ClinicalEvidence

Parkinson's disease

Search date November 2006

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ABSTRACT

INTRODUCTION: Around 1% of adults have Parkinson's disease, with a median time of 9 years between diagnosis and death. METHODS AND OUTCOMES: We conducted a systematic review and aimed to answer the following clinical questions: What are the effects of drug treatments in people with early-stage Parkinson's disease? What are the effects of adding other treatments in people with Parkinson's disease who have motor complications from levodopa? What are the effects of surgery in people with later Parkinson's disease? What are the effects of nursing and rehabilitation treatments in people with Parkinson's disease? We searched: Medline, Embase, The Cochrane Library and other important databases up to November 2006 (BMJ Clinical Evidence reviews are updated periodically, please check our website for the most up-to-date version of this review). We included harms alerts from relevant organisations such as the US Food and Drug Administration (FDA) and the UK Medicines and Healthcare products Regulatory Agency (MHRA). RESULTS: We found 59 systematic reviews, RCTs, or observational studies that met our inclusion criteria. We performed a GRADE evaluation of the quality of evidence for interventions. CONCLUSIONS: In this systematic review we present information relating to the effectiveness and safety of the following interventions: adding a catechol-methyl transferase inhibitor, or dopamine agonist to levodopa; amantadine; dopamine agonists; levodopa (immediate-release, modified-release); monoamine oxidase B inhibitors; occupational therapy; pallidal deep brain stimulation; pallidotomy; Parkinson's disease nurse specialist interventions; physiotherapy; speech and language therapy; subthalamic nucleus deep brain stimulation; subthalamotomy; swallowing therapy; thalamic deep brain stimulation; and thalamotomy.

QUESTIONS

INTERVENTIONS

DRUGS IN EARLY PARKINSON'S

Beneficial

Trade off between benefits and harms

Unknown effectiveness

Unlikely to be beneficial

LEVODOPA PLUS ADJUVANT TREATMENT

Likely to be beneficial

Trade off between benefits and harms

SURGERY IN LATER PARKINSON'S

Trade off between benefits and harms

Unknown effectiveness

NURSING AND REHABILITATION

Likely to be beneficial

Unknown effectiveness

Footnote

† We have used the term "levodopa" to refer to a combination of levodopa and a peripheral decarboxylase inhibitor.

*Categorisation based on consensus.

Key points

- Around 1% of adults have Parkinson's disease, with a median time of 9 years between diagnosis and death.
- Levodopa is considered effective at reducing symptoms in early Parkinson's disease, but can cause irreversible dyskinesias and motor fluctuation in the long term. We don't know whether levodopa, or any other treatment, improves survival.

  Modified-release levodopa seems no more effective than immediate-release levodopa at improving symptoms, and delaying motor complications.
- Monoamine oxidase B inhibitors (MAOBIs) may improve symptoms, reduce motor fluctuations, and delay the need for levodopa, but can cause adverse effects.
- We don't know whether amantadine is beneficial for people with early Parkinson's disease, although it is currently used to treat dyskinesia. People taking amantadine for dyskinesia in early Parkinson's may have a higher risk of psychiatric adverse effects in the later stages of the disease.
- Adding a catechol-O-methyl transferase (COMT) inhibitor or dopamine agonist to levodopa, or using dopamine agonists as monotherapy, may reduce 'off' time and improve symptoms compared with levodopa alone, but can cause adverse effects.

  The COMT inhibitor tolcapone can cause fatal hepatic toxicity.
- Surgery may be considered in people with later Parkinson's disease, but can cause fatalities. Post-operative complications include speech problems and apraxia.

  Although evidence is lacking, many clinicians feel that both pallidal deep brain stimulation and subthalamic nucleus deep brain stimulation improve symptoms of advanced Parkinson's disease.

  Bilateral subthalamic nucleus deep brain stimulation may lead to greater improvement in motor symptoms, but more cognitive impairment, than pallidal deep brain stimulation. Pallidal deep brain stimulation is associated with severe intraoperative complications.

  Adding subthalamic nucleus deep brain stimulation to medical treatment may improve quality of life and motor symptoms compared with medical treatment alone or other forms of surgery. It can, however, cause neurological complications, neuropsychological adverse effects, and fatal surgical complications.

  Unilateral pallidotomy may improve symptoms and function more than medical treatment, but may be less effective than bilateral subthalamic stimulation.

  We don't know whether subthalamotomy or thalamotomy are effective.
- Nurse specialist interventions, occupational therapy, physiotherapy, speech and language therapy and swallowing therapy are generally considered effective and safe in people with Parkinson's disease, although few studies have been found.

DEFINITION

Idiopathic Parkinson's disease is an age-related neurodegenerative disorder, which is associated with a combination of asymmetrical bradykinesia, hypokinesia, and rigidity, sometimes combined with rest tremor and postural changes. Clinical diagnostic criteria have a sensitivity of 80% and a specificity of 30% (likelihood ratio +ve test 1.14, –ve test 0.67) compared with the gold standard of diagnosis at autopsy. [1] The primary pathology is progressive loss of cells that produce the neurotransmitter dopamine from the substantia nigra in the brainstem. Treatment aims to replace or compensate for the lost dopamine. A good response to treatment supports, but does not confirm, the diagnosis. Several other catecholaminergic neurotransmitter systems are also affected in Parkinson's disease. There is no consistent definition distinguishing early from late-stage Parkinson's disease. In this review, we consider people with early-stage disease to be those who have not yet developed motor complications associated with long-term levodopa treatment (such as dyskinesias and motor fluctuations, also known as "on/off" fluctuations). Late-stage Parkinson's disease is taken to mean that motor complications of long-term levodopa treatment are present.

INCIDENCE/ PREVALENCE

Parkinson's disease occurs worldwide, with equal incidence in both sexes. In 5–10% of people who develop Parkinson's disease, the condition appears before the age of 40 (young onset). The mean age of onset is about 65. Overall age-adjusted prevalence is 1% worldwide, and 1.6% in Europe, rising from 0.6% at age 60–64 to 3.5% at age 85–89. [2] [3]

AETIOLOGY/ RISK FACTORS

The cause is unknown. Parkinson's disease may represent different conditions with a final common pathway. People may be affected differently by a combination of genetic and environmental factors (viruses, toxins, 1-methyl-4-phenyl-1, 2, 3, 6-tetrahydropyridine, well water, vitamin E, and smoking). [4] [5] [6] [7] First-degree relatives of affected people may have twice the risk of developing Parkinson's disease (17% chance of developing the condition in their lifetime) compared with the general population. [8] [9] [10] However, purely genetic varieties probably affect a small minority of people with Parkinson's disease. [11] [12] The parkin gene on chromosome 6 may be associated with Parkinson's disease in families with at least one member with young-onset Parkinson's disease;

and multiple genetic factors, including the tau gene on chromosome 17q21, may be involved in idiopathic late-onset disease. [13] [14]

PROGNOSIS

Parkinson's disease is currently incurable. Disability is progressive, and is associated with increased mortality (RR of death compared with matched control populations ranges from 1.6–3.0). [15] Treatment can reduce symptoms and slow progression, but rarely achieves complete control. Whether treatment reduces mortality remains controversial. [16] Levodopa seemed to reduce mortality in the UK for 5 years after its introduction, before a "catch-up" effect was noted, and overall mortality rose towards previous levels. This suggested a limited prolonging of life. [17] An Australian cohort study followed 130 people treated for 10 years. [18] The standardised mortality ratio was 1.58 (P < 0.001). At 10 years, 25% had been admitted to a nursing home, and only four people were still employed. The mean duration of disease until death was 9.1 years. In a similar Italian cohort study conducted over 8 years, the relative risk of death for affected people compared with healthy controls was 2.3 (95% CI 1.60 to 3.39). [19] Age at initial census date was the main predictor of outcome (for people aged < 75 years: RR of death 1.80, 95% CI 1.04 to 3.11; for people aged > 75 years: RR of death 5.61, 95% CI 2.13 to 14.80).

AIMS OF INTERVENTION

To improve symptoms and quality of life; to slow disease progression; to limit short- and long-term adverse effects of treatment, such as motor fluctuations.

OUTCOMES

Disease severity; severity of drug induced symptoms or signs; rate of progression of symptoms; need for levodopa or other treatment; adverse effects of treatment; withdrawals from treatment; and quality-of-life measures. There are no universal scales, but commonly used scales are the Unified Parkinson's Disease Rating Score (UPDRS), the Hoehn and Yahr disability staging scale, the Webster rating scale, the Core Assessment Programme for Intracerebral Transplantation, [20] [21] the Parkinson's Disease Quality of Life questionnaire, [22] and the Parkinson's Disease questionnaire. [23]

METHODS

BMJ Clinical Evidence search and appraisal November 2006. The following databases were used to identify studies for this systematic review: Medline 1966 to November 2006, Embase 1980 to November 2006, and The Cochrane Database of Systematic Reviews and Cochrane Central Register of Controlled Clinical Trials 2006, Issue 4. Additional searches were carried out using these websites: NHS Centre for Reviews and Dissemination (CRD) — for Database of Abstracts of Reviews of Effects (DARE) and Health Technology Assessment (HTA), Turning Research into Practice (TRIP), and National Institute for Health and Clinical Excellence (NICE). Abstracts of the studies retrieved from the initial search were assessed by an information specialist. Selected studies were then sent to the author for additional assessment, using pre-determined criteria to identify relevant studies. Studies were augmented by authors' own searches, attendance at conferences, and regular contact with experts in the field. Study design criteria for inclusion in this review were: published systematic reviews and RCTs in any language, containing more than 20 individuals for drug papers, and more than five individuals for surgical papers. There is no study size limit for rehabilitation papers. More than 80% of subjects were followed up. There was no minimum length of follow-up required to include studies. In addition, we use a regular surveillance protocol to capture harms alerts from organisations such as the US Food and Drug Administration (FDA) and the UK Medicines and Healthcare products Regulatory Agency (MHRA), which are added to the reviews as required. Unless stated otherwise, we have used the term "levodopa" to refer to a combination of levodopa and a peripheral dopa decarboxylase inhibitor. We have performed a GRADE evaluation of the quality of evidence for interventions included in this review (see table, p 30).

QUESTION What are the effects of drug treatments in people with early stage Parkinson's disease?

OPTION IMMEDIATE-RELEASE LEVODOPA

Disease severity

Compared with placebo Levodopa reduces disease severity after 42 weeks compared with placebo in people with early Parkinson's disease (high-quality evidence).

Activities of daily living

Compared with modified-release levodopa Immediate-release levodopa may be less likely to improve activities of daily living scores compared with modified-release levodopa (very low-quality evidence).

Adverse effects

Consensus is that long-term use of levodopa causes dyskinesias and motor fluctuations, which are irreversible.

Dyskinesia

Compared with modified-release levodopa Immediate-release levodopa is as likely as modified-release levodopa to cause dyskinesia after 5 years (low-quality evidence).

Motor fluctuations
Compared with modified-release levodopa Immediate-release levodopa is as likely as modified-release levodopa to cause motor fluctuations after 5 years (low-quality evidence).

For GRADE evaluation of interventions for Parkinson's disease, see table, p 30 .

Benefits:

Levodopa versus placebo:
We found no systematic review but found one RCT. [24] The RCT compared three different doses of immediate-release levodopa (150 mg, 300 mg, 600 mg daily) versus placebo over 42 weeks. It found that levodopa reduced the deterioration in the Unified Parkinson's Disease Rating Scale total score compared with placebo at 42 weeks, with the highest dose being the most effective (361 people with early Parkinson's disease; mean score change: +1.9 with 150 mg levodopa *v* +1.9 with 300 mg levodopa *v* –1.4 with 600 mg levodopa *v* +7.8 with placebo; P < 0.001 for overall comparison). Levodopa also significantly improved the Unified Parkinson's Disease Rating Scale motor component score (mean score change: + 1.4 with 150 mg levodopa *v* +1.4 with 300 mg levodopa *v* –1.4 with 600 mg levodopa *v* +5.2 with placebo; P < 0.001 for overall comparison), and Unified Parkinson's Disease Rating Scale activities of daily living component score (mean score change: +0.5 with 150 mg levodopa *v* +0.4 with 300 mg levodopa *v* –0.3 with 600 mg levodopa *v* +2.3 with placebo; P < 0.001 for overall comparison) compared with placebo at 42 weeks.

Immediate-release levodopa versus modified-release levodopa:
See benefits of modified-release levodopa, p 21 .

Harms:

Levodopa versus placebo:
The RCT found that the highest dose of immediate-release levodopa increased dyskinesia compared with placebo (3/92 [3%] with 150 mg levodopa *v* 2/88 [2%] with 300 mg levodopa *v* 15/91 [16%] with 600 mg levodopa *v* 3/90 [3%] with placebo; P < 0.001 for overall comparison). [24]

Immediate-release levodopa versus modified-release levodopa:
See harms of modified-release levodopa, p 21 .

