Treatment interventions for Parkinson’s disease: an evidence-based assessment

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We did a systematic review, with a uniform method of assessment of efficacy and safety, to assess the different interventions available for the management of Parkinson’s disease (drugs, surgical interventions, and physical treatments) with respect to the following indications: prevention of disease progression, symptomatic treatment of motor features (parkinsonism), symptomatic control of motor complications, prevention of motor complications, and symptomatic treatment of non-motor features. Our aim was not to define practice guidelines, but rather to improve clinicians’ knowledge of the presently available published clinical evidence, based mainly on randomised controlled trials. We hope that our review will help doctors to incorporate this background into their own decision-making strategy to make appropriate choices with respect to the treatment of individual patients with Parkinson’s disease.

Treatment of Parkinson’s disease is complex due to the progressive nature of the disease and the array of motor and non-motor features combined with early and late side-effects associated with therapeutic interventions. A growing number of medical and surgical treatment options are available. Most have a strong pathophysiological rationale but, for many, their actual role in clinical practice is not firmly established on grounds of sound clinical data. With the support of the Movement Disorders Society (MDS), we did a systematic review to assess the efficacy and safety of each of the different antiparkinsonian therapeutic interventions based on the robustness of clinical evidence. The extensive publication of this initiative reviews separately each drug, surgical intervention, and rehabilitation procedure as a separate chapter. The present article distils and reorganises this work differently, each section summarising a practical clinical problem faced when one manages patients with Parkinson’s disease: prevention of disease progression, control of motor symptoms, management of motor complications, treatment of non-motor symptoms.

An extensive description of the methods used to do this work appears in the above-mentioned Movement Disorders Journal Supplement. Briefly, we reviewed the different therapeutic interventions according to a prespecified set of criteria, and rated for efficacy, safety, and clinical usefulness (panel 1). We did literature searches with specific search terms and electronic databases, including Medline (1966–2000), the central database in the Cochrane Library (1948–2000), and systematic checking of reference lists published in review articles and other clinical reports. Papers were included for analysis if they were full paper citations (English peer-reviewed literature, excluding abstracts and books), reporting randomised controlled trials, that enrolled at least 20 patients with an established diagnosis of Parkinson’s disease, used objective scales for measuring outcomes, and had a minimum of 4-week follow-up. Once selected, randomised controlled trials were rated and stratified for study quality with a published checklist relevant for ascertaining the methodological soundness of the trial (a percentage score was used as an indicator of the overall quality of the study). When no randomised controlled trials that met selection criteria were identified, smaller or shorter trials and non-randomised controlled or non-controlled studies were reviewed. For safety, sources other than randomised controlled trials were used, including regulatory publications issued by the European Committee of Proprietary Medicinal Products and the US Food and Drugs Administration. Because the list of references to document all statements is large, only the most representative are cited. The full list of references can be consulted elsewhere.

Treatments for Parkinson’s disease

In Parkinson’s disease, features of parkinsonism are simplistically explained by a model in which the striatum plays a key part within cerebral motor pathways: dopaminergic nigrostriatal neurons degenerate, leading to impaired dopamine striatal modulation and abnormal motor behaviour release. The model predicts that increasing dopamine stimulation, or reducing cholinergic or glutamatergic stimulation, will improve symptoms. There are three types of therapeutic interventions considered in this review: drug treatments, surgical procedures, and rehabilitation techniques (panel 2).

Among dopaminergic drugs, levodopa standard and controlled release formulations are marketed as fixed associations with a dopa-decarboxylase inhibitor—carbidopa or benzeraside. There are several dopamine agonists, with different receptor binding, pharmacokinetic profiles, and routes of administration, and two types of indirect dopamine transmission enhancers, monoamineoxidase-B (MAO-B) and catechol-O-methyltransferase (COMT) inhibitors. Among non-dopaminergic medications there are several anticholinergics, although amantadine is the only drug widely available for antiglutamatergetic effects.
Panel 1: Standard definitions of the terms used to qualify efficacy, clinical usefulness, and safety of therapeutic interventions

