merits of CBT in patients whom had failed to respond to medication changes. The GDG noted that CBT should not be used as first-line treatment without first assessing contribution of dopaminergic medication to ICD behaviours. • The GDG noted that it was not possible to assume that both the CBT and waitlist control (WLC) groups were entirely comparable, as it was noted that the waitlisted patients may have had their medication changed during the study period to alter their ICD behaviours. It was also noted that the medication load may have been reduced in the CBT groups, however this was not reported in the paper. • The GDG noted that DA use was reported at baseline, but not at the end of the study – this was cited as a key omission. • Average ICD score indicated that patients were only mildly affected • The GDG cited a follow-up paper to this study that suggested that less

severe ICD patients respond better to CBT than severely affected patients (Okai et al., 2014).

- The GDG noted that often cognition changes as a result of ICD development – this can be difficult to change by just reducing medication. The rationale for CBT is that there is a need to address changes in cognition as well as medication.
- The GDG recognised specialist CBT to be significantly resource intensive – 6 months in total with frequent home visits.
- The GDG also agreed that the NPI finding was small and not specifically related to ICD. However, the GDG considered the change in NPI as probably a clinically-meaningful change to patient experience and quality of life.
- The GDG agreed that CBT may be useful but needs to be very specialised – this raises a potential problem of service provision.

Naltrexone

The GDG discussed the evidence that Naltrexone caused frequent, common side effects – this was considered a serious problem.

The GDG was therefore reluctant to recommend this, especially with limited evidence of efficacy available (only 1 study available and only one outcome showed a positive significant difference).

Amantadine

The GDG discussed their experience of patients with Parkinson's disease developing de novo ICDs when taking amantadine.

The rationale for using amantadine to treat ICD was noted as unclear, especially where amantadine may be an important contributory factor to the development of ICD.

Case studies suggest that amantadine may be beneficial when modification of DA therapy fails.

The GDG was reluctant to recommend this based on low quality evidence.

Modification of dopaminergic therapy

- The GDG discussed the evidence presented for modification of dopaminergic therapy and raised the problem within the field of the availability of high quality RCT or cohort evidence. It was discussed that it has been long-known that if ICD occurs, clinicians should first adjust dopaminergic treatment, so no high quality research is being carried out in this area.
- The key concern for clinicians and patients is the trade-off of the clinical benefit of dopaminergic treatment with the potential for the development of ICD side effects
- Dopamine agonist withdrawal syndrome (DAWS) was discussed as perhaps less common in the groups clinical experience than reported in study
- The GDG noted that gradually reducing dopamine agonists is key to avoiding DAWS, where DAWS is more likely to occur if dopamine agonist is abruptly stopped. This gradual reduction of DA should take place before reducing levodopa.
- Dysphoria and low mood were considered relatively common after a reduction in DA, and motor effects can also occur.
- The GDG noted that clinicians should be aware of the potential for DAWS if they are reducing a patient's DA.
- The GDG considered that in practice, if an ICD arose, clinicians would reduce the most recent medication change first and assume this change was what had caused the ICD to arise.
- The GDG discussed the need to work with the patient to establish what balance is acceptable to them between Parkinson's disease symptom control and a reduction in ICD behaviours.
- The GDG discussed that patients experiencing ICD behaviours should be

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	under the care of a specialist. • The GDG noted a clear trade-off between the management of Parkinson's disease symptoms which lead to taking a DA in the first place, and ICD behaviours which were identified as problematic by either patient, clinician, or carer. • The GDG thought it was important to note that it should not be a non-specialist i.e. a GP changing dopaminergic medication, and that a specialist should oversee any dopaminergic medication changes. • The GDG also noted that any delay in seeing a specialist could be problematic. There is a need to be able to act quickly if i.e. gambling behaviour is occurring or other behaviours which are likely to impact detrimentally on the patient's personal or social life. The GDG noted that patients can lose insight into their problems, however after a reduction in medication and the behaviours subside, patients can regain insight and often realise their altered ICDs to be problematic. • It was noted that patients may lack the capacity to make informed decisions. However, because patients can make decisions and remember and repeat information, they pass a formal test of capacity, even if their reasoning and insight is impaired. • The GDG noted that a patient may then not want to reduce DA therapy because they are happy with their quality of life and don't consider their behaviour to be problematic. However behaviours can be highly problematic for significant others. Patients often lose insight into the effects of their behaviours on themselves and others. In this circumstance, the healthcare professional may make a clinical judgement on the appropriate course of action. • The GDG also discussed the importance of carefully balancing a patient preference with the potential risks when considering any medication changes
Trade-off between net health benefits and resource use	No economic evidence was identified for this review question, and original economic analysis was not prioritised. The GDG agreed that CBT has been shown to be highly effective at treating ICDs, but there were also resource implications and constratints in supply. Therefore, they agreed that CBT should only be used once other alternatives (specifically, modification of dopaminergic therapy) had been tried. The GDG agreed this medicine management was likely to prove successful in the majority of cases, and therefore the number of people needing to move on to CBT would be low, thus considerably reducing the total cost. Moreover, in those cases where CBT provides the only potential treatment for ICDs, its costs are very likely to be justified by its benefits, as uncontrolled ICDs have ruinous consequences for the quality of life of patients and their carers.
Quality of evidence	The overall quality of evidence presented ranged from low to high. The GDG noted the key problem in this field is the lack of evidence. It was considered common practice to reduce dopaminergic medication, particularly dopamine agonists if ICD occurs but there is a paucity of research within this field.