Comment:

Clinical guide:
Immediate-release levodopa preparations remain one of the main treatments for early Parkinson s disease with support from recent guidelines from the National Institute for Health and Clinical Excellence. [25] Over 30 years of clinical experience with levodopa, and RCTs comparing dopamine agonists versus levodopa (see dopamine agonist versus levodopa in early disease, p 6 ; or dopamine agonists plus rescue levodopa versus levodopa alone in early disease, p 5), have shown that levodopa is an effective treatment at all stages of Parkinson s disease, but that long-term use causes dyskinesias and motor fluctuations, which are irreversible. There have been insufficient RCTs comparing levodopa versus other drug classes (i.e. monoamine oxidase B inhibitors and dopamine agonists) to decide which should be used as initial therapy. Further large comparative trials are required, and one such trial (the PD MED trial) is currently ongoing in the UK (Clarke CE, personal communication, 2007).

OPTION MODIFIED-RELEASE LEVODOPA (COMPARED WITH IMMEDIATE-RELEASE LEVODOPA)

Activities of daily living
Compared with immediate-release levodopa Modified-release levodopa may improve activities of daily living scores compared with immediate-release levodopa (very low-quality evidence).

Adverse effects
Consensus is that long-term use of levodopa causes dyskinesias and motor fluctuations, which are irreversible.

Dyskinesia
Compared with immediate-release levodopa Modified-release levodopa is as likely as immediate-release levodopa to cause dyskinesia after 5 years (low-quality evidence).

Motor fluctuations
Compared with immediate-release levodopa Modified-release levodopa is as likely as immediate-release levodopa to cause motor fluctuations after 5 years (low-quality evidence).

Note
The National Institute for Health and Clinical Excellence has recently recommended against the use of modified-release levodopa to delay motor complications.

For GRADE evaluation of interventions for Parkinson's disease, see table, p 30 .

Benefits:

Modified-release levodopa versus immediate-release levodopa:
We found no systematic review but found two RCTs. [26] [27] The first RCT (134 people with early Parkinson's disease) compared modified-release versus immediate-release levodopa, and found no significant difference at 5 years in the incidence of dyskinesia (41% with modified-release levodopa *v* 34% with immediate-release levodopa; RR 1.21, 95% CI 0.59 to 1.92). It also found no significant difference in the incidence of motor fluctuations (59% with modified release *v* 57% with immediate release; RR 1.03, 95% CI 0.60 to 1.39), motor impairment (reported as non-significant, data not presented), or activities of daily living (Unified Parkinson's Disease Rating Scale total scores: data presented graphically, P = 0.53). [26] The second RCT (618 people with early Parkinson's disease) compared modified-release versus immediate-release levodopa. It found no significant difference in dyskinesia or motor fluctuations measured by diary data at 5 years, but found that modified-release levodopa significantly improved Unified Parkinson's Disease Rating Scale 2 activities of daily living compared with immediate-release levodopa (combined incidence of dyskinesia or motor fluctuations: 22% with modified-release levodopa *v* 21% with immediate-release levodopa, reported as non-significant, P value not reported; mean improvement in Unified Parkinson's Disease Rating Scale 2 activities of daily living score at 5 years: + 0.8 with modified-release levodopa *v* –0.2 with immediate-release levodopa, P = 0.03). [27]

Harms:

Modified-release levodopa versus immediate-release levodopa:
The second RCT found that immediate-release levodopa significantly increased withdrawals caused by nausea compared with modified-release levodopa (figures not provided; P = 0.007). [27] [27]

Comment:

The first RCT had a high withdrawal rate (withdrawal: 42% with immediate release *v* 54% with modified release; analyses were per protocol). [26]

Clinical guide:
Modified-release levodopa preparations should not be used to delay motor complications in early Parkinson s disease. Although it was initially thought that modified-release levodopa might reduce motor complications compared with immediate-release levodopa, studies have not shown any benefits for dyskinesia, motor fluctuations, or motor impairment, and the National Institute for Health and Clinical Excellence has recently recommended against the use of modified-release levodopa to delay motor complications. [25] Therefore, there is currently little reason to use modified-release levodopa, which is more expensive than immediate-release levodopa. Modified-release levodopa is, however, sometimes used at night, before bedtime.

OPTION DOPAMINE AGONISTS PLUS RESCUE LEVODOPA VERSUS LEVODOPA ALONE IN EARLY DISEASE

Motor function
Bromocriptine plus levodopa compared with levodopa alone Bromocriptine plus levodopa may be no more effective at reducing motor complications compared with levodopa alone (low-quality evidence).

Other dopamine agonists plus levodopa compared with levodopa alone Adding other dopamine agonists to levodopa (pergolide, cabergoline, pramipexole, lisuride) may reduce motor complications compared with levodopa alone (low-quality evidence), but may be less effective at reducing disability compared with levodopa alone.

Adverse effects
Pramipexole plus rescue levodopa has been associated with increased somnolence and hallucinations compared with levodopa alone. In light of recent evidence linking pergolide with heart valve damage, ergot-derived dopamine agonists (pergolide and cabergoline) have recently been withdrawn from use in the United States, and the use of pergolide and cabergoline has been restricted to second-line therapy, after non-ergot dopamine agonists, by the UK Medicines and Healthcare products Regulatory Agency.

Note
We found no clinically important results about the effects of different dopamine agonists compared with each other in people with early Parkinson's disease.

For GRADE evaluation of interventions for Parkinson's disease, see table, p 30 .

Benefits:

We found one systematic review (search date 2000, 5 RCTs, 803 people) [28] and five additional RCTs (see table) [29] [30] [31] [32] [33] The review found no consistent evidence of a difference between bromocriptine plus levodopa and levodopa alone in motor impairment, activities of daily living, or motor complications. [28] Four of the additional RCTs found that dopamine agonists plus levodopa reduced dyskinesia or motor fluctuations compared with levodopa alone. [29] [30] [31] [32] The other small RCT found no significant difference between lisuride (lysuride) plus levodopa

and levodopa alone in motor complications at 5 years. [33] Two of the RCTs found that levodopa alone was better than combined treatment in improving motor impairments. [29] [30] Two RCTs also found that levodopa alone was better than combined treatment in improving disability. [30] [31]

Harms:

The review found no significant difference between bromocriptine plus levodopa and levodopa alone in occurrence of adverse effects, but found that the combined treatment reduced withdrawals (see table). [28] The first additional RCT found that adverse effects, including nausea, vomiting, dizziness, confusion, and delusions, were similar in both treatment groups, although the incidence of hallucinations was higher with ropinirole (see table). [29] The second additional RCT found that pramipexole plus levodopa significantly increased somnolence and hallucinations compared with levodopa alone (see table). [30]

People treated with dopamine agonists, especially at high doses, have been reported as exhibiting signs of pathological gambling, increased libido, and hypersexuality, which are generally reversible on reduction of the dose or treatment discontinuation. [34]

In light of recent evidence linking pergolide with heart valve damage, ergot-derived dopamine agonists (pergolide and cabergoline) have recently been withdrawn from use in the United States, and the use of pergolide and cabergoline has been restricted to second-line therapy, after non-ergot dopamine agonists, by the UK Medicines and Healthcare products Regulatory Agency. [35]

Drug safety alert:

A drug safety alert has been issued on the increased risk of fibrosis, particularly cardiac fibrosis associated with chronic use of ergot-derived dopamine agonists (http://www.mhra.gov.uk/home/idcplg?IdcService=GET_FILE&dDocName=CON020567&RevisionSelectionMethod=LatestReleased).

Comment:

The RCTs with 5 years of follow-up had withdrawal rates of about 50%. [29] [31] [33] In the fourth additional RCT, the levodopa doses used were low. [32] We found no direct comparisons of individual dopamine agonists in people with early stage Parkinson's disease. See also the option on dopamine agonists alone, p 6 .

Clinical guide:

Dopamine agonists are less effective for improving motor function but cause fewer motor complications than levodopa alone. Large trials are needed to compare the effects of levodopa versus dopamine agonists on quality of life and health economics outcomes. One such trial (the PD MED trial) is currently ongoing in the UK (Clarke CE, personal communication, 2007).

OPTION DOPAMINE AGONISTS VERSUS LEVODOPA IN EARLY DISEASE

Motor complications

Compared with levodopa Dopamine agonist monotherapy (bromocriptine or pergolide) reduces the risk of motor complications compared with levodopa (moderate-quality evidence).

Motor function

Compared with levodopa Dopamine agonist monotherapy is less effective than levodopa at improving motor function (moderate-quality evidence).

Adverse effects

In light of recent evidence linking pergolide with heart valve damage, ergot-derived dopamine agonists (pergolide and cabergoline) have recently been withdrawn from use in the United States, and the use of pergolide and cabergoline has been restricted to second-line therapy, after non-ergot dopamine agonists, by the UK Medicines and Healthcare products Regulatory Agency.

For GRADE evaluation of interventions for Parkinson's disease, see table, p 30 .

Benefits:

Dopamine agonists versus levodopa:

We found one systematic review (search date 1999, 6 RCTs, 1170 people) [36] and one subsequent RCT (published only as an abstract). [37] The review compared bromocriptine versus levodopa. [36] It found limited evidence that bromocriptine delayed motor complications and dyskinesias compared with levodopa (data presented graphically), and that, compared with bromocriptine, levodopa reduced motor impairment during the first year of therapy. It found no significant difference between groups for disability (data presented graphically). The subsequent RCT (294 people) found that pergolide significantly reduced the proportion of people experiencing one or more motor complications at 3 years compared with levodopa (16% with pergolide *v* 33% with levodopa; $P < 0.004$), but the Unified Parkinson's Disease Rating Scale motor scores were worse in the pergolide group. [37]

Harms:

Dopamine agonists versus levodopa:
The systematic review comparing bromocriptine versus levodopa identified three RCTs, which reported on the incidence of adverse effects. [36] The first RCT identified by the review reported nausea in 12/24 (50%) people with levodopa compared with 7/23 (30%) with bromocriptine; the second RCT found that one person in each group experienced hallucinations; and the third RCT found more nausea and hallucinations in those people taking levodopa (further details not given). None of these adverse effects led to withdrawal from the trial. The largest RCT identified by the review found that significantly more people in the bromocriptine group withdrew for all causes than people taking levodopa (RR 2.81, 95% CI 2.20 to 3.58). The RCT comparing pergolide versus levodopa found that significantly more people in the pergolide group withdrew from treatment (18% with pergolide *v* 10% with levodopa; P < 0.05). [37] See also dopamine agonists plus rescue levodopa, p 5 .

People treated with dopamine agonists, especially at high doses, have been reported as exhibiting signs of pathological gambling, increased libido, and hypersexuality, which are generally reversible on reduction of the dose or treatment discontinuation. [34]

In light of recent evidence linking pergolide with heart valve damage, ergot-derived dopamine agonists (pergolide and cabergoline) have recently been withdrawn from use in the United States, and the use of pergolide and cabergoline has been restricted to second line therapy after non-ergot dopamine agonists by the UK Medicines and Healthcare products Regulatory Agency. [35] .

Drug safety alert:
A drug safety alert has been issued on the increased risk of fibrosis, particularly cardiac fibrosis associated with chronic use of ergot-derived dopamine agonists (http://www.mhra.gov.uk/home/idcplg?IdcService=GET_FILE&dDocName=CON020567&RevisionSelectionMethod=LatestReleased).

Comment:

See also dopamine agonists plus rescue levodopa, p 5 .

Clinical guide:
Dopamine agonists are less effective than levodopa for treating motor function, but cause fewer motor complications. Recent guidelines from the National Institute for Health and Clinical Excellence support the use of dopamine agonists as monotherapy. [25] However, large trials are needed to compare the effects of dopamine agonists versus levodopa on quality of life and health economics outcomes. One such trial (the PD MED trial) is currently ongoing in the UK (Clarke CE, personal communication, 2007).

OPTION MONOAMINE OXIDASE B INHIBITORS

Disease severity
Compared with placebo Monoamine oxidase B inhibitors (MAOBIs) improve disease severity over 10–12 weeks compared with placebo in people with early Parkinson's disease who may be taking other anti-parkinsonian drugs (moderate-quality evidence).

Motor function
Compared with placebo MAOBIs improve motor function over 10–12 weeks compared wtih placebo in people with early Parkinson's disease who may be taking other anti-parkinsonian drugs (moderate-quality evidence).

MAOBIs compared with other anti-parkinsonian drugs Selegiline may be less effective at improving motor function compared with bromocriptine, levodopa, or lisuride (moderate-quality evidence).

Adverse effects
Selegiline has been associated with increased mortality in one study, but MAOBIs overall do not seem to increase mortality compared with placebo or control (moderate-quality evidence).

Note
We found no clinically important results about the effects of MAOBIs versus other drug classes in early Parkinson's disease.

For GRADE evaluation of interventions for Parkinson's disease, see table, p 30 .