**Efficacy**

- **Efficacious**: Evidence shows that the intervention has a positive effect on studied outcomes (based on data from at least one high quality [score ≥75%] RCT and no conflicting data from other RCTs)
- **Efficacy likely**: Evidence suggests, but is not sufficient to show, that the intervention has a positive effect on studied outcomes (based on data from any RCT and no conflicting data from other RCTs)
- **Efficacy unlikely**: Evidence suggests that the intervention does not have a positive effect on studied outcomes (based on data from any RCT and no conflicting data from other RCTs)
- **Non-efficacious**: Evidence shows that the intervention does not have a positive effect on studied outcomes (based on data from at least one high quality [score ≥75%] RCT and no conflicting data from other RCTs)
- **Insufficient evidence**: There is no data available or available data do not provide enough evidence either for or against the use of the intervention in treatment of Parkinson’s disease (all the circumstances not covered by the previous statements)

**Clinical usefulness**

- **Clinically useful**: For a given situation, evidence available is sufficient to conclude that the intervention provides clinical benefit
- **Possibly useful**: For a given situation, evidence available suggests, but is insufficient to conclude, that the intervention provides clinical benefit
- **Investigational**: Available evidence is insufficient to support the use of the intervention in clinical practice, but further study is warranted
- **Not useful**: For a given situation, available evidence is insufficient to say that the intervention provides no clinical benefit

**Safety**

- **Acceptable risk without specialised monitoring**
- **Acceptable risk, with specialised monitoring**
- **Unacceptable risk**
- **Insufficient evidence to make conclusions on the safety of the intervention**

Functional neurosurgery for Parkinson’s disease attempts to restore functional balance in basal ganglia relays. There are currently three targets: the ventral intermediate nucleus of the thalamus, the internal segment of the Globus Pallidus, and the subthalamic nucleus. Either CNS lesions (thalamotomy, pallidotomy, or subthalamic nucleus lesions) or implants of chronic stimulating electrodes at these sites (deep brain stimulation) can be used.1 Reconstructive surgery involves the implantation of human fetal mesencephalic cells (fetal transplant) or other dopamine producing cells into the striatum.10

Rehabilitation for Parkinson’s disease (speech, occupational, and physical therapies) has been applied empirically based on its accepted use in other chronic disorders.

**Prevention of disease progression**

Parkinson’s disease progresses over time, the rate of nigral-cell death being estimated at 10% per year.11 Over time, parkinsonism worsens and the need for symptomatic medications increases. The quality of drug response deteriorates and new symptoms develop. A major aim is the limitation or halting of this process. Primary prevention, before Parkinson’s disease has developed, is not possible in the absence of an identified biological marker or risk factor, apart from ageing and genetic transmission in some rare families. Secondary prevention, once Parkinson’s disease has been diagnosed, should slow down, stop, or even reverse neuronal death. According to various known biochemical pathways that might play a part in cell death, several drugs are potential candidates for neuroprotection.11

The design of randomised controlled trials to show neuroprotection in Parkinson’s disease is controversial.13 There is no way to measure directly neuronal loss in vivo, and it is unclear how clinical symptoms correlate with neuronal death. It is difficult to separate symptomatic from protective effects clinically. A popular clinical endpoint, for example, is to measure the hazard function of early untreated patients who reach the need for levodopa at a particular point in time. In one study,14 selegiline decreased this hazard compared with placebo, a result that was initially interpreted as neuroprotection. A subsequent report,15 however, noted that when treatment with selegiline was stopped the difference disappeared, indicating that the drug had an unsuspected mild symptomatic effect that was large enough to delay the need for levodopa. Use of neuroimaging measures, such as [18F]-levodopa uptake, could eliminate this difficulty, but such endpoints are still exploratory, expensive, and remain surrogates.11

Among the randomised controlled trials done to test neuroprotection in Parkinson’s disease with drugs such as tocopherol,16 selegiline,11 or bromocriptine,16 none produced definite evidence for neuroprotection. There are on-going trials with other candidates, but no conclusion can yet be drawn. There have been theoretical concerns that levodopa could accelerate progression of Parkinson’s disease, because of toxic free-radical generation, but there is no clinical evidence for such toxicity.17

Neuroprotection is an unmet need in Parkinson’s disease and no drug can be recommended yet for this purpose in practice. Any intervention remains investigational, but because several agents are under study at Parkinson’s disease centres, clinicians should consider referring interested patients before prescribing symptomatic treatments.