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11.2.6 Recommendations

82. If a person with Parkinson's disease has developed a problematic impulse control disorder, seek advice from a healthcare professional with specialist expertise in Parkinson's disease before modifying dopaminergic therapy. [new 2017]

83. Discuss the following with the person and their family members and carers (as appropriate):

- How the impulse control disorder is affecting their life.
- Possible treatments, such as reducing or stopping dopaminergic therapy.

- The benefits and disadvantages of reducing or stopping dopaminergic therapy. [new 2017]

84. When managing impulse control disorders, modify dopaminergic therapy by first gradually reducing any dopamine agonist before reducing levodopa. Monitor whether the impulse control disorder improves and whether the person has any symptoms of dopamine agonist withdrawal. [new 2017]

85. Offer specialist cognitive behavioural therapy targeted at impulse control disorders if modifying dopaminergic therapy is not effective. [new 2017]

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12 Palliative care

What are the needs of people with Parkinson's disease for advance directives and palliative care plans throughout the course of their disease?

12.1.1 Introduction

The aim of this review question was to determine the needs of people with Parkinson's disease for advance directives and palliative care plans throughout the course of their disease. The review focused on identifying studies that fulfilled the conditions specified in Table 26.

Table 26: PICO table for palliative care and advanced directives in Parkinson's disease

Population	Patients with a confirmed diagnosis of Parkinson's disease
Information needs	• Information needs to help people process and plan for the various stages of their disease until end of life. • Information needs to aid people with Parkinson's disease and their family and carers to put advance care directives into place
Comparators	None
Outcomes	• Patient information needs ○ Legal power of attorney ○ sharing of information with family and carer ○ psychiatric support ○ social support • Carer and family needs ○ Information ○ Psychiatric support ○ Social support • Resource use and cost • Information for carers • End of life nutritional management • End of life medication management • Carer quality of life

For full details of the review protocol, please see Appendix C. Qualitative surveys or interviews were considered to be the most appropriate study design to derive patient and carer information needs, and were therefore considered to be the highest quality within a modified GRADE framework. Case reports were excluded from this review.

12.1.2 Evidence review

A systematic search was conducted (see appendix I) which identified 1,377 references. The references were screened on their titles and abstracts and full papers of 18 references were obtained and reviewed against the inclusion and exclusion criteria in the review protocol (see appendix C). This review question was not considered in the previous Parkinson's disease guideline (CG35), no further studies were therefore identified.

Overall, 14 studies were excluded as they did not meet the eligibility criteria such as narrative reviews with no primary data collection. A detailed list of excluded studies and reasons for their exclusion is provided in appendix G.

The 4 remaining published papers did meet eligibility criteria and were included. An additional 5 new papers were identified through rerun searches at the end of the guideline, of

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which 1 was included and 4 excluded. Therefore, a total of 5 papers were included in the final analysis.

The overall quality of the evidence from these 5 published papers ranged from very low to moderate.

The included studies examined the patient and carer's perspectives on the palliative care pathway and their experience of this, providing information on patient and carer quality of life, information needs, and palliative and advanced care preferences.

Evidence tables for included studies can be found in Appendix D, with GRADE profiles reported in Appendix E.