Benefits:

MAOBIs versus placebo or no MAOBIs:
We found one systematic review [38] and one subsequent RCT. [39] The review (search date 2003, 17 RCTs, 3525 people) compared MAOBIs versus control (placebo or no MAOBI treatment) in early Parkinson s disease. [38] The review identified 13 RCTs of selegiline, three RCTs of lazabemide, and one RCT of rasagiline. The review included trials where people in both groups were taking drugs other than the MAOBIs, mainly levodopa. It found that, at 3 months, selegiline reduced

Unified Parkinson's Disease Rating Score (UPDRS) total score (5 RCTs, 1066 people; mean score difference: –2.7, 95% CI –1.4 to –4.1), motor impairment (6 RCTs, 1121 people; mean difference in UPDRS motor score: –1.8, 95% CI –0.8 to –2.7), and disability (5 RCTs, 979 people; mean difference in UPDRS activities of daily living score: –0.9, 95% CI –1.4 to –0.5) compared with control. It found that MAOBIs reduced the need for levodopa compared with placebo at 13 months' median follow-up (8 RCTs, 1897 people; OR 0.57, 95% CI 0.48 to 0.67). The subsequent RCT compared rasagiline at a range of doses (1, 2, 4 mg/day) versus placebo over 10 weeks. [39] It found that rasagiline 2 mg/day significantly improved UPDRS total score compared with placebo over 10 weeks (56 people with early Parkinson's disease not receiving levodopa; mean score change: –1.8 with 1 mg/day rasagiline *v* –3.6 with 2 mg/day rasagiline *v* –3.6 with 4 mg/day rasagiline *v* –0.5 with placebo; significance assessment for mean change at 10 weeks not performed; P < 0.05 for repeated measures analysis over 10 weeks of 2 mg/day rasagiline *v* placebo; 1 mg/day and 4 mg/day rasagiline *v* placebo reported as not significant, P values not reported).

MAOBIs versus other drugs:
We found one systematic review, [38] which found one RCT (475 people) comparing selegiline versus levodopa, bromocriptine, and lisuride. [40] All four drugs improved functional ability, but improvement was significantly lower with selegiline than with the other drugs after a mean of 2 months (mean improvement in UPDRS 2 activities of daily living score: 1.4 with selegiline *v* 2.5 with levodopa *v* 1.9 with bromocriptine *v* 2.6 with lisuride; P = 0.03 for selegiline *v* all other treatments). [40] The RCT found no significant difference between selegiline and the other treatments in improving motor function scores (mean improvement in UPDRS 3 motor score: 2.4 with selegiline *v* 3.4 with levodopa *v* 2.3 with bromocriptine *v* 3.2 with lisuride; P value not reported). [40] The authors of the RCT did not report separate statistical differences for selegiline compared with each of the other drugs, so the clinical importance of the results is unclear.

Harms:

MAOBIs versus placebo:
Although in one RCT identified by the review selegiline was associated with increased mortality compared with placebo, [41] the review found no significant difference in mortality between the MAOBIs and control in overall analyses (11 RCTs, 2651 people; AR for death: 20% with MAOBIs *v* 21% with control; OR 1.13, 95% CI 0.94 to 1.34). [38] The review found that MAOBIs increased overall adverse events compared with control (OR 1.36, 95% CI 1.02 to 1.80). It also found that MAOBIs reduced the incidence of motor fluctuations compared with control (5 RCTs, 1128 people; OR 0.75, 95% CI 0.59 to 0.95), but found no difference in the incidence of dyskinesia (3 RCTs, 985 people; OR 0.97, 95% CI 0.75 to 1.26).The subsequent RCT reported no significant difference in adverse events between rasagiline (all doses pooled) and placebo (pain: 30% with rasagiline *v* 15% with placebo, P = 0.48; headache: 26% with rasagiline *v* 31% with placebo, P = 0.73; dizziness: 23% with rasagiline *v* 15% with placebo, P = 0.71).

MAOBIs versus other drugs:
The RCT identified by the review found no significant difference between selegiline and levodopa in mortality (OR 0.96, 95% CI 0.52 to 1.76) or dyskinesia (OR 0.80, 95% CI 0.50 to 1.29). [38] It found that selegiline reduced motor fluctuations compared with levodopa (OR 0.60, 95% CI 0.40 to 0.90). [38] The RCT did not report on harms in the other treatment arms (bromocriptine and lisuride).

Comment:

Clinical guide:
MAOBIs reduce motor impairments, improve activities of daily living, delay the need for levodopa, and reduce long-term motor fluctuations without any substantial increase in side effects or mortality. Guidelines from the National Institute for Health and Clinical Excellence support the use of MAOBIs as monotherapy in early Parkinson's disease. [25] However, there have been insufficient RCTs comparing MAOBIs with other drug classes (such as levodopa and dopamine agonists) to decide which drug class should be used first. Further large comparative trials are required, and one such trial (the PD MED Trial) is currently ongoing in the UK (Clarke CE, personal communication, 2007).

OPTION AMANTADINE New

We found no clinically important results about the effects of amantadine for the treatment of motor symptoms in people with early Parkinson's disease.

For GRADE evaluation of interventions for Parkinson's disease, see table, p 30 .

Benefits:

Amantadine versus placebo: We found one systematic review (search date 2001, 6 RCTs, 215 people that compared amantadine versus placebo in early Parkinson's disease. [42] The review included RCTs in which people were taking drugs other than amantadine, mainly levodopa. Because

of methodological issues with the RCTs identified by the review, it did not report any data from the individual RCTs, and provided insufficient evidence to assess the effects of amantadine.

Harms: **Amantadine versus placebo:** The review found few adverse effects with amantadine, but the doses used were relatively low (maximum 200 mg/d). [42] Possible adverse effects of amantadine included livido reticularis and peripheral oedema.

Comment: **Clinical guide:** Most of the evidence for the efficacy of amantadine comes from 70 uncontrolled studies excluded from the systematic review. Although there is no RCT evidence for the comparative efficacy of amantadine with other agents used in early Parkinson's disease, levodopa, dopamine agonists, or MAOB inhibitors tend to be preferred treatments, as supported by recent guidelines from the National Institute for Health and Clinical Excellence. [25]

QUESTION What are the effects of adding other treatments in people with Parkinson's disease who have motor complications from levodopa?

OPTION ADDING A CATECHOL-O-METHYL TRANSFERASE (COMT) INHIBITOR TO LEVODOPA

Motor function

Compared with placebo Catechol-O-methyl transferase inhibitors (entacapone and tolcapone) plus levodopa may improve motor function and decrease "off" time compared with levodopa plus placebo (low-quality evidence).

Adverse effects

Tolcapone was withdrawn from the European market and its use restricted in other countries because of three cases of fatal hepatic toxicity. It has recently been reintroduced for use in those who fail on entacapone, provided that stringent liver-function test monitoring is performed.

For GRADE evaluation of interventions for Parkinson's disease, see table, p 30 .

Benefits: **Catechol-O-methyl transferase inhibitors versus placebo:**
We found one systematic review [43] and two subsequent RCTs. [44] [45] The review (search date 2003, 14 RCTs, 2566 people) compared adding catechol-O-methyl transferase inhibitors (entacapone or tolcapone) or placebo to levodopa as adjuvant treatments. It found that entacapone reduced "off" time (4 RCTs, 610 people; WMD 0.68 hours, 95% CI 0.22 hours to 1.13 hours; P = 0.004), and reduced levodopa dose (4 RCTs, 837 people; WMD 55 mg/day, 95% CI 37 mg/day to 74 mg/day; P < 0.00001), compared with placebo. It found that entacapone improved Unified Parkinson's Disease Rating Score (UPDRS), motor scores, and activities-of-daily-living scores in four out of five RCTs (figures not reported, all P < 0.05). It also found that tolcapone 100 mg three times daily produced a clinically and statistically significant reduction in "off" time (2 RCTs, 259 people; WMD 1.53 hours, 95% CI 0.90 hours to 2.16 hours; P = 0.00001), and reduced levodopa dose (3 RCTs, 394 people; WMD 151.2 mg/day, 95% CI 80.8 mg/day to 214.5 mg/day; P = 0.00001) compared with placebo. Significant improvements were also seen for other doses of tolcapone in "off" times and in levodopa dose reduction (data not reported here). There was no significant difference in UPDRS, motor scores, or activities-of-daily-living scores between tolcapone (any dose) and placebo in four of five RCTs. One RCT identified by the systematic review found that tolcapone 200 mg three times daily significantly improved UPDRS and motor scores compared with placebo (1 RCT, 59 people; improvement in motor score: –6.5; P < 0.01). Another RCT identified by the systematic review found that tolcapone 200 mg three times daily significantly improved UPDRS, motor scores, and activities-of-daily-living scores (1 RCT, 58 people; figures not reported; P < 0.01). The first subsequent RCT found that entacapone reduced daily "off" time compared with placebo (mean change from baseline: –1.60 hours with entacapone *v* –0.05 hours with placebo; P < 0.0001) and reduced total UPDRS score (mean change from baseline: –7.3 with entacapone *v* -3.0 with placebo; P < 0.05), after 12 weeks. [44] The second subsequent RCT compared three treatments: entacapone, rasagiline, and placebo. [45] It found that, compared with placebo, entacapone significantly reduced "off" time (adjusted mean change from baseline: –1.20 hours with entacapone *v* –0.40 hours with placebo; difference –0.80 hours, 95% CI –1.20 to –0.41; P < 0.0001), and reduced levodopa dose (–19 mg/day with entacapone *v* + 5 mg/day with placebo; P = 0.0024). Entacapone also significantly improved UPDRS, motor scores, and activities-of-daily-living scores at 18 weeks (mean difference in UPDRS score: –2.73, CI not reported, P < 0.0001; mean difference in UPDRS activities-of-daily-living score: –1.38, CI not reported, P = 0.0006).

Harms: **Catechol-O-methyl transferase inhibitors versus placebo:**
The systematic review found that entacapone significantly increased adverse events compared with placebo including dyskinesia (5 RCTs, 1134 people; OR 2.23, 95% CI 1.68 to 2.96), nausea (5 RCTs, 1134 people; OR 1.93, 95% CI 1.32 to 2.80), vomiting (2 RCTs, 465 people; OR 4.16, 95% CI 1.39 to 12.5), diarrhoea (4 RCTs, 929 people; OR 2.69, 95% CI 1.67 to 4.34), constipation

(3 RCTs, 637 people; OR 2.27, 95% CI 1.25 to 4.13), and dizziness (2 RCTs, 548 people; OR 1.95, 95% CI 1.15 to 3.31). [43] Tolcapone significantly increased the risk of dyskinesia (2 RCTs, 162 people, 50 mg tolcapone, OR 3.48, 95% CI 1.79 to 6.76; 3 RCTs, 394 people, 100 mg tolcapone, OR 3.96, 95% CI 2.62 to 6.00; 6 RCTs, 623 people, 200 mg tolcapone, OR 4.51, 95% CI 3.23 to 6.31), nausea (2 RCTs, 162 people, 50 mg tolcapone, OR 2.89, 95% CI 1.15 to 7.27; 3 RCTs, 394 people, 100 mg tolcapone, OR 2.03, 95% CI 1.26 to 3.26; 6 RCTs, 623 people, 200 mg tolcapone, OR 2.64, 95% CI 1.80 to 3.89; 3 RCTs, 224 people, 400 mg tolcapone, OR 2.80, 95% CI 1.80 to 6.05), and vomiting (2 RCTs, 162 people, 50 mg tolcapone, OR 5.60, 95% CI 1.44 to 21.81; 2 RCTs, 259 people, 100 mg tolcapone, OR 4.28, 95% CI 1.40 to 13.08; 5 RCTs, 490 people, 200 mg tolcapone, OR 3.67, 95% CI 1.53 to 8.78). At the 200 mg dose, tolcapone significantly increased the risk of diarrhoea (4 RCTs, 394 people; OR 2.52, 95% CI 1.36 to 4.65) and hallucinations (5 RCTs, 506 people; OR 2.65, 95% CI 1.42 to 4.96).The first subsequent RCT reported no significant increase in adverse events associated with entacapone (dyskinesia: 9% with entacapone *v* 10% with placebo; hallucinations: 6% with entacapone *v* 1% with placebo; differences reported as not significant). [44] The second subsequent RCT found that the incidence of adverse events was similar with entacapone and placebo (27% with entacapone *v* 23% with placebo; significance assessment not performed). [45] Tolcapone was withdrawn from the European market, and its use restricted in other countries because of three cases of fatal hepatic toxicity. It has recently been reintroduced for use in those who fail on entacapone, provided that stringent liver-function test monitoring is performed.

Comment:

Clinical guide:
Adding catechol-O-methyl transferase inhibitors to levodopa in people with motor fluctuations can reduce “off” time and levodopa dose, with small beneficial effects on motor impairments. This is at the expense of more dopaminergic adverse effects. The initial increase in dyskinesia with adjuvant agonist therapy can be reduced by decreasing levodopa dose. These conclusions are based on trials conducted in a relatively young population with Parkinson s disease, and may not be generalisable to older people. However, recent guidelines from the National Institute for Health and Clinical Excellence support the use of COMT inhibitor adjuvant therapy. [25]

OPTION ADDING A DOPAMINE AGONIST TO LEVODOPA

Disease severity
Compared with placebo Adding certain dopamine agonists to levodopa reduces disease severity compared with adding placebo in people with response fluctuations to levodopa (moderate-quality evidence).

Adjuvant dopamine agonists compared with each other Bromocriptine is as effective as other dopamine agonists at improving disease severity (low-quality evidence).

Motor function
Compared with placebo Adding certain dopamine agonists to levodopa reduces "off" time and improves motor impairment and activities of daily living scores compared with adding placebo in people with response fluctuations to levodopa (moderate-quality evidence).

Adjuvant dopamine agonists compared with each other Bromocriptine may be as effective at improving motor function compared with other dopamine agonists (low-quality evidence).