**Symptomatic treatments of parkinsonism**

Tremor, bradykinesia, rigidity, and later on gait and balance difficulties cause motor disability in patients with Parkinson’s disease. This section addresses two situations: patients with early Parkinson’s disease who are not on levodopa and who receive another drug as monotherapy, and more advanced patients already on levodopa with...
stable or fluctuating responses, who receive adjunct treatment to maintain control of parkinsonism.

In both situations, randomised controlled trials are usually parallel short-term (6 months or less) comparisons of the intervention group with placebo or an active comparator. Levodopa is usually the active comparator in the first situation (monotherapy trials) and bromocriptine the active comparator in the second situation (levodopa-treated patients). Assessment of surgery is often limited to comparisons between start and end of treatment. The most widely used standardised scale to assess parkinsonism is the unified Parkinson’s disease rating scale (UPDRS).18 In levodopa-treated patients with motor fluctuations, the primary outcome measure usually focuses on fluctuations (see next section), whereas parkinsonism, rated early in the morning before medication (off) or at peak medication effect (on), is monitored as a secondary outcome.

### Panel 2: Therapeutic interventions for signs and symptoms of Parkinson’s disease according to main mechanism of action*

<table>
<thead>
<tr>
<th>Drugs</th>
<th>Promote dopamine synthesis</th>
<th>Activate specific receptors</th>
<th>Prolong dopamine availability</th>
<th>Prolong Levodopa bioavailability</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dopaminergic</td>
<td>Levodopa†</td>
<td>Dopamine agonists</td>
<td>MAO-B inhibitors</td>
<td>COMT inhibitors</td>
</tr>
<tr>
<td></td>
<td>dopa-decarboxylase inhibitor</td>
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<tr>
<td>Antiglutamatergic</td>
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<tr>
<td>Anticholinergic</td>
<td></td>
<td></td>
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<tr>
<td>Surgery</td>
<td>Lesion</td>
<td>Deep brain stimulation</td>
<td>Transplantation</td>
<td></td>
</tr>
<tr>
<td>Thalamotomy</td>
<td>Thalamus</td>
<td>Fetal mesencephalic cells</td>
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<tr>
<td>Pallidotomy</td>
<td>Pallidum</td>
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<tr>
<td>Subthalamic nucleotomy</td>
<td>Subthalamic nucleus</td>
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<tr>
<td>Rehabilitation procedures</td>
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<td></td>
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<td>Physical therapy</td>
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<td>Occupational therapy</td>
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<td></td>
<td></td>
<td>Speech therapy</td>
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</tbody>
</table>

MAO-B=monoamine oxidase-B. COMT=catechol-O-methyltransferase. Therapeutic interventions for comorbidities are those of the comorbidities; they are not specific to Parkinson’s disease. †Not available for oral administration. ‡Use restricted or suspended in many countries due to hepatotoxicity. §Mechanism of action not fully known; the antiglutamatergic action is just part of a more complex effect.

### Panel 3: Symptomatic interventions for the treatment of parkinsonism as monotherapies in patients with early Parkinson’s disease

<table>
<thead>
<tr>
<th>Medications</th>
<th>Efficacious*</th>
<th>Likely efficacious*</th>
<th>Insufficient evidence*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Standard levodopa†</td>
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<td></td>
<td></td>
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<tr>
<td>Bromocriptine†</td>
<td></td>
<td></td>
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<tr>
<td>Lisuride‡</td>
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<tr>
<td>DHEC†</td>
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<td></td>
<td></td>
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<tr>
<td>Anticholinergics‡</td>
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<tr>
<td>Pergolide†</td>
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<tr>
<td>Pramipexole†</td>
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<tr>
<td>Amantadine‡</td>
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<tr>
<td>Ropinirole†</td>
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<tr>
<td>Selegiline†</td>
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Surgery

| All interventions§ |

DHEC=dihydroergocriptine. *See panel 1 for definitions. †Clinically useful (safety=acceptable risk without specialised monitoring). ‡Possibly useful (safety=acceptable risk without specialised monitoring). §Based on their mechanism of action, catechol-O-methyltransferase inhibitors are not considered as efficacious when used as monotherapy, but no published clinical trial was identified. ¶Investigational.