12.1.3 Description of included studies

Two studies (Giles et al., 2009; Hasson et al., 2010) employed a semi-structured interview approach in order to explore the palliation, advance directive, and end of life care needs of people with Parkinson's disease and their family members and carers. One study (Giles et al., 2009; N=7) interviewed 3 family groupings of patients with Parkinson's disease for between 45 and 90 minutes. One of the 3 patients had severe dementia and was excluded from questioning, however 2 of his family members contributed data. The mean age of participants was 74 years old. Mean duration of disease in patients was unreported. Another study (Hasson et al., 2010; N=15) utilised a semi-structured interview to explore end of life and palliative care issues in carers of an immediate family member who had recently (between 6–24 months) died with Parkinson's disease. All carers were over the age of 55 years.

One study (Tuck et al., 2015) administered a survey to 255 patients with Parkinson's disease to determine preferences for timing and initiation of discussions regarding treatment, prognosis, advanced care planning and end-of-life options. Age ranged from 18 to 80+ (10 patients were in the age range between 18–49 years). Disease duration mainly ranged between 2 to 16+ years, with one patient less than 1 year.

One study (Kwak et al., 2014) utilised a battery of questionnaires to explore goals of care, end of life scenario choices, and treatment options with 64 carers of patients with idiopathic Parkinson's disease. Carers were questioned on how they would respond to certain crisis in care situations, their preferences for end of life care decision making, and their own experiences of advanced care directives. Mean age of age of carers was 75 years (SD 6.8). All patients were considered to be in advanced stages of disease (mean UPDRS function=21.5 (SD 7.6); UPDRS motor=31. (SD 12.3)) and 31% of patients had a dementia diagnosis.

Another study (Kristjanson et al., 2006) administered a survey to 174 patients with Parkinson's disease and 141 carers to explore service use and support needs, quality of life, symptoms associated with Parkinson's disease, general health, and family support. Participants were allowed 30 minutes to complete the survey. The mean age of both patients and carers was 60 years old; disease duration in patients was not reported.

12.1.4 Evidence statements

Patient information needs

Support needs

Low-quality evidence from 1 study of 174 patients with Parkinson's disease reported that the greatest self-reported support needs of patients (a mean score of > 2.5 out of 5) to be: information about the disease (mean score=3.5), and equipment for daily living (mean score

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=2.62). All other dimensions, such as activities of daily living, finances, and housekeeping were rated by the majority of patients as requiring little to no help. Overall, 78% of patients were reported to be satisfied with the level of care they received.

Need for open discussion concerning treatment and care

Very low-quality evidence from 1 study of 4 carers and 2 patients with Parkinson's disease reported from one patient that they felt a need for more open dialogue with their physician when discussing treatment options

"I'm the type of woman, I'm afraid to ask too many questions because sometimes I feel like they would say, like you're asking too many questions, just take the pills" (Giles et al., 2009)

Carer and family information needs

Advanced care directives

Moderate-quality evidence from 1 study of 64 spouses of patients with Parkinson's disease reported that 93.7% of patients completed a will; 90.6% of patients shared their will with their spouse; and 37.5% of patients shared a copy of their will with their treating physician.

Low-quality evidence from 2 further studies (Hasson et al., 2010; Giles et al 2009) of 22 carers of patients with Parkinson's disease reported the need for greater input from the healthcare team to inform advanced care planning:

"To help the family or as a group decide what would be the best care situation for the person, and you know what to expect" (Giles et al., 2009)

Advance care planning

Moderate-quality evidence from 1 study reported that patients preferred discussions based on disease treatment early in the course of the disease. Furthermore, they wanted their family members involved early in these discussions. Half wanted to discuss advanced care documents early in the disease and while many wanted to defer discussions about life expectancy and the practical aspects of end-of-life care until their condition worsened, about 12% to 13% wanted to discuss these issues at the time of diagnosis.

Support needs

Moderate-quality evidence from 1 study of 141 carers of patients with Parkinson's disease reported that the greatest self-reported support needs of carers (a mean score of > 2.5 out of 5) to be: information about how to provide care (mean score =3.31); reliable, ongoing, dependable support workers (mean score =2.84); financial assistance for care (mean score =2.72); and flexible home support programme access (mean score =2.52).

Decision making

Moderate quality evidence from 1 study of 64 spouses of patients with Parkinson's disease reported the following preferences for decision making during end of life care: 53% of carers reported they would like to discuss end of life with several people but have one person decide on actions; 28% chose to have one person decide on action alone; 14% chose for several people to decide on action together; 92% believed the carer should be involved in decision making; 72% believed that other family members should be involved in decision-making; 70% reported that they believed physicians should be involved in decision making; and 52% thought all 3 (carer, other family members, and the physician) should be involved.