Adverse effects
Adding dopamine agonists increases dopaminergic adverse effects and dyskinesia compared with placebo. There is increasing concern about the risks of pleural, pericardial, and peritoneal reactions with ergot-derived dopamine agonists (bromocriptine, cabergoline, lisuride, and pergolide). In light of recent evidence linking pergolide with heart valve damage, ergot-derived dopamine agonists (pergolide and cabergoline) have recently been withdrawn from use in the United States.

For GRADE evaluation of interventions for Parkinson's disease, see table, p 30 .

Benefits:

Adjuvant dopamine agonist versus placebo:
We found six systematic reviews and one subsequent RCT. [46] [47] [48] [49] [50] [51] [52] The first review compared bromocriptine versus placebo. [46] Heterogeneity in trial design and outcomes made it impossible to draw reliable conclusions. The second review comparing lisuride (lysuride) versus placebo identified no RCTs. [47] Four further systematic reviews found that pergolide, pramipexole, ropinirole, and cabergoline all significantly reduced levodopa dosage compared with placebo. [48] [49] [50] [51] The third and fourth reviews found that pergolide and pramipexole significantly reduced “off” time and significantly improved Unified Parkinson's Disease Rating Score (UPDRS) activities-of-daily-living scores, [48] [49] while the third review found that pergolide also improved motor function. The fifth review found insufficient evidence to assess the effects of ropinirole on motor impairment and disability. [50] The sixth review found that cabergoline showed

no significant improvement in “off” time compared with placebo, but there was limited evidence of small but significant benefits in UPDRS, activities-of-daily-living, and motor scores. [51] The subsequent RCT found that pramipexole significantly improved UPDRS, activities-of-daily-living, and motor scores compared with placebo, but did not report on “off” time and levodopa dose changes. [52] For full details, see table 2, p 26 .

Adjuvant dopamine agonists versus each other:
We found five systematic reviews [53] [54] [55] [56] [57] and one subsequent RCT. [52] The reviews compared lisuride, pergolide, pramipexole, ropinirole, and cabergoline versus bromocriptine. [53] [54] [55] [56] [57] The first systematic review found that lisuride showed no significant difference in motor fluctuations or Columbia University Rating Scale compared with bromocriptine. [53] However, follow-up may have been too short and the study too small to detect clinically important differences. [53] The second systematic review found that pergolide significantly increased the proportion of people with “marked or moderate improvement” compared with bromocriptine, as measured using a seven-point clinician's global assessmeanon 41961][anon 41960][anon 41958][anon 41957][Mizuno 2003]nt scale, but it found no significant difference in reduction in levodopa dose after 8–12 weeks. Two of the RCTs identified by the second review found that pergolide significantly improved motor impairment compared with bromocriptine. [54] The third systematic review found that pramipexole reduced “off” time compared with bromocriptine. [55] The fourth systematic review found that ropinirole improved “off” time and reduced levodopa dose compared with bromocriptine after 8–25 weeks, but these differences were not significant. [56] No significant difference in motor impairments and disability ratings were found between ropinirole and bromocriptine. [56] The fifth systematic review found that cabergoline improved “off” time compared with bromocriptine after 12–36 weeks, but the difference was not significant. [57] Four of the RCTs identified by the review found no significant difference between cabergoline and bromocriptine in motor scores, activities-of-daily-living scores, and levodopa dose reduction. [57] The subsequent RCT compared pramipexole versus bromocriptine versus placebo. [52] It found no significant difference in Unified Parkinson's Disease Rating Score, activities-of-daily-living scores, and motor scores between pramipexole and bromocriptine, but was underpowered to detect differences between the two. [52] For full details, see table 1, p 28 .

Harms:

Adjuvant dopamine agonist versus placebo:
Six systematic reviews and one subsequent RCT found that dopamine agonist treatment significantly increased dopaminergic adverse effects compared with placebo (see table 2, p 26). [46] [47] [48] [49] [50] [51] [52] In particular, dyskinesia was significantly increased with pergolide, pramipexole, and ropinirole. [48] [49] [50] Rates of withdrawal from treatment were significantly lower with pramipexole than with placebo. [49] There was no significant difference in withdrawal rates between placebo compared with pergolide, ropinirole, or cabergoline. [48] [50] [51]

Adjuvant dopamine agonists versus each other:
One review reported a similar frequency of most dopaminergic adverse events with lisuride and bromocriptine. [53] Three systematic reviews and one subsequent RCT found no significant difference in adverse events between pergolide and bromocriptine, [54] or between pramipexole and bromocriptine, [52] [55] but nausea was significantly less frequent with ropinirole compared with bromocriptine. [56] Dyskinesias and confusion were reported as adverse events more commonly with cabergoline than with bromocriptine, but there was no significant difference in the frequency of other dopaminergic adverse effects. [57] We found no studies directly comparing other dopamine agonists. There is increasing concern about the risks of pleural, pericardial, and peritoneal reactions, as well as cardiac valvulopathy, with ergot-derived dopamine agonists (bromocriptine, cabergoline, lisuride, and pergolide). It is now suggested that people treated with an ergot-derived dopamine agonist have renal function, erythrocyte sedimentation rate, and chest radiography performed before therapy and at yearly intervals. In some units, regular echocardiography may be available for such people. In view of these problems, the National Institute for Health and Clinical Excellence has now suggested that people are given a non-ergot-derived dopamine agonist (e.g. ropinirole, pramipexole, or rotigotine). [25]

People treated with dopamine agonists, especially at high doses, have been reported as exhibiting signs of pathological gambling, increased libido and hypersexuality, generally reversible upon reduction of the dose or treatment discontinuation. [34]

In light of recent evidence linking pergolide with heart valve damage, ergot-derived dopamine agonists (pergolide and cabergoline) have recently been withdrawn from use in the United States, and the use of pergolide and cabergoline has been restricted to second line therapy, after non-ergot dopamine agonists, by the UK Medicines and Healthcare products Regulatory Agency. [35]

Drug safety alert:
A drug safety alert has been issued on the increased risk of fibrosis, particularly cardiac fibrosis associated with chronic use of ergot-derived dopamine agonists

(http://www.mhra.gov.uk/home/idcplg?IdcService=GET_FILE&dDocName=CON020567&RevisionSelectionMethod=LatestReleased).

Comment: **Clinical guide:**
Dopamine agonists, when added to levodopa in people with motor fluctuations, can reduce 'off' time and levodopa dose, with small benefits for motor impairments. This is at the expense of increasing the rates of dopaminergic adverse events. The initial increase in dyskinesia with adjuvant agonist therapy can be reduced by decreasing the levodopa dose. These conclusions are based on trials conducted in a relatively young population with Parkinson s disease, and may not be generalisable to older people. However, recent guidelines from the National Institute for Health and Clinical Excellence support the use of non-ergot dopamine agonist adjuvant therapy. [25]

OPTION ADDING AMANTADINE TO REDUCE DYSKINESIA New

Motor function
Compared with placebo The effects of amantadine on motor function and dyskinesia are unclear compared with placebo (very low-quality evidence).

Adverse effects
People taking amantadine for dyskinesia may have a higher risk of psychiatric adverse effects in the later stages of Parkinson's disease.

Note
Despite insufficient available evidence, amantadine is currently being used to reduce dyskinesia, and its use is supported by recent guidelines from the National Institute for Health and Clinical Excellence.

For GRADE evaluation of interventions for Parkinson's disease, see table, p 30 .

Benefits: **Amantadine versus placebo:**
We found one systematic review and two subsequent RCTs. [58] [59] [60] The review (search date 2001, 3 RCTs, 53 people) compared amantadine versus placebo in people with Parkinson's disease and dyskinesia. [58] All three trials identified by the review were crossover RCTs. There was no wash-out period in two RCTs, and none reported results prior to crossover. In view of this, and of the small number of participants, the authors concluded that there was insufficient evidence about the effects of amantadine for dyskinesia in people with Parkinson's disease. The first subsequent RCT (40 people with advanced Parkinson's disease and dyskinesia) compared amantadine versus placebo. [59] It found that amantadine significantly reduced dyskinesia on the UPDRS subscale 4, item 32–34 compared with placebo (mean UPDRS subscale 4 scores decreased from 6.7 at baseline to 2.3 at 15 days with amantadine *v* 6.6 at baseline to 6.1 with placebo; $P < 0.001$). However, this effect was not apparent after 8 months of treatment (mean UPDRS subscale 4 scores at 8 months: 6.1 with amantadine *v* 6.7 with placebo, P value not reported). [59] Dyskinesia increased in 11 people when amantadine was withdrawn. The second subsequent RCT (20 people with Parkinson's disease) compared amantadine with placebo. [60] The RCT found that amantadine produced a borderline significant reduction in UPDRS dyskinesia score (part 4a) after 3 weeks of treatment (UPDRS score decreased from 4.3 at baseline to 2.8 after 3 weeks with amantadine *v* 4.1 to 3.7 with placebo; $P < 0.04$), but amantadine produced no significant reduction in dyskinesia measured by another rating scale (the CDRS score) at 3 weeks (P value not reported). Analysis was not by intention to treat. [60]

Harms: **Amantadine versus placebo:**
The review found one RCT, which reported adverse effects of amantadine (dose range 100-300 mg/d) in 8 of 18 participants, including confusion and worsening of hallucinations. [58] One subsequent RCT reported that two people developed hyperthermia and confusion after amantadine withdrawal, which raises the possibility of early neuroleptic malignant syndrome. [59] The second subsequent RCT reported no adverse effects. [60]

Comment: **Clinical guide:**
Although RCT evidence for the comparative efficacy and safety of amantadine for dyskinesia in Parkinson's disease is poor, amantadine is currently being used for this indication, and its use is supported by recent guidelines from the National Institute for Health and Clinical Excellence. [25] People taking amantadine for dyskinesia should be carefully monitored because of the higher risk of psychiatric adverse effects in the later stages of the disease.

QUESTION What are the effects of surgery in people with later Parkinson's disease?

OPTION PALLIDOTOMY

Disease severity
Compared with medical treatment Unilateral pallidotomy reduces disease severity scores after 6 months compared with medical treatment (moderate-quality evidence).

Compared with pallidal deep brain stimulation Pallidotomy seems to be as effective as pallidal deep brain stimulation at improving symptoms of Parkinson's disease (moderate-quality evidence).

Compared with subthalamic brain stimulation Pallidotomy may be less effective at reducing symptoms of Parkinson's disease compared with bilateral subthalamic brain stimulation (low-quality evidence).

Motor function
Compared with medical treatment Unilateral pallidotomy improves motor function after 6 months compared with medical treatment (moderate-quality evidence).

Adverse effects
There is a high incidence of adverse effects with pallidotomy, with serious or persistent adverse effects in 3–15% of people.

For GRADE evaluation of interventions for Parkinson's disease, see table, p 30 .

Benefits:

Pallidotomy versus medical treatment:
We found two systematic reviews. [61] [62] The earlier review (search date 1999) [61] identified two RCTs, and the more recent review (search date 2004) [62] identified a subsequent publication of one of these RCTs. Both reviews evaluated mainly unilateral posteroventral pallidotomy in people with later stage Parkinson's disease. The first RCT [63] was published only as an abstract at the time it was identified by the first review. [61] The full report of the RCT was identified by the second review, [62] and found that pallidotomy significantly improved total Unified Parkinson's Disease Rating Scale scores compared with medical therapy at 6 months (36 people, mean UPDRS score improvement: +25.5 with pallidotomy *v* –3.8 with medical therapy; P < 0.0001). [64] It also found that, compared with medical therapy, pallidotomy significantly improved the "off" phase outcomes for contralateral tremor, bradykinesia, contralateral rigidity, gait, postural stability, motor fluctuations, dyskinesias, and "off" time (mean improvement from baseline scores, contralateral tremor: 0.7 with pallidotomy *v* 0.1 with medical therapy, P = 0.0007; bradykinesia: 0.8 with pallidotomy *v* ± 0.0 with medical therapy, P = 0.004; contralateral rigidity: 2.0 with pallidotomy *v* 0.1 with medical therapy, P = 0.0003; gait: 0.8 with pallidotomy *v* ± 0.0 with medical therapy, P = 0.0002; postural stability: +0.6 with pallidotomy *v* –0.3 with medical therapy, P = 0.002; motor fluctuations: +1.38 with pallidotomy *v* –0.02 with medical therapy, P < 0.0001; dyskinesias: +1.8 with pallidotomy *v* –0.1 with medical therapy, P < 0.0001). [64] The second RCT identified by the first systematic review (37 people) compared unilateral pallidotomy versus medical treatment. [65] It found that, at 6 months, pallidotomy significantly improved "off" phase assessment for UPDRS 3 motor examination, Barthel index activities of daily living, UPDRS 2 activities of daily living, and Schwab and England scale, but not pain ratings (UPDRS 3 motor score median improvement: +15 with pallidotomy *v* –2 with medical therapy, P = 0.0004; Barthel index activities of daily living median improvement in score [scale of 0–20; an increase denotes greater functional independence]: +2.5 with pallidotomy *v* –0.5 with medical treatment, P = 0.004; UPDRS 2 median improvement: +7 with pallidotomy *v* –2 with medical treatment, P = 0.002; Schwab and England scale median improvement: +15 with pallidotomy *v* –5 with medical treatment, P = 0.0009; pain score on a 100 mm visual analogue scale: decreased from 27 mm to 14 mm with pallidotomy *v* increased from 15 mm to 22 mm with medical treatment, P = 0.13, CIs not reported). [65]

Pallidotomy versus pallidal deep brain stimulation:
We found one systematic review (search date 2000, 1 RCT). [66] The RCT (13 people) in the systematic review found no significant difference between pallidotomy and pallidal deep brain stimulation for symptoms, activities of daily living, and adverse effects over 3 months, but it may have been too small to detect clinically important differences. [67]

Pallidotomy versus subthalamic deep brain stimulation:
We found one systematic review (search date 2004), [62] which identified one RCT. [68] The RCT (34 people) compared unilateral pallidotomy versus bilateral subthalamic deep brain stimulation. [68] It found that unilateral pallidotomy was less effective than bilateral subthalamic stimulation in improving parkinsonian symptoms (median improvement in UPDRS scores after 6 months: 7 with unilateral pallidotomy *v* 19 with bilateral subthalamic deep brain stimulation, P = 0.002; improvement

in "on" phase UPDRS motor score: 1 for unilateral pallidotomy *v* 7 for bilateral subthalamic stimulation, P = 0.02; dyskinesias duration score: unchanged with unilateral pallidotomy *v* improved by 1 point with bilateral subthalamic stimulation, P = 0.004). However, there was no significant difference in severity of dyskinesia; P = 0.7).