Patients with early Parkinson’s disease on monotherapy without levodopa (panel 3)

Standard levodopa was not tested against placebo, but over 30 years of experience with its consistent and large effect size has clearly established its efficacy without randomised controlled trials.19 Subsequently, the drug proved better than other dopamine agonists in several randomised controlled trials.20-22 Results of trials that compared standard and controlled release levodopa indicate that both formulations are equally effective in controlling parkinsonism.23 Among the dopamine agonists,
Control of parkinsonism in patients with Parkinson's disease already on levodopa (panel 4)

Several medications showed efficacy in this situation based on placebo-controlled randomised trials: bromocriptine,34 cabergoline,35 pergolide,35 pramipexole,35,36 and entacapone and tolcapone.37–39 Controlled release levodopa improved parkinsonism as well as standard levodopa.40,41 Anticholinergics,42 amantadine,43 and apomorphine44 could only be classified as likely efficacious due to the lower quality of available randomised controlled trials. There were no placebo-controlled randomised trials with lisuride, but stable parkinsonian scores over years and required a smaller increase in levodopa daily dose than did patients who remained on levodopa monotherapy.45 For other pharmacological interventions, there was not enough evidence for efficacy. Surgical interventions have only been assessed in levodopa-treated patients who exhibited motor complications, and not in stable patients. Only unilateral pallidotomy and human fetal transplants have been tested against medical management in randomised controlled trials. Unilateral pallidotomy was judged likely efficacious because it greatly improved parkinsonism in the off condition in a randomised controlled trial with moderate quality score.46 Because studies with human fetal transplants have had mixed results, possibly related to differences in grafting technique,47–50 we considered the data insufficient to draw a conclusion. Thalamotomy, thalamic, pallidal, and subthalamic deep brain stimulation have been mainly tested without randomised medically managed control groups, and responses have been compared before and after surgery, sometimes with comparisons between different surgical interventions.51–53 Based on the results of one randomised controlled trial, assessing parkinsonism in a cross-over design in patients on or off stimulation, subthalamic and pallidial deep brain stimulation were considered as likely efficacious.54 Data from small open-label trials have been reported, which indicate a strong positive result on tremor for thalamic interventions.55 Although encouraging, the data are still insufficient to establish efficacy.

Most drug treatments have reasonable safety profiles, although dopaminergic side-effects and rare idiosyncratic reactions can happen. All dopaminergic drugs share a common safety profile, reflecting dopaminergic stimulation: nausea, vomiting, hypotension, confusion, and hallucinations. In already dyskinetic patients, most interventions (except amantadine and pallidotomy) enhance dyskinesias. Abnormal daytime sleepiness has also been reported.56–58 Findings of some randomised controlled trials show that hallucinations are more frequent with dopamine agonists than levodopa,59,60 with no differences among agonists.41 In the sole randomised controlled trial, comparing an agonist with a COMT inhibitor, dyskinesia, orthostatic complaints, oedema, and hallucinations were more frequent on bromocriptine, and cramps, dystonia, and xerostomia on tolcapone.61 Diarrhoea is associated with COMT inhibitors and hepatotoxicity with tolcapone.62 Leg oedema is associated with amantadine and dopamine agonists. Pleuropulmonary and retroperitoneal fibrosis can arise with ergot agonists.63,64 Anticholinergic adverse effects are urinary retention, constipation, dry mouth, increase in intraocular pressure, confusion, and hallucinations.7

Usually, such potential safety problems are managed in the context of standard patient care and information, without the need for specialised monitoring. However, due to liver toxicity, tolcapone risk is considered unacceptable in Europe, where its use has been suspended. In other countries, such as the USA, frequent hepatic enzyme monitoring is mandatory, and patients should not be treated with tolcapone if they can be managed with other medications.

Mortality and morbidity (haemorrhage, infarction, infection, seizures, confusion, depression, dysarthria) are adverse effects reported with functional surgery. All surgical therapies require special surgical and post-operative expertise, which restrict such interventions to specialised centres that do these interventions after other treatments have failed. There is little published data on bilateral pallidotomy, but safety concerns include speech, balance, and irreversible cognitive problems.