Multidisciplinary care

Low-quality evidence from 2 studies of 22 carers of patients with Parkinson's disease reported the need for a multidisciplinary team to coordinate all aspects of care

"There seems to be a vague boundary between the responsibilities that one person has and the responsibilities another has. They just don't seem to work as a team or have any team effort as such. You are nearly taking pot luck with each one in turn" (Giles et al., 2009)

"it was very frustrating because you were the liaison...you were at them to constantly go back and say this isn't working" (Giles et al., 2009)

"that would be amazing if we didn't have to call 50 million different places and like try and figure out if they're able to do it and care for the people". (Hasson et al., 2010)

Information needs

Very low-quality evidence from 1 study of 5 family members and 2 patients with Parkinson's disease reported a primary concern of carers to be the lack of information received regarding prognosis, diagnosis, and homecare services, and not knowing or being able to ask for what is missing. Many wished they had been given more information.

"I didn't get the brochures or anything from the doctors... There's not really much help". (Giles et al., 2009)

"you have to be prepared and understand it's just kind of a shocker and no one really explained to us what all of this meant"

Moderate-quality evidence from 1 study of 15 former carers of patients with Parkinson's disease advocated the need to be better prepared for the advancement of disease:

"I knew he was deteriorating but I didn't expect him to die so soon" (Hasson et al., 2010)"

Carer and family social needs

Satisfaction with care

Low-quality evidence from 1 study of 141 carers of patients with Parkinson's disease reported that, in general, families were between ambivalent and satisfied with the care that they receive. A total of 69% of cares were satisfied with information giving; 80% were satisfied with physical care; 63% were satisfied with psychosocial care; and 71% were satisfied with the availability of care, as assessed by the mean family satisfaction with care (FAMCARE) scale.

Respite opportunities and availability of care

Low-quality evidence from 2 studies of 22 carers of patients with Parkinson's disease reported that carers felt that respite opportunities were essential to their own health and wellbeing, however accessing these was cited as very difficult.

"they (government homecare) still haven't called us …so we're lucky that, you know, we finally made the decision to move on. Because I don't know what we would have done… I don't think my mom would have lasted"

Access to domiciliary palliative care services

Low-quality evidence from 2 studies of 22 carers of patients with Parkinson's disease cited that the goal of providing care at home for as long as possible was prevented by a lack of information about domiciliary palliative care services such as hospice care, with few carers who reported to be aware of the existence of these services. All carers expressed frustration

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that professional care was not in place for patients and carers at the start of the disease trajectory.

"not that I was great at looking after him, but that's what I wanted to do anyway, I wanted him to be at home" . (Hasson et al., 2010)

Patient quality of life (QoL)

Low-quality evidence from 1 study of 174 patients with Parkinson's disease reported a mean (scale: 0=poor QoL, 10=excellent QoL) patient-rated score of 6.87 (2.29) and mean patient satisfaction with their QoL was reported to be 5.55 (2.68)). A total of 30% of patients were reported to suffer from moderate to severe depression, and 20% of patients were reported to suffer moderate to severe anxiety, as assessed by the hospital anxiety and depression scale scores (HADS). Patients rated the following symptoms as the worst that they experience on a symptom assessment scale (SAS; where 0 =no problem, to 10=worst possible problem): fatigue and tiredness (mean score =5.1 (SD 2.9)); concentration (mean score=3.9 (SD 3.1)); and sleeping (mean score=4.1 (SD 3.3)).

Carer quality of life

Low-quality evidence from 1 study of 141 carers of patients with Parkinson's disease reported a mean (scale: 0=poor QoL, 10=excellent QoL) carer-rated score of 6.59 (SD 2.27) and a mean carer satisfaction with their QoL score of 6.35 (SD 2.58). A total of 19% of carers reported experiencing overall dysfunction in anxiety and depression, as assessed by the general health questionnaire (GHQ) index. .

End of life nutritional management

No evidence was found on end of life nutritional management in Parkinson's disease

End of life medication management

No evidence was found on end of life medication management in Parkinson's disease

12.1.5 Health economic evidence

No health economic evidence was identified for this question.