Harms:

Pallidotomy versus medical treatment:
The full report of the first RCT (36 people) identified by the first review [61] comparing pallidotomy versus medical treatment found that 2/18 (11%) people receiving pallidotomy had seizures and 1/18 (6%) had subcortical haemorrhage and transient speech impairment. [64] In the second RCT (35 people), comparing pallidotomy versus medical treatment, 6/19 (31%) people who had unilateral pallidotomy had adverse effects persisting for 6 months after surgery, including dysarthria, dysphasia, facial paresis, and urinary incontinence (further data not reported). [65] We found two RCTs assessing neuropsychological, cognitive, or behavioural effects of pallidotomy versus medical treatment. [69] [70] The first RCT (35 people) found that left-sided, but not right-sided, pallidotomy reduced verbal fluency (deterioration in category fluency: 8.7 after left pallidotomy *v* 3.1 after right pallidotomy, P = 0.04, Kruskal–Wallis test; change in Controlled Oral Word Association Test letter fluency [negative score = deterioration]: –8.0 after left pallidotomy *v* +2.6 after right pallidotomy, P = 0.01, Kruskal–Wallis test). [69] The second RCT (33 people) found subtle changes on measures of frontal lobe function after 6 months in people with unilateral pallidotomy, and that surgery — particularly left-sided surgery — reduced letter fluency compared with medical management at 3 months (actual figures not reported, P = 0.011). [70] One systematic review of case series (search date 1998) found that the incidence of permanent adverse effects of unilateral pallidotomy was 4–46%, with a risk of a serious complication (including death) of 3–10%. [71] Another systematic review of case series (search date 1998) estimated a 10–15% incidence of persistent adverse effects with unilateral pallidotomy. [72]

Pallidotomy versus pallidal deep brain stimulation:
One systematic review (1 RCT, 13 people) found that adverse effects and surgery complications occurred in 6/13 [46%] people and were mild, transient, and unrelated to optic tract injury (adverse effects: 3/16 [19%] with pallidotomy *v* 3/16 [19%] with pallidal deep brain stimulation). [67] One RCT (6 people) compared bilateral pallidotomy versus unilateral pallidotomy plus contralateral pallidal deep brain stimulation. [73] It found that all three people with bilateral pallidotomy experienced severe adverse effects. This led to discontinuation of the study.

Pallidotomy versus subthalamic nucleus deep brain stimulation:
The RCT identified by the review, [62] found that adverse effects included one suicide in the pallidotomy group and emotional instability in the subthalamic nucleus deep brain stimulation group (emotional instability: 0/14 [0%] with unilateral pallidal deep brain stimulation *v* 6/20 [30.0%] with bilateral subthalamic nucleus deep brain stimulation; P values not reported). [68] A separate report on the same RCT assessed the neuropsychological effects of the surgeries. [74] It found no significant difference between unilateral pallidotomy and bilateral subthalamic nucleus deep brain stimulation in 16 out of 18 the neuropsychological measures at 6 months. The pallidotomy group performed significantly better on the Stroop Color Word test and the Trailmaking test at 6 months (mean change in Stroop Color Word test score: –2.9 with pallidotomy *v* +2.8 with subthalamic stimulation, effect size 0.94; mean change in Trailmaking test: –0.7 with pallidotomy *v* +0.9 with subthalamic stimulation, effect size 0.80). However, there were no significant differences between groups on any of the measures at 12 months. These results should be interpreted with caution, because multiple tests were performed without an adjustment in the level of significance, and the study is likely to have been underpowered to detect differences between groups.

Comment:

One cohort study found that the improvements seen after unilateral pallidotomy were maintained for 12 months. [75] One non-systematic review and consensus statement suggested that gait, balance disorders, and hypophonia were less responsive to surgery than were other features of parkinsonism (no further data reported). [76] Transplants and implants of dopaminergic tissue remain experimental.

Clinical guide:
Uncontrolled studies and limited RCT information suggest that adverse effects may be more frequent after lesioning procedures than with deep brain stimulation, and are more likely to be permanent. Bilateral lesioning is likely to carry a high risk of adverse axial effects. In general, complication rates decline as surgeons develop experience in performing pallidotomy. [76] Most surgeons now suggest that, if bilateral procedures are required, deep brain stimulation rather than lesioning should be carried out on at least one side of the brain.

OPTION PALLIDAL DEEP BRAIN STIMULATION

Disease severity

Compared with pallidotomy Pallidal deep brain stimulation seems to be as effective as pallidotomy at reducing the symptoms of Parkinson's disease (moderate-quality evidence).

Compared with subthalamic nucleus deep brain stimulation Pallidal deep brain stimulation may be as effective as subthalamic nucleus deep brain stimulation at improving symptoms of Parkinson's disease (low-quality evidence).

Motor function
Compared with subthalamic nucleus deep brain stimulation Pallidal deep brain stimulation may be less effective at imrpoving motor function than subthalamic nucleus deep brain stimulation (very low-quality evidence).

Adverse effects
Adverse effects, including several intraoperative complications leading to persistent neurological deficits, have been reported with pallidal stimulation, but are probably less frequent with pallidal deep brain stimulation than with pallidotomy. Bilateral pallidal stimulation may lead to less cognitive impairment than subthalamic stimulation.

Note
We found no clinically important results about the effects of pallidal deep brain stimulation compared with medical treatment.

For GRADE evaluation of interventions for Parkinson's disease, see table, p 30 .

Benefits:

Pallidal deep brain stimulation versus medical treatment:
We found two systematic reviews (search dates 2000 [66] and 2004 [62]), which identified no RCTs comparing pallidal deep brain stimulation versus medical treatment. [62] [66] We found no subsequent RCTs.

Pallidal deep brain stimulation versus pallidotomy:
See benefits of pallidotomy, p 13 .

Pallidal deep brain stimulation versus subthalamic nucleus deep brain stimulation:
We found two RCTs comparing bilateral pallidal deep brain stimulation versus bilateral subthalamic deep brain stimulation. [77] [78] The first RCT found no significant difference in Unified Parkinson's Disease Rating Scale(UPDRS) motor or activities of daily living scores after 12 months (23 people; UPDRS motor score improvement: 39% with pallidal stimulation *v* 48% with subthalamic stimulation, P = 0.40; UPDRS activities-of-daily-living score improvement: 18% with pallidal stimulation *v* 28% with subthalamic stimulation, P = 0.48). Subthalamic stimulation reduced the required levodopa dose more than did pallidal stimulation, but this difference did not reach significance (reduction: 38% with pallidal stimulation *v* 3% with subthalamic stimulation; P = 0.08). Both pallidal stimulation and subthalamic stimulation reduced dyskinesia over 12 months, with no significant difference between groups (dyskinesia measured on a scale of 0 [least severe] to 24 [most severe]; change in median dyskinesia severity score during stimulation and levodopa use: –8 with pallidal stimulation *v* –6 with subthalamic stimulation; P = 0.27). [78] The second RCT (32 people, published only as an abstract) found no significant difference between the groups at 1 year, except that reduction of dyskinesia was significantly greater with pallidal stimulation (reduction in dyskinesia score: 63% for pallidal stimulation *v* 14% for subthalamic nucleus stimulation; P = 0.049). [77]

Harms:

Pallidal deep brain stimulation versus medical treatment:
We found two systematic reviews (search dates 2000, 2004) which identified no RCTs comparing pallidal deep brain stimulation versus medical treatment. [62] [66]

Pallidal deep brain stimulation versus pallidotomy:
See harms of pallidotomy, p 13 .

Pallidal deep brain stimulation versus subthalamic nucleus deep brain stimulation:
We found two RCTs comparing bilateral pallidal deep brain stimulation versus bilateral subthalamic deep brain stimulation. [77] The first RCT (20 people) reported several intraoperative complications during pallidal stimulation, including one case of intraoperative stroke (1/11 [9%]) resulting in persistent neurological deficits. There were three cases of infraclavicular haematoma (group not reported). No intraoperative complications were reported with subthalamic stimulation, but perioperative complications included three cases of mild delirium (3/12 [25%]), two cases of transient anxiety (2/12 [17%]), and one case of hallucinations (1/12 [8%]). There was one case of persistent cognitive impairment (short term memory, problems concentrating, apathetic mood), and one case of progressively declining cognitive function and increased parkinsonism, both in the subthalamic stimulation group. [78]

Comment:

Pallidal deep brain stimulation versus subthalamic nucleus deep brain stimulation:
The systematic review conducted for the National Institute for Health and Clinical Excellence guidelines suggested that bilateral subthalamic nucleus deep brain stimulation may lead to greater improvement in motor scores, and greater reduction in levodopa dose and depression scores, than pallidal deep brain stimulation. However, it found that bilateral pallidal deep brain stimulation may lead to less cognitive impairment than subthalamic stimulation. [25]

Although subthalamic nucleus stimulation is increasingly the more popular procedure, it is premature to rule out pallidal stimulation as treatment for advanced Parkinson's disease.

One recent non-systematic review and consensus statement suggested that gait, balance disorders, and hypophonia were less responsive to surgery than were other features of parkinsonism (no further data reported). [76] Transplants and implants of dopaminergic tissue remain experimental. Uncontrolled studies and limited RCT information suggest that adverse effects may be more frequent after lesioning procedures than with deep brain stimulation, and are more likely to be permanent. Bilateral lesioning is likely to carry a high risk of adverse axial effects. Many surgeons propose that, if bilateral procedures are required, then deep brain stimulation rather than lesioning should be carried out on at least one side of the brain. Adverse effects linked with deep brain stimulation include: haemorrhage; lead displacement; visual deficit; speech, motor, or sensory disturbances; psychosis; confusion; and disorientation. Eventually, equipment or battery replacement may be needed, which will require further surgery.

Clinical guide:
Despite the lack of RCTs comparing pallidal deep brain stimulation versus medical therapy, many clinicians feel that both pallidal deep brain stimulation and subthalamic nucleus stimulation improve symptoms of advanced Parkinson's disease. A systematic review that included observational studies, which was conducted to prepare guidelines for the National Institute for Health and Clinical Excellence (search date 2005), reported that pallidal stimulation is rarely performed in the UK, but recommended criteria for the use of pallidal stimulation that were the same as those for subthalamic nucleus stimulation. [25]

OPTION SUBTHALAMIC NUCLEUS DEEP BRAIN STIMULATION

Motor function
Compared with no stimulation Subthalamic nucleus deep brain stimulation plus medical care may improve motor function compared with medical care alone in people with advanced Parkinson's disease (low-quality evidence).

Compared with pallidotomy Compared with pallidal deep brain stimulation Subthalamic nucleus deep brain stimulation may be more effective than pallidal deep brain stimulation at improving motor function (very low-quality evidence).

Disease severity
Compared with pallidotomy Bilateral subthalamic brain stimulation may be more effective than unilateral pallidotomy at reducing disease severity (low-quality evidence).

Compared with pallidal deep brain stimulation Subthalamic nucleus deep brain stimulation may be as effective as pallidal deep brain stimulation at improving disease severity (low-quality evidence).

Adverse effects
Subthalamic nucleus deep brain stimulation has been associated with neuropsychological adverse effects, surgical complications such as infection, intracranial haemorrhage, and neurological deficits.

For GRADE evaluation of interventions for Parkinson's disease, see table, p 30 .

Benefits:

Subthalamic nucleus deep brain stimulation versus medical treatment:
Three systematic reviews (search dates 2000, 2004 and 2003) identified no RCTs of sufficient quality comparing subthalamic nucleus deep brain stimulation (neurostimulation) versus medical treatment. [66] [62] [79]

We found one subsequent RCT (156 people with advanced Parkinson's disease) that compared subthalamic nucleus deep brain stimulation plus medical treatment over 6 months versus medical treatment alone. [80] The RCT used a random-pair design. It found that subthalamic nucleus deep brain stimulation plus medical treatment significantly improved quality of life using the PDQ-39 summary index (quality-of-life scores improved for 50/78 comparison pairs with neurostimulation plus medical treatment *v* 28/78 pairs with medical treatment alone; P = 0.02; mean improvement in PDQ-39 summary index: 9.5 points with neurostimulation plus medical treatment *v* -0.2 points with medical treatment; P = 0.02). Subthalamic nucleus deep brain stimulation plus medical treatment significantly improved off-medication motor scores compared with medical treatment alone (im-

provement in UPDRS-III in 55 /78 comparison pairs with neurostimulation plus medical treatment *v* 21/78 with medical treatment, P < 0.001; mean improvement in UPDRS-III: 19.6 points with neurostimulation plus medical treatment *v* 0.4 points with medical treatment, P < 0.001). Neurostimulation plus medical treatment also significantly improved on-medication dyskinesia and PDQ-39 subscales for mobility, activities of daily living, emotional well being, stigma, and bodily discomfort at 6 months compared with medical treatment alone (on-medication dyskinesia score: mean change from baseline at 6 months: 3.4 with neurostimulation plus medical treatment *v* –0.4 with medical treatment, P < 0.01; PDQ-39 scales: mobility score: mean change from baseline at 6 months: 14.8 with neurostimulation plus medical treatment *v* –0.8 with medical treatment, P < 0.01; activities-of-daily-living score: mean change from baseline at 6 months: 20.7 with neurostimulation plus medical treatment *v* –2 with medical treatment, P < 0.01; mean emotional wellbeing score: mean change from baseline at 6 months: 11.5 with neurostimulation plus medical treatment *v* –0.8 with medical treatment, P < 0.01; mean score for stigma: mean change from baseline at 6 months: 11.1 with neurostimulation plus medical treatment *v* –0.1 with medical treatment, P < 0.01; mean bodily discomfort score: mean change from baseline at 6 months: 11.3 with neurostimulation plus medical treatment *v* 3.1 with medical treatment alone). The RCT found no significant difference in cognition, communication, or scores for dementia (Mattis dementia rating scale), depression (Montgomery and Asberg Depression Rating Scale) or general mental health (Brief Psychiatric Rating scale) between the groups. Neurostimulation plus medical treatment resulted in a significant decrease in required levodopa-equivalent medication doses (mean change from baseline: 593 mg with neurostimulation *v* 95 mg with medical treatment alone; P<0.001).

Subthalamic nucleus deep brain stimulation versus pallidotomy:
See benefits of pallidotomy, p 13 .

Subthalamic nucleus deep brain stimulation versus pallidal deep brain stimulation:
See benefits of pallidal deep brain stimulation, p 14 .

Harms:

Subthalamic nucleus deep brain stimulation versus medical treatment:
Three systematic reviews (search dates 2000, 2004 and 2003) identified no RCTs of sufficient quality comparing subthalamic nucleus deep brain stimulation versus medical treatment. [66] [62] [79] One RCT found that subthalamic nucleus deep brain stimulation plus medical treatment significantly increased the proportion of people with adverse effects (10/78 [13%] with neurostimulation *v* 3/78 [4%] with medical treatment alone, P = 0.04). [80] It found that combination treatment increased mortality compared with medical treatment (3/78 [4%] with neurostimulation plus medical treatment *v* 1/78 [1%] with medical treatment alone, P value not reported). In the neurostimulation group, one person died of intracerebral haemorrhage, and there was one suicide. However, there were fewer total non-serious adverse events with neurostimulation compared with medical treatment alone (77 with neurostimulation *v* 96 with medical treatment).

Subthalamic nucleus deep brain stimulation versus pallidotomy:
See harms of pallidotomy, p 13 .

Subthalamic nucleus deep brain stimulation versus pallidal deep brain stimulation:
See harms of pallidal deep brain stimulation, p 14 .

Comment:

Although there are many studies of people treated with subthalamic nucleus deep brain stimulation, most make historical comparisons with the presurgical condition, or comparisons between on and off stimulation states. Most of the patients were relatively young (aged around 60), so the results may not be generalisable to all people with Parkinson's disease.

A systematic review of subthalamic nucleus deep brain stimulation done to prepare guidelines for the National Institute for Health and Clinical Excellence (search date 2005) included large case series with a minimum sample size of 40 people. [25] It found benefits for quality of life, motor symptoms, and complications such as fluctuations and on-drug dyskinesias. It reported that, in some studies, benefits lasted for over 5 years. There was less improvement in older people, people with more prolonged disease, and if there was no preoperative response to levodopa. It reported neuropsychological adverse effects including suicide attempts, confusion, mania, depression and hallucinations; other adverse effects including surgical complications such as infection, intracranial haemorrhage or neurological deficits; and equipment failure or stimulator-induced adverse effects.

Although one recent RCT compared deep brain stimulation versus medical treatment over 6 months and found overall benefit with stimulation, [80] larger and longer-term RCTs are needed to compare the effects of pallidal versus subthalamic stimulation. A large RCT comparing quality of life and costs of subthalamic or pallidal lesioning and deep brain stimulation surgery versus best medical treatment is currently under way in the UK (Clarke CE, personal communication, 2007).

Clinical guide:
National Institute for Health and Clinical Excellence guidelines recommend that bilateral subthalamic nucleus deep brain stimulation may be used in people with Parkinson's disease who have motor complications refractory to best medical treatment, who are biologically fit with no clinically significant active comorbidity, and who are levodopa responsive and have no clinically significant active mental health problems — for example, depression or dementia. [25] Other adverse effects linked with deep brain stimulation include haemorrhage, lead displacement, visual deficit, speech, motor or sensory disturbances, psychosis, confusion, and disorientation. Eventually, equipment or battery replacement may be needed, which requires further surgery.

OPTION SUBTHALAMOTOMY

We found no clinically important results about the effects of subthalamotomy in people with Parkinson s disease.

For GRADE evaluation of interventions for Parkinson's disease, **see table, p 30 .**

Benefits: We found one systematic review (search date 2004), which found no RCTs of subthalamotomy in people with Parkinson s disease. [62]

Harms: We found no RCTs.

Comment: None.

OPTION THALAMIC DEEP BRAIN STIMULATION

Disease severity
Compared with thalamotomy Thalamic deep brain stimulation may be more effective at improving functional status compared with thalamotomy (low-quality evidence).

Adverse effects
Thalamic deep brain stimulation has been associated with serious adverse effects such as cerebral infarction and haemorrhage, but may have fewer adverse effects than thalamotomy.

Note
We found no clinically important information about the effects of thalamic deep brain stimulation compared with medical treatment.

For GRADE evaluation of interventions for Parkinson's disease, **see table, p 30 .**

Benefits:

Thalamic deep brain stimulation versus medical treatment:
We found two systematic reviews (search date 2000, [66] search date 2004 [62]). They found no RCTs of thalamic deep brain stimulation versus medical treatment.

Thalamic deep brain stimulation versus thalamotomy:
See benefits of thalamotomy, p 19 .

Harms:

Thalamic deep brain stimulation versus medical treatment:
The two systematic reviews (search dates 2000, [66] , 2004 [62] did not identify any RCTs.

Thalamic deep brain stimulation versus thalamotomy:
See harms of thalamotomy, p 19 .

Comment: One review [66] found limited evidence from case series that thalamic surgery may not be as useful as pallidal or subthalamic surgery for parkinsonian features other than tremor. [61] [72]

Clinical guide:
A systematic review conducted to prepare guidelines for the National Institute for Health and Clinical Excellence (search date 2005), that included three observational studies, found that thalamic deep brain stimulation effectively reduced tremor. It recommended that thalamic stimulation may be considered for people with Parkinson's disease who predominantly have a disabling tremor, and in whom subthalamic stimulation cannot be performed. [25] The review found that thalamic deep brain stimulation carried a risk of serious complications such as cerebral infarction and haemorrhage, and a higher risk of stimulation-induced adverse effects with bilateral than with unilateral stimulation (52% *v* 31%, P value not reported). [25]

OPTION THALAMOTOMY

Disease severity
Compared with thalamic deep brain stimulation Thalamotomy may be less effective at improving functional status compared with thalamic deep brain stimulation (low-quality evidence).

Adverse effects
Thalamotomy has been associated with a risk of permanent complications such as speech disturbance, apraxia, or death, in 14–23% of people.

Note
We found no clinically important information about the effects of thalamotomy compared with medical treatment.

For GRADE evaluation of interventions for Parkinson's disease, see table, p 30 .

Benefits:

Thalamotomy versus medical treatment:
We found three systematic reviews (search dates 1999, [61] 1998, [72] and 2004 [62]), which identified no RCTs comparing thalamotomy versus medical treatment for Parkinson's disease (see comment below).

Thalamotomy versus thalamic deep brain stimulation:
We found one systematic review (search date 2000). [66] It identified one RCT (68 people with tremor, 45 of whom had Parkinson's disease), which compared thalamotomy versus thalamic deep brain stimulation. [81] Subgroup analysis in people with Parkinson's disease found that thalamic deep brain stimulation significantly improved functional status after 6 months compared with thalamotomy (outcome assessed using Frenchay Activities Index: 0 = worst score, 60 = best score; improvement in score: 5.5 with deep brain stimulation *v* 0.8 with thalamotomy, 95% CI for between-group difference 1.2 to 8.0).

Harms:

Thalamotomy versus medical treatment:
Case series included in one systematic review [72] found that thalamotomy was associated with reversible complications (lasting < 3 months) in 36–61% of people, and with permanent complications, including speech disturbance, apraxia, or death, in 14–23%. [72] Bilateral thalamotomy carries a high risk of speech disturbance. [72]

Thalamotomy versus thalamic deep brain stimulation:
We found one systematic review (search date 2000). [66] One RCT found that adverse effects, including somnolence, cognitive deterioration, dysarthria, weakness, and ataxia, were significantly less common with deep brain stimulation than with thalamotomy after 6 months (AR 47% with thalamotomy *v* 18% with deep brain stimulation; P = 0.02). [81]

Comment:

The reviews found limited evidence from case series that thalamic surgery may not be as useful as pallidal or subthalamic surgery for parkinsonian features other than tremor. [61] [72]

Thalamotomy versus medical treatment:
The second systematic review did not describe fully the case series it identified, focusing on results from “key studies”. [72]

QUESTION What are the effects of nursing and rehabilitation treatments in people with Parkinson's disease?

OPTION PARKINSON S DISEASE NURSE SPECIALIST INTERVENTIONS

Disease severity
Nurse specialist care compared with usual care Nurse specialist care may not improve motor functioning after 2 years compared with usual care, although global health scores may be higher with specialist nursing care than with usual care (low-quality evidence).

Psychosocial outcomes
Increased frequency of contact compared with usual care Increased frequency of contact with a nurse practitioner may not improve psychosocial outcomes compared with usual care (low-quality evidence).

For GRADE evaluation of interventions for Parkinson's disease, see table, p 30 .

Benefits:

Parkinson s disease nurse specialist versus standard care:
We found two RCTs. [82] [83] The first RCT compared community-based Parkinson s disease nurse specialist care versus standard care. [82] It found that nurse specialist care improved self-reported global health in people with Parkinson's disease compared with standard care over 2 years (1859 people with Parkinson's disease; higher global health questionnaire scores indicate greater deterioration of health; mean global health questionnaire score: 4.79 with nurse specialist care *v* 5.02 with standard care; mean difference: –0.23, 95% CI –0.06 to –0.40). However, there were no significant differences between groups in functioning and wellbeing (measured by the Parkinson's Disease Questionnaire [PDQ-39]; score range 0–100, higher score = worse function; mean score: 39.7 with nurse specialist care *v* 39.2 with standard care; mean difference: 0.47, 95% CI –2.72 to +3.66), or in health-related quality of life (Euroqol questionnaire; score range –0.59 to +1, higher score indicates better quality of life; mean score: 0.37 with nurse specialist care *v* 0.39 with standard care; mean difference: –0.02, 95% CI –0.06 to +0.02). The second RCT (40 people) compared more frequent contact with a nurse practitioner (2 home visits and 5 phone calls) versus standard care, in people at a single specialist neurology unit over 6 months. [83] The RCT did not perform between-group significance assessments. However, it found no significant changes from baseline in either group at 6 months in any of the psychosocial measures (including the Beck Depression Inventory, Spielberger Trait Anxiety Scale, Acceptance of Illness Scale, and Functional disability Questionnaire).

Harms:

Parkinson s disease nurse specialist versus standard care:
Adverse events were not reported in either of the RCTs. [82] [83]

Comment:

The first RCT has been criticised for evaluating the specialist nurses soon after specialist training, and for a lack of support from secondary care for the nurses. [82]

Clinical guide:
Clinical experience in the UK strongly supports the value of specialist nursing in the care of people with Parkinson s disease. This is supported by guidelines from the National Institute for Health and Clinical Excellence. There is limited evidence for the benefits of Parkinson s disease nurse specialist interventions — most of which concern the delivery of service — but they have been shown to be cost neutral.

OPTION OCCUPATIONAL THERAPY

Disease severity
Compared with no treatment The effects of occupational therapy on symptoms of Parkinson's disease compared with no treatment are unclear (very low-quality evidence).

For GRADE evaluation of interventions for Parkinson's disease, see table, p 30 .

Benefits:

We found one systematic review (search date 2000, 2 RCTs, 84 people with early stage or late stage Parkinson's disease). [84] One RCT in the review compared occupational therapy versus no treatment, and the other compared occupational therapy plus physiotherapy versus physiotherapy alone. The review was unable to draw conclusions on the effects of occupational therapy, because of the small number of people in the RCTs, flawed methods, trial heterogeneity, and the variety of outcome measures used. [84]

Harms:

The RCTs in the review gave no information on adverse effects. [84]

Comment:

Clinical guide:
Although there is no good RCT evidence of the effectiveness of occupational therapy in Parkinson s disease, clinical experience suggests that it can be effective and safe. This is supported by guidelines from the National Institute for Health and Clinical Excellence. [25] However, further, larger, well-designed, RCTs are needed to decide what forms of therapy should be used and when.

OPTION PHYSIOTHERAPY

Disease severity
Compared with no treatment or other physical treatments The effects of physiotherapy in people with Parkinson's disease are unclear compared with no treatment or other physical treatments (very low-quality evidence).

Benefits:

We found two systematic reviews and two subsequent RCTs. [85] [86] [87] [88] The first review (search date 2000, 11 RCTs, 280 people with early or late stage Parkinson's disease) compared physiotherapy versus no treatment or versus inactive physiotherapy. [85] The review was unable to draw conclusions on the effects of physiotherapy in Parkinson's disease, because of the small

numbers of people, flawed methods, different types of physiotherapy used, and the wide variety of outcome measures in the RCTs. The second systematic review (search date 1999, 8 RCTs included in the first review, 4 quasi-randomised studies) compared physiotherapy versus no treatment or versus other treatment (occupational therapy, regular exercises, non-specified psychological treatment). [86] It also found that flawed methods and trial heterogeneity made it difficult to draw conclusions on the effects of physiotherapy. The subsequent crossover RCT (17 people with early Parkinson's disease) found that speed-dependent treadmill training and limited progressive treadmill training were more effective than conventional gait training or a control intervention in improving speed and stride length. [87] However, these results must be viewed with caution, because the numbers in the study were small, the intervention lasted only 1 day, and no washout period was included. The second subsequent crossover RCT compared group physiotherapy plus medical treatment versus medical treatment alone over 6 weeks. [88] It found that physiotherapy plus medication improved the Sickness Impact Profile (SIP) mobility score, Unified Parkinson's Disease Rating Scale (UPDRS) activities of daily living, and total scores compared with medication alone at 6 weeks (68 people; precrossover results; mean change in SIP mobility score: –1.5 with physiotherapy and medication *v* +0.2 with medication alone, P < 0.05; mean change in UPDRS ADL score: –2.1 with physiotherapy plus medication *v* –0.3 with medication alone, P < 0.05; mean change in UPDRS total score: –6.2 with physiotherapy plus medication *v* –1.0 with medication alone, P < 0.05). It found no significant difference between groups in change in UPDRS motor score and in SIP total score at 6 weeks (mean change in UPDRS motor score: –3.0 with physiotherapy plus medication *v* –0.2 with medication alone; mean change in SIP total score: –1.5 with physiotherapy plus medication *v* –0.5 with medication alone; differences reported as not significant; P values not reported).

Harms: The systematic reviews and subsequent RCTs gave no information on adverse effects. [85] [86] [87] [88]

Comment: **Clinical guide:**
Although RCTs have not conclusively shown evidence of the effectiveness of physiotherapy in Parkinson s disease, clinical experience suggests that it can be effective and safe. This is supported by guidelines from the National Institute for Health and Clinical Excellence. [25] However, further, larger, well-designed RCTs are needed to evaluate what forms of therapy are effective, and how often it should be performed.

OPTION SPEECH AND LANGUAGE THERAPY FOR SPEECH DISTURBANCE

Speech disturbance
Compared with no treatment The effects of speech and language therapy on speech disturbance are unclear compared with no treatment in people with later Parkinson's disease (very low-quality evidence).

For GRADE evaluation of interventions for Parkinson's disease, see table, p 30 .

Benefits: We found one systematic review (search date 2000, 3 RCTs, 63 people), which compared speech and language therapy versus no treatment for speech disturbance. [89] It was unable to draw conclusions on the effects of speech and language therapy because of the small number of people, flawed methods, and the variety of outcome measures used in the RCTs.

Harms: The RCTs in the review gave no information on adverse effects. [89]

Comment: **Clinical guide:**
The RCT evidence of the value of speech and language therapy in Parkinson s disease is relatively poor, but clinical experience suggests that it can be effective and safe. This is supported by guidelines from the National Institute for Health and Clinical Excellence. [25] However, further, larger, well-designed RCTs are required to evaluate what form of therapy should be used and when.

OPTION SWALLOWING THERAPY FOR DYSPHAGIA

We found no clinically important results about the effects of swallowing therapy for dysphagia.

For GRADE evaluation of interventions for Parkinson's disease, see table, p 30 .

Benefits: We found one systematic review (search date 2000) of swallowing therapy for dysphagia, which did not identify any RCTs. [90]

Harms: We found one systematic review (search date 2000) of swallowing therapy for dysphagia, which did not identify any RCTs. [90]

Comment: **Clinical guide:**
In the absence of trial evidence, clinical experience suggests that people with Parkinson s disease who develop dysphagia should be referred to a speech and language therapist for a swallowing assessment. Various treatments are available (e.g. thickening fluids, nutritional supplements), but these have not undergone trials in Parkinson s disease.

GLOSSARY

Axial effects Changes affecting axial body sections, such as head and trunk, rather than the limbs.
Barthel index Assessment of functional ability to perform activities of daily living, using 14 different items and a scale of 0–20; a higher score denotes greater functional independence.
Columbia University Rating Scale Assessment of motor impairment and activities of daily living against 13 items, using a five point scale for each to give a total score between 0 = normal to 65 = maximum disability.
Controlled Oral Word Association Test (COWAT) Most frequently used for assessing verbal fluency and the ease with which a person can think of words that begin with a specific letter; a higher score denotes greater verbal fluency. Different forms of this procedure exist.
Conventional gait training (CGT) Physiotherapeutic gait therapy based on the latest description of the principles of the proprioceptive neuromuscular facilitation and Bobath concepts.
Dopaminergic adverse effects Include dyskinesia, hallucinations, and psychosis.
Dyskinesias Abnormal or involuntary writhing or jerky movements distinct from tremor.
Hoehn and Yahr scale Five stage disability scale: stage one = least severe; stage five = most severe. This rating system has been largely supplanted by the Unified Parkinson s Disease Rating Scale, which is much more complicated.
Limited progressive treadmill training (LTT) The patient's maximum overground walking speed is determined before the first training session. Training speed is increased over a number of sessions by a percentage of the maximum initial walking speed.
Motor fluctuations Fluctuations in motor symptoms, such as bradykinesia, rigidity, and tremor, during a day. Motor fluctuations are sometimes called “on/off” fluctuations.
Pallidal, thalamic, or subthalamic nucleus deep brain stimulation Focal electrical brain stimulation through a stereotactically implanted wire.
Pallidotomy Making a permanent surgical lesion, usually thermally or electrically, in the globus pallidum.
Schwab and England scale Assessment of functional disability on a scale of 0% = vegetative to 100% = completely independent (able to do all chores without slowness, difficulty, or impairment).
Speed dependent treadmill training The patient's maximum overground walking speed is determined before the first training session. After a warm up, the belt speed is increased, in communication with the patient, to the highest speed at which the patient can walk safely and without stumbling. At each subsequent training session, the treadmill is set (after a short warm up) to the last achieved maximum speed from the previous session.
Subthalamic surgery Includes subthalamotomy, in which a lesion is made in the subthalamic nucleus, or subthalamic deep brain stimulation, in which a stimulator is placed in the subthalamic nucleus.
Unified Parkinson's Disease Rating Scale (UPDRS) A scale used to measure the severity of Parkinson's disease. A higher score denotes greater disability. It has six parts: mentation, behaviour, and mood (UPDRS 1); activities of daily living (UPDRS 2); motor examination (UPDRS 3); complications of treatment (UPDRS 4); a global disability staging score (UPDRS 5); and a global activities of daily living score (UPDRS 6).
Webster rating scale Assessment of severity of disease and clinical impairment against 10 items using a scale of 0 = normal to 3 = maximum impairment: bradykinesia, rigidity, posture, upper extremity swing, gait, tremor at rest, facies, seborrhoea, speech, and self care.
“Off” time Periods when treatment is not working. “On” time is the period when treatment is working. “On/off” fluctuations are sometimes known as motor fluctuations.
High-quality evidence Further research is very unlikely to change our confidence in the estimate of effect.
Low-quality evidence Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.
Moderate-quality evidence Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.
Very low-quality evidence Any estimate of effect is very uncertain.

SUBSTANTIVE CHANGES

New option added Amantadine.
New option added Adding amantadine to reduce dyskinesia.
Subthalamic nucleus deep brain stimulation One RCT added; [80] Recategorised to Trade-off between benefits and harms.
Pallidal deep brain stimulation Categorisation changed to Trade-off between benefits and harms.

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Competing interests: APM has been reimbursed by various manufacturers for attending and speaking at conferences, and for consulting. CC has been paid by various manufacturers of the drugs dealt with above for speaking at meetings and attending conferences.

Disclaimer

TABLE 1 **Adding a dopamine agonist to levodopa in people with motor complications: adjuvant dopamine agonist versus placebo.**

Ref	Study design	Interventions	Participants	Motor impairment	Activities of daily living	Motor complications	"Off" time/dose reductions	Adverse effects
[46]	Systematic review, search date not reported	Adjuvant bromocriptine *v* placebo	7 RCTs, 396 people with Parkinson's disease taking levodopa	Heterogeneity in trial design and outcomes made it impossible to draw reliable conclusions for any outcome				
[47]	Systematic review, search date not reported	Lisuride (lysuride) *v* placebo	No RCTs identified.					
[48]	Systematic review, search date 1998	Pergolide *v* placebo	1 RCT, 376 people with Parkinson's disease taking levodopa	Pergolide improved motor function (modified Columbia University Rating Scale motor score: 46.6 with pergolide *v* 22.3 with placebo; P < 0.001)	Pergolide improved activities of daily living scores (modified Columbia rating scale activities of daily living score: 9.7 with pergolide *v* 2.8 with placebo, P < 0.001)		Pergolide significantly reduced daily "off" time over 24 weeks compared with placebo (mean difference in "off" time: 1.6 hours/day; P < 0.001). Pergolide significantly reduced daily levodopa dose (mean reduction in dose: 235 mg/day with pergolide *v* 51 mg/day with placebo; P < 0.001)	Pergolide significantly increased dyskinesia compared with placebo (OR 4.6, 95% CI 3.1 to 7.0). There was no significant difference in withdrawals (1 RCT, 376 people: OR 0.88, 95% CI 0.51 to 1.51)
[49]	Systematic review, search date not reported	Pramipexole *v* placebo	4 RCTs, 669 people with later Parkinson's disease taking levodopa		Pramipexole improved activities-of-daily-living scores compared with placebo (data presented graphically)		Pramipexole significantly reduced "off" time compared with placebo (WMD 1.8 hours, 95% CI 1.2 hours to 2.3 hours). Pramipexole significantly reduced levodopa dose compared with placebo (WMD 115 mg, 95% CI 87 mg to 143 mg).	Pramipexole significantly increased dyskinesia (OR 2.1, 95% CI 0.44 to 0.93). Pramipexole significantly reduced withdrawal from treatment compared with placebo (4 RCTs, 669 people; OR 0.64, 95% CI 0.44 to 0.93)
[50]	Systematic review, search date not reported	Ropinirole *v* placebo	1 RCT, 149 people with Parkinson's disease taking levodopa	Complete information on motor impairment was not available	Complete information on disability was not available		Ropinirole significantly reduced the required dose of levodopa (WMD 180 mg, 95% CI 106 mg to 253 mg)	Ropinirole significantly increased dyskinesia compared with placebo (OR 2.9, 95% CI 1.4 to 6.2). There was no significant difference in withdrawals (1 RCT, 149 people: OR 0.52, 95% CI 0.24 to 1.09)

Ref	Study design	Interventions	Participants	Motor impairment	Activities of daily living	Motor complications	"Off" time/dose reductions	Adverse effects
[51]	Systematic review, search date not reported	Cabergoline *v* placebo	3 RCTs, 268 people with Parkinson's disease taking levodopa	Limited evidence of small but significant benefit in UPDRS motor score with cabergoline (2 RCTs, data presented graphically)	Limited evidence of small but significant benefit in UPDRS activities of daily living score with cabergoline (data presented graphically)		No significant difference between cabergoline and placebo in "off" time (2 RCTs, 61 people, WMD +1.14 hours, 95% CI –0.06 hours to +2.33 hours). Cabergoline significantly reduced the required dose of levodopa (1 RCT, 188 people with mean levodopa reduction: 175 mg with cabergoline *v* 25.5 mg with placebo: WMD 150 mg, 95% CI 94 mg to 205 mg).	There was no significant difference in withdrawals (3 RCTs, 268 people; OR 0.58, CI not stated; P = 0.13).
[52]	RCT	Pramipexole *v* placebo	313 people	Pramipexole significantly improved motor scores (improvement: 11.75 with pramipexole *v* 5.55 with placebo; P < 0.001)	Pramipexole significantly improved UPDRS activities of daily living score (improvement: 3.98 with pramipexole *v* 2.03 with placebo; P < 0.001)		NR	NR

NR, not reported; UPDRS, Unified Parkinson's Disease Rating Scale

TABLE 2 **Adding a dopamine agonist to levodopa in people with motor complications: adjuvant dopamine agonists versus each other.**

Ref	Study design	Interventions	Participants	Motor impairment	Activities of daily living	Motor complications	Off Time/ dose reductions	Adverse effects
[52]	RCT	Pramipexole *v* bromocriptine *v* placebo	Not reported	No significant differences in UPDRS motor scores, but the study was underpowered to detect the differences between the two (improvement in UPDRS III motor scores: 11.8 with pramipexole *v* 10.0 with bromocriptine; P = 0.38)	No significant differences in UPDRS activities of daily living scores, but the study was underpowered to detect the differences between the two (improvement in UPDRS II activities of daily living score: 4.0 with pramipexole *v* 3.3 with bromocriptine; P = 0.18)			No significant difference in adverse effects
[53]	Systematic review, search date not reported	Lisuride (lysuride) *v* bromocriptine	1 RCT, 20 people with Parkinson's disease taking levodopa			No significant difference in motor fluctuations (data not presented). No significant difference in the Columbia University Rating Scale after 12 weeks (improvement in mean total score: 20.8 with lisuride *v* 16.2 with bromocriptine; no P value or CI reported)		Similar frequency of dopaminergic adverse effects (nausea: 26% with lisuride *v* 21% with bromocriptine; postural hypotension: 5% with lisuride *v* 21% with bromocriptine; hallucinations: 5% in both groups; significance assessment not performed)
[54]	Systematic review, search date 1997	Pergolide *v* bromocriptine	3 RCTs, 293 people with Parkinson's disease taking levodopa	Two RCTs found that pergolide significantly improved motor impairment compared with bromocriptine (data presented graphically)	Pergolide significantly increased the proportion of people with "marked or moderate improvement" compared with bromocriptine, as measured using a seven point clinician's global assessment scale (2 RCTs, 305 people; AR: 43% with pergolide *v* 30% with bromocriptine; RR 1.45, 95% CI 1.08 to 1.95)		No significant difference in reduction of levodopa dose after 8–12 weeks, as measured using a seven point clinicians global assessment scale (3 RCTs; WMD +3 mg/day, 95% CI –4 mg/day to +10 mg/day)	No significant difference in adverse effects between pergolide and bromocriptine
[55]	Systematic review, search date not reported	Pramipexole *v* bromocriptine	1 RCT, 163 people with Parkinson's disease taking levodopa	Similar UPDRS scores (no quantitative data provided)	Similar UPDRS scores (no quantitative data provided)	Similar dyskinesias (no quantitative data provided)	Pramipexole reduced "off" time compared with bromocriptine (1 RCT, 152 people; mean "off" time reduction: 2.6 hours/day with pramipexole *v* 1.2 hours/day with bromocriptine; WMD 1.4 hours/day, 95% CI 0.00 hours/day to 2.8 hours/day)	No significant difference in adverse effects between pramipexole and bromocriptine

Ref	Study design	Interventions	Participants	Motor impairment	Activities of daily living	Motor complications	Off Time/ dose reductions	Adverse effects
[56]	Systematic review, search date not reported	Ropinirole *v* bromocriptine	3 RCTs, 482 people with Parkinson's disease taking levodopa	No significant differences between ropinirole and bromocriptine in motor impairments (UPDRS motor scores: data presented graphically)	No significant differences between ropinirole and bromocriptine in disability ratings (clinical global impression scale "much" or "very much" improved, 2 RCTs, 332 people: OR 1.36, 95% CI 0.87 to 2.13)		Ropinirole improved "off" time and levodopa dose reduction compared with bromocriptine after 8–25 weeks, but these differences were not significant (off time reduction, 2 RCTs, 201 people: WMD +0.8 hours/day, 95% CI –0.1 hours/day to +1.7 hours/day; difference in levodopa dose reduction, 2 RCTs, 203 people: +50 mg/day, 95% CI -49 mg/day to +150 mg/day)	Nausea was significantly less frequent with ropinirole compared with bromocriptine (OR 0.5, 95% CI 0.3 to 0.8)
[57]	Systematic review, search date not reported	Cabergoline *v* bromocriptine	5 RCTs, 1071 people with Parkinson's disease taking levodopa	Four RCTs found no significant difference in UPDRS motor scores (data presented graphically)	Four RCTs found no significant difference in UPDRS activities of daily living scores (data presented graphically)		Cabergoline improved "off" time compared with bromocriptine after 12–36 weeks; but the difference was not significant ("off" time, 4 RCTs, 612 people: WMD +0.3 hours/day, 95% CI –0.1 hours/day to +0.7 hours/day). Four RCTs found no significant differences in levodopa dose reduction (4 RCTs, 909 people: WMD: +6.0, 95% CI –21.8 to +33.8)	Dyskinesia and confusion were reported as adverse events more commonly with cabergoline than with bromocriptine, but there was no significant difference in the frequency of other dopaminergic adverse events (dyskinesia: OR 1.6, 95% CI 1.1 to 2.4; confusion: OR 2.0, 95% CI 1.1 to 3.8).

UPDRS, Unified Parkinson's Disease Rating Scale

TABLE **GRADE evaluation of interventions for Parkinson's disease**

Important outcomes	Disease severity, progression of symptoms, need for additional treatment, quality of life, adverse effects								
Number of studies (participants)	**Outcome**	**Comparison**	**Type of evidence**	**Quality**	**Consistency**	**Directness**	**Effect size**	**GRADE**	**Comment**
What are the effects of drug treatments in people with early stage Parkinson's disease?									
1 (361) [24]	Severity of disease	Levodopa *v* placebo	4	0	+1	0	0	High	Consistency point added for dose–response effect
2 (752) [26] [27]	Dyskinesia and motor fluctuations	Modified-release levodopa *v* immediate-release levodopa	4	–2	0	0	0	Low	Quality point deducted for incomplete reporting of results and poor follow-up
2 (752) [26] [27]	Activities of daily living	Modified-release levodopa *v* immediate-release levodopa	4	–2	–1	0	0	Very low	Quality point deducted for incomplete reporting of results and poor follow-up. Consistency point deducted for conflicting results
5 (803) [28]	Motor function	Bromocriptine plus levodopa v levodopa alone	4	-1	-1	0	0	Low	Quality point deducted for incomplete reporting of results. Consistency point deducted for conflicting results
5 (1160) [29] [30] [32] [31] [33]	Motor function	Other dopamine agonists plus levodopa *v* levodopa alone	4	–1	–1	0	0	Low	Quality point deducted for methodological flaws in some studies. Consistency point deducted fro conflicting results depending on outcomes
7 (1464) [36] [37]	Motor function and complications	Dopamine agonists *v* levodopa	4	–1	0	0	0	Moderate	Quality point deducted for incomplete reporting of results
18 (3581) [38] [39]	Disease severity	MAOBIs *v* placebo	4	0	0	–1	0	Moderate	Directness point deducted for only assessing some interventions
18 (3581) [38] [39]	Motor function	MAOBIs *v* placebo	4	0	0	–1	0	Moderate	Directness point deducted for only assessing some interventions
1 (475) [40]	Motor function	Selegiline *v* levodopa *v* bromocriptine *v* lisuride	4	–1	0	0	0	Moderate	Quality point deducted for incomplete reporting of results
11 (2651) [38]	Mortality	MAOBIs *v* placebo	4	0	–1	0	0	Moderate	Consistency point deducted for conflicting results
What are the effects of adding other treatments in people with Parkinson's disease who have motor complications from levodopa?									
16 (at least 2566) [43] [44] [45]	Motor function	Catechol-O-methyl transferase inhibitor plus levodopa *v* placebo plus levodopa	4	–1	–1	0	0	Low	Quality point deducted for incomplete reporting of results. Consistency point deducted for conflicting results
17 (2171) [51] [50] [49] [48] [47] [46] [52]	Disease severity	Dopamine agonist plus levodopa *v* placebo plus levodopa	4	0	–1	–1	0	Low	Consistency point deducted for study heterogeneity. Directness point deducted for inclusion of younger people only
17 (2171) [51] [50] [49] [48] [47] [46] [52]	Motor function	Dopamine agonist plus levodopa *v* placebo plus levodopa	4	0	–1	0	0	Low	Consistency point deducted for study heterogeneity. Directness point deducted for inclusion of younger people only
14 (at least 2029) [52] [53] [54] [56] [57] [55]	Motor function	Bromocriptine plus levodopa *v* other dopamine agonists plus levodopa	4	0	–1	–1	0	Low	Consistency point deducted for conflicting results. Directness point deducted for inclusion of younger people only

Important outcomes	Disease severity, progression of symptoms, need for additional treatment, quality of life, adverse effects								
Number of studies (participants)	**Outcome**	**Comparison**	**Type of evidence**	**Quality**	**Consistency**	**Directness**	**Effect size**	**GRADE**	**Comment**
13 (at least 1866) [52] [53] [54] [56] [57]	Motor function	Bromocriptine plus levodopa *v* other dopamine agonists plus levodopa	4	0	0	–1	0	Moderate	Consistency point deducted for conflicting results. Directness point deducted for inclusion of younger people only
5 (113) [58] [59] [60]	Motor function	Amantadine *v* placebo	4	–3	–1	0	0	Very low	Quality points deducted for sparse data, incomplete reporting of results, and other methodological flaws. Consistency point deducted for conflicting results
What are the effects of surgery in people with later Parkinson's disease?									
2 (73) [61] [62]	Disease severity	Pallidotomy *v* medical therapy	4	–1	0	0	0	Moderate	Quality point deducted fro sparse data
2 (73) [61] [62]	Motor function	Pallidotomy *v* medical therapy	4	–1	0	0	0	Moderate	Quality point deducted for sparse data
1 (13)] [66]	Disease severity	Pallidotomy *v* pallidal deep brain stimulation	4	–1	0	0	0	Moderate	Quality point deducted for sparse data
1 (34) [68]	Disease severity	Pallidotomy *v* subthalamic deep brain stimulation	4	–1	–1	0	0	Low	Quality point deducted for sparse data. Consistency point deducted for conflicting results depending on outcome
2 (55) [77] [78]	Disease severity	Pallidal deep brain stimulation *v* subthalamic nucleus deep brain stimulation	4	–2	0	0	0	Low	Quality points deducted for sparse data and incomplete reporting of results
At least 2 (55) [77] [78] [25]	Motor function	Pallidal deep brain stimulation *v* subthalamic nucleus deep brain stimulation	4	–2	–1	0	0	Very low	Quality points deducted for sparse data and incomplete reporting of results. Consistency point deducted for conflicting results
1 (156) [80]	Motor function	Subthalamic nucleus deep brain stimulation plus medical care *v* medical care alone	4	–1	0	–1	0	Low	Quality point deducted for sparse data. Directness point deducted for inclusion of younger adults only
1 (68) [81]	Disease severity	Thalamic deep brain stimulation *v* thalamotomy	4	–1	0	–1	0	Low	Quality point deducted for sparse data. Directness point deducted for inclusion of people without Parkinson's disease
What are the effects of nursing and rehabilitation treatments in people with Parkinson's disease?									
1 (1859) [82]	Motor function	Nurse specialist care *v* usual care	4	–1	–1	0	0	Low	Quality point deducted for methodological issues. Consistency point deducted for conflicting results for different outcomes
1 (40) [83]	Motor function	More frequent contact with nurse practitioner *v* usual care	4	–1	0	-1	0	Very low	Quality point deducted for sparse data. Directness point deducted for no direct comparison between groups
2 (84) [84]	Disease severity	Occupational therapy *v* no treatment	4	–2	–1	–1	0	Very low	Quality points deducted for sparse data and methodological flaws. Consistency point deducted for heterogeneity between studies. Directness point deducted for inclusion of different outcomes

Important outcomes	Disease severity, progression of symptoms, need for additional treatment, quality of life, adverse effects								
Number of studies (participants)	**Outcome**	**Comparison**	**Type of evidence**	**Quality**	**Consistency**	**Directness**	**Effect size**	**GRADE**	**Comment**
16 (at least 348) [85] [86] [88]	Disease severity	Physiotherapy *v* no treatment or other physical treatments	4	–1	–1	–1	0	Very low	Quality point deducted for methodological flaws. Consistency point deducted for heterogeneity between studies. Directness point deducted for inclusion of different outcomes and comparisons
3 (63) [89]	Speech disturbance	Speech and language therapy *v* no treatment	4	–2	–1	–1	0	Very low	Quality points deducted for sparse data and methodological flaws. Consistency point deducted for heterogeneity between studies. Directness point deducted for inclusion of different outcomes

Type of evidence: 4 = RCT; 2 = Observational; 1 = Non-analytical/expert opinion. Consistency: similarity of results across studies.
Directness: generalisability of population or outcomes.
Effect size: based on relative risk or odds ratio.