Safety and efficacy data show that several interventions can be considered as clinically useful or possibly useful to control motor features in Parkinson's disease (panels 3 and 4). Randomised controlled trials, which compare these interventions, are rare. With respect to efficacy, levodopa was better than most other medications. Despite kinetic or binding differences, orally active agonists are very similar.
Ropinirole and pramipexole showed greater efficacy than bromocriptine, but the relevance of this finding remains uncertain. No efficacy difference was reported between tolcapone and bromocriptine.

For each patient, the choice among the useful and possibly useful interventions is, therefore, subjective, incorporating empirical experience and considerations related to age, needs, expectations, comorbidity, safety, efficacy, technical experience, and costs. The weight of all these factors varies with patients and doctors, according to cultural and socioeconomical environments. In de novo patients, the main question is often to decide if and when to start levodopa, based on short-term need for rapid efficacy balanced with concerns about long-term evolution and motor complications (see below). In stable patients without motor complications any useful or possibly useful orally active adjunct therapy devoid of special safety restriction is acceptable. In patients with motor complications, usually the problem of fluctuations or dyskinesia drives the decision. Because of invasiveness, technical demand, and safety, non-orally active treatments (surgery, apomorphine) are considered only if patients also have troublesome motor complications (see next section). Finally, although rehabilitation is frequently prescribed, it is insufficient to assess efficacy. Although subthalamic deep brain stimulation has remarkable effects on off periods, as reported in open-label trials, efficacy has not yet been definitely established versus medical management in randomised controlled trials.

**Symptomatic treatment of motor complications**

Motor complications are frequent and disabling after surgery special expertise requirements, have already been described. They involve fluctuations, erratic or unstable responses to medications also known as the wearing-off and on-off phenomena, and dyskinesias or involuntary movements. Prolonging dopamine stimulation, blocking glutamate transmission, or resetting basal ganglia outputs by surgical means are expected to be potentially helpful. Because treatments have differing effects on fluctuations and dyskinesias, these behaviours are considered separately.

Panel 5 shows interventions used among medications, three agonists (pergolide, pramipexole, and ropinirole) and both COMT inhibitors significantly reduced off time during the day in placebo-controlled randomised controlled trials. Results of one randomised comparison of unilateral pallidotomy versus continued medical management, and several open-label trials showed efficacy with enhanced on time without dyskinesia and diminished off time. Other orally active agonists (bromocriptine, cabergoline) have been studied with less strong placebo-controlled comparisons, but based on documented improvements these agents were considered likely efficacious. The same was true for apomorphine. For other medications as well as all other surgical interventions, including fetal transplantation, data are insufficient to assess efficacy. Although subthalamic deep brain stimulation has remarkable effects on off periods, as reported in open-label trials, efficacy has not yet been definitely established versus medical management in randomised controlled trials.

**Dyskinesias**

Only amantadine was considered as efficacious for treating dyskinesias according to its positive effects in small placebo-controlled randomised controlled trials. Of all results related to pallidotomy, the most consistent has been the control of dyskinesias, especially contralateral to the side of the lesion. However, this finding is only based on uncontrolled data. Similarly, although open label observations on subthalamic and pallidal deep brain stimulation, and subcutaneous apomorphine infusion suggest that dyskinesias improved, there are no randomised controlled trial results on which to base conclusions.

Of the efficacious medications for treating motor complications, pergolide, pramipexole, ropinirole, entacapone, and amantadine have acceptable side-effect profiles (see above) and are therefore clinically useful without special monitoring. Tolcapone restricted use, and surgery special expertise requirements, have already been described.

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**Panel 5: Symptomatic interventions for the treatment of motor fluctuations (MF) and dyskinesias (D) in levodopa-treated patients with Parkinson’s diseases and motor complications**

<table>
<thead>
<tr>
<th>Medication</th>
<th>Efficacious*</th>
<th>Likely efficacious*</th>
<th>Insufficient evidence*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pergolide (MF)†</td>
<td></td>
<td>Apomorphine (MF)§</td>
<td>Controlled release Levodopa</td>
</tr>
<tr>
<td>Pramipexole (MF)†</td>
<td></td>
<td>Bromocriptine (MF)¶</td>
<td>DHEC</td>
</tr>
<tr>
<td>Ropinirole (MF)†</td>
<td></td>
<td>Cabergoline (MF)¶</td>
<td>Lisuride</td>
</tr>
<tr>
<td>Entacapone (MF)†</td>
<td></td>
<td></td>
<td>Piribedil</td>
</tr>
<tr>
<td>Tolcapone (MF)‡</td>
<td></td>
<td></td>
<td>Selegiline</td>
</tr>
<tr>
<td>Amantadine (D)†</td>
<td></td>
<td>Unilateral pallidotomy (MF)**</td>
<td>Anticholinergics</td>
</tr>
<tr>
<td>Surgical intervention</td>
<td></td>
<td></td>
<td>All other interventions</td>
</tr>
<tr>
<td>Rehabilitation</td>
<td></td>
<td></td>
<td>All interventions</td>
</tr>
</tbody>
</table>

DHEC=dihydroergocriptine. *See panel 1 for definitions. †Clinically useful (safety=acceptable risk without specialised monitoring). ‡Tolcapone is considered as possibly useful to manage motor fluctuations in patients who have failed alternative medications but requires regular liver function monitoring (safety=acceptable risk with special monitoring). §Possibly useful (safety=acceptable risk with trained referring staff for subcutaneous pump infusions management). ¶Possibly useful (safety=acceptable risk without specialised monitoring). 52 Investigational. **Possibly useful (safety=acceptable risk with special surgical expertise and monitoring).
Based on this evidence, the management of motor complications in clinical practice involves several considerations. First, for simplicity and safety, useful oral medications with no safety restrictions are indicated. Results of randomised controlled trials have shown no preference between agonists or to entacapone. The clinical decision relies on clinical preferences and, based on extrapolations from short-term efficacy assessments of isolated treatments, most advanced, fluctuating patients will eventually receive a combination of different medications. Second, despite its efficacy, subcutaneous apomorphine is rarely used, often because it has to be prescribed with domperidone, a peripheral dopamine blocking agent, which is not marketed in several countries (including USA). Furthermore, the infusion pumps required for its continuous delivery are difficult to use and require a trained staff at a referring centre. Third, despite the absence of controlled data, and because of strong positive effects in open label trials, there is a growing interest for surgery among movement-disorder specialists. Subthalamic deep brain stimulation is promoted instead of pallidotomy based on three considerations: deep brain stimulation does not induce structural or irreversible lesions; seems to have a strong positive effect on parkinsonism and motor complications; and induces fewer side-effects than pallidotomy when surgery is done bilaterally, a common need in most advanced patients. To establish the best and safest of these complex interventions, future randomised controlled trials should compare subthalamic deep brain stimulation, pallidotomy, and apomorphine pumps.

Prevention of motor complications

The incidence of motor complications is 10% per year of levodopa therapy. Over time, they become more disabling and difficult to manage. Prevention is, therefore, important. A current pathophysiological hypothesis is that non-physiologial pulsatile dopamine receptor stimulation, due to levodopa’s short elimination half-life, and progressive dopamine denervation induce long-lasting changes within the basal ganglia, releasing abnormal motor outputs. Maintaining steady dopamine stimulation or neuroprotective agents should reduce the risk of motor complications.

Randomised controlled trials, assessing the ability of an intervention to prevent motor complications prospectively, compare the probability of developing motor complications for up to 5 years in previously untreated patients who receive an intervention drug versus levodopa-treated controls. There was no standardised method used to define when a patient began motor complications, and each trial used its own definition, with consequent variable numbers from one study to another. Panel 6 shows preventive interventions of motor complications in levodopa-naïve patients.

Large randomised controlled trials identified three efficacious dopamine agonists: cabergoline, ropinirole, and pramipexole. Bromocriptine was considered as likely efficacious because of lower quality randomised controlled trials. Although this property might be a class effect of all agonists, the absence of published randomised controlled trials or inconsistent findings preclude the ability to conclude on the efficacy of lisuride, DHEC, pergolide, and piribedil. Conversely, the early use of continuous release levodopa formulations, to provide in theory more continuous dopamine stimulation, induced the same rate of motor complications as standard levodopa in two 5-year trials. No adequate published randomised controlled trials were identified to conclude on other compounds, including entacapone, which might also theoretically attenuate levodopa pulsatility.

The dopamine agonists with established efficacy for reducing the development of motor complications have reasonable safety profiles and are therefore considered clinically useful. There is no indication that one is better than another. Conversely, the early use of levodopa controlled release formulations offers no advantage over standard formulations. In the absence of adequate clinical evidence, other interventions remain investigational.

Despite the evidence in favour of the early use of these agonists, the decision to start a particular patient on one such agonist rather than levodopa alone can depend on other considerations beside efficacy. Levodopa has a fast acting and strong antiparkinsonian efficacy, and some patients might require rapid improvement. For other patients, levodopa is thought to have a better tolerance profile with respect to some side-effects, such as hallucinations, although for nausea and hypotension no pronounced differences have been well documented in double-blind randomised controlled trials. Furthermore, levodopa is relatively inexpensive, and it remains to be established if the benefit obtained with agonists persists after 5 years. Irrespective of these issues, based on conclusions of

**Panel 6: Preventive interventions of motor complications in levodopa-naïve patients with Parkinson’s disease**

<table>
<thead>
<tr>
<th>Medication</th>
<th>Efficacious *</th>
<th>Likely efficacious *</th>
<th>Non-efficacious *</th>
<th>Insufficient data *</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Cabergoline†</td>
<td>Bromocriptine‡</td>
<td>Controlled release</td>
<td>Apomorphine§</td>
</tr>
<tr>
<td></td>
<td>Pramipexole†</td>
<td></td>
<td>levodopa§</td>
<td>Dihydroergocriptine¶</td>
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<tr>
<td></td>
<td>Ropinirole†</td>
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<td>Lisuride¶</td>
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<tr>
<td>Surgery</td>
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<td>..</td>
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<td>Pergolide¶</td>
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<tr>
<td>Rehabilitation</td>
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<td>..</td>
<td>Piribedil¶</td>
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</tbody>
</table>

*See panel 1 for definitions. †Clinically useful (safety=acceptable risk without specialised monitoring). ‡Possibly useful (safety=acceptable risk without specialised monitoring). §Not useful. ¶Investigational.
randomised controlled trials, there is a growing consensus in favour of the early use of such agonists, especially in young patients, since they are most prone to development of motor complications. Findings of randomised controlled trials indicate that an adequate control of parkinsonism is easily maintained over years if low doses of levodopa are combined with agonists early or added late when necessary. Before such levodopa supplementation, the risk of motor complication on agonist monotherapy is nearly nil. Once levodopa is added, the risk increases, but remains lower overall than that seen from levodopa monotherapy.

Symptomatic treatment of non-motor features (panel 7)

Although Parkinson’s disease is often considered a prototypic movement disorder, most patients have additional non-motor symptoms. These include autonomic dysfunction, depression, cognitive decline, and eventually dementia, sleep problems, sensory complaints, and pain.

Available trials on non-motor features of Parkinson’s disease have major methodological limitations—eg, lack of randomised control groups, insufficient power and follow-up, non-validated outcome measures, and heterogeneous study populations. As a result, the evidence is weak in most instances.

Dementia

Prevalence estimates of dementia in Parkinson’s disease remain imprecise, but a generally accepted figure is a third of patients, particularly those with older age at onset. There is some ongoing controversy with respect to the nosological distinction between Parkinson’s disease with dementia and dementia with Lewy bodies, the latter being defined by progressive dementia before or within the first year of onset of parkinsonian symptoms plus combinations of fluctuating cognition, and spontaneous visual hallucinations and parkinsonism.

So far only results of one placebo-controlled randomised controlled trial have shown that rivastigmine improves scores of an established neuropsychological inventory in dementia with Lewy bodies. No randomised controlled trials, targeting cognitive decline and dementia in idiopathic Parkinson’s disease, have been published, and the routine use of rivastigmine or other cholinesterase inhibitors remains investigational. Because the cholinergic system antagonises dopaminergic function at the level of the striatum, patients treated with anticholinesterase agents should be monitored carefully in clinical practice for possible motor decline.

Psychosis

Drug-induced psychosis is another major non-motor therapeutic challenge, particularly in patients with advanced Parkinson’s disease and cognitive decline, in whom up to 22% may be affected. It is frequently impossible to stop the dopaminergic drugs to a concentration that will maintain sufficient symptomatic motor control. These patients need antipsychotic therapy that will not induce aggravation of parkinsonism.

Several atypical antipsychotics with low putative potential of causing extrapyramidal adverse reactions have been studied, but to date there have been only three randomised controlled trials, all involving clozapine. Two studies were placebo-controlled and a third compared clozapine with olanzapine. All established the short-term efficacy of clozapine on hallucinosis without significant motor worsening. Effective doses were much lower than those needed in schizophrenia. The safety profile, however, of clozapine is unfavourable with a definite albeit low risk of agranulocytosis. Therefore, there is continuing interest in atypical antipsychotics with improved safety profiles. Olanzapine as one candidate has been reported to induce unacceptable worsening of motor symptoms. Quetiapine might be another promising candidate, but no data from randomised trials are yet available. Until then, clozapine is the drug of first choice for the short-term management of patients with Parkinson’s disease who develop drug-induced psychosis.

Depression

Depression affects about 40% of patients with Parkinson’s disease and has a major effect on quality of life. It has not been established whether depression is a reaction to the patient’s perceived loss of autonomy or whether it is an endogenous manifestation of Parkinson’s disease itself.

There is a striking lack of randomised controlled trials assessing antidepressants specifically in Parkinson’s disease. Of several hundred articles identified in the MDS review, there were only two randomised trials, one comparing
nortriptyline with placebo" and the other comparing moclobemide with moclobemide plus selegiline." None allowed definite conclusions. Current treatment of depression in Parkinson’s disease is, therefore, based on the assumption that antidepressants will have similar effects in patients with and without Parkinson’s disease. Although this assumption might be a valid one, biological substrates of depression in patients with Parkinson’s disease might not be identical, and safety profiles could be different when these drugs are administered in conjunction with antiparkinsonian agents.

Autonomic dysfunction
Although much less prevalent than in atypical parkinsonian disorders such as multiple system atrophy, symptomatic orthostatic hypotension is still seen in 15–20% of patients with Parkinson’s disease. Constipation is another common non-motor symptom, possibly resulting from Lewy body degeneration of neurons in the myenteric plexus. Neurogenic bladder disturbances include urinary frequency, urgency, and incontinence. Sexual dysfunction is also part of the spectrum of dysautonomia.

A similar mismatch between therapeutic need and available evidence could be seen in patients with Parkinson’s disease in the arena of autonomic dysfunction. No single trial, studying the effect of any antihypotensive agent in a homogenous study population with Parkinson’s disease, has been done. Randomised controlled trials in patient groups with neurogenic orthostatic hypotension, some of whom have Parkinson’s disease, are available for midodrine,101,102 and one trial has assessed the efficacy of dihydroergotamine in patients with non-neurogenic orthostatic hypotension.103 Other commonly used drugs—eg, tetrahydrozoline and fluidrocortisone—have not been tested in randomised trials. The same is true for the noradrenaline precursor L-threo-3,4-dihydroxyphenylserine (L-Threo-DOPS). Likewise, there are no safety data specifically in patients with Parkinson’s disease. Although these drugs could be options to treat parkinsonian orthostatic hypotension in clinical practice, such use must be considered investigational. Despite its effect on subjective well-being of patients, interventions to improve constipation have not been the subject of several interventions were efficacious. Frequently, when an intervention was not classified as having an established efficacy, the primary limitation was the absence of enough data from clinical trials to clearly judge. One important finding of the project was to identify the numerous situations where data remained insufficient to conclude. For example, the lack of evidence with respect to everyday practice routine interventions, like rehabilitation, the treatment of depression, dementia, or dysautonomia, is striking. There are nearly no data for comparisons between interventions. If choices among equivalent therapeutic options will always remain a matter of clinical expertise and individual preferences, a lot remains to be done to identify which options are equivalent. Similarly, there is a lack of data to assess the potential interest of simultaneous or successive combinations of different interventions. There are insufficient data on long-term outcomes and mortality. We hope that, by pointing out these insufficiencies, we will encourage the scientific community to do the appropriate investigations to correct such lacunas.

Conclusion
We have summarised the published clinical evidence that lends support to the use of therapeutic interventions for Parkinson’s disease. The assessment panel recognises that its conclusions are constrained by some factors. Inclusion criteria to incorporate trials into the review process were restrictive. Publication practices bias toward reports with favourable results. The database analysis was closed in January, 2001, and it is expected that more recently published trials and future randomised controlled