12.1.6 Evidence to recommendations

Relative value of different outcomes	Information provision was considered the most valued outcome for both patients and carers. Specifically, the GDG considered information regarding understanding the diagnosis, and prognosis, as well as the availability of support services. Information to prompt and support patients and their family members to consider planning for end of life and financial and social arrangements for this, including lasting power of attorney and drafting a will was also considered an important outcome of interest.
Trade-off between benefits and harms	The GDG discussed the implications of the review and concluded that the most important consideration was that adequate information should be given to patients and their families, and those patients and their families should be given the opportunity to discuss palliative care from an early stage within the disease. The GDG recognised that it was common practice to leave the discussion of palliative issues too late and that clinicians need encouragement to introduce this early. The GDG discussed the need to differentiate between palliative and terminal care. It was discussed that many healthcare professionals avoid raising terminal are issues because they do not want to unnecessarily upset patients

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	or their families. However, it was raised that palliative care issues such as advance care planning and lasting power of attorney were not related to terminal care and were components of long term palliation planning, and therefore should be raised early within the disease course. The main issue that was raised as specifically relevant to Parkinson's disease was the management of dopaminergic medication by a palliative care team in the end stages of the disease. There is no clear guidance on how dopaminergic medication should be managed during end of life care. Signposting to palliative care teams was raised as important, and a need for stronger multidisciplinary working and increased information provision between teams. The GDG raised a need to get these teams involved from earliest stages of disease, rather than disadvantage patients by raising these issues late in the disease course when they have less time to prepare. The issue of when to raise end of life care planning was discussed by the GDG at length. In some people Parkinson's disease is a life limiting condition, however in others Parkinson's disease runs alongside other comorbidities that may contribute to death. How to deal with palliation in these two groups may be different and needs to be taken into consideration. It was agreed that the most appropriate time to initiate end of life care planning discussion was when patients are beginning to fail and deteriorate in terms of their motor and non-motor features. It was also discussed at length the problem of deciding who leads on the initiation and follow up of palliation conversation. Healthcare professionals were discussed as being reluctant to take the step to initiate palliation discussion because of a fear of upsetting patients. However, members of the group discussed anecdotal evidence that in fact patients are nearly always very willing to have the discussion and tend more towards wanting to plan. The GDG noted that multiple people are affected by palliative care issues and that healthcare professionals must also consider impact of discussing palliation on the carer. Carers were discussed to have different needs from those of the patient that need to be considered. Often carers need more information about the disease progression, availability of care, prognosis, and what to expect.
Trade-off between net health benefits and resource use	No economic evidence was identified for this review question. The GDG took the view that the costs that may be incurred by its recommendations are unlikely to be significant. This is because the provision of information is inexpensive and because the recommendations reflect current practice in the care of many people with Parkinson's disease in the NHS. For these reasons, the marginal cost of standardising practice was believed to be low. The group noted that an increase in referrals to palliative care services would have the potential to incur some costs, though this would be offset by savings that could be expected from a consequent reduction in inappropriate care in other parts of the system.
Quality of evidence	The overall quality of evidence was low and the GDG recognised that the strength of the recommendations should reflect this. Therefore, the recommendation around referral to a palliatve care team was kept at the 'consider' level, as the evidence was not felt to support being stronger than this. The GDG discussed the problem of drawing conclusions from qualitative evidence, and particularly the interview studies, which had very low numbers of participants. It was agreed that the self-reported outcomes of personal experience were very subjective and may not be representative of the general carer experience. The patient populations considered within each of the studies were people with moderate to advanced disease, which limited the GDG's ability to draw any valid conclusions about the experience of palliation from the perspective of people with early Parkinson's disease.

12.1.7 Recommendations

86. Offer people with Parkinson's disease and their family members and carers (as appropriate) opportunities to discuss the prognosis of their condition. These discussions should promote people's priorities, shared decision-making and patient-centred care. [new 2017]

87. Give people with Parkinson's disease and their family members and carers (as appropriate) oral and written information about the following, and record that the discussion has taken place:

- Progression of Parkinson's disease.
- Possible future adverse effects of Parkinson's disease medicines.
- Advance care planning, including Advanced Decisions to Refuse Treatment (ADRT) and Do Not Attempt Resuscitation (DNACPR) orders, and Lasting Power of Attorney for finance and/or health and social care.
- Options for future management.
- What could happen at the end of life.
- Available support services, for example, personal care, equipment and practical support, financial support and advice, care at home and respite care. [new 2017]

88. Recognise that family members and carers may have different information needs from the person with Parkinson's disease when discussing palliative care. [new 2017]

89. Consider referring people at any stage of Parkinson's disease to the palliative care team to give them and their family members or carers (as appropriate) the opportunity to discuss palliative care and care at the end of life. [new 2017]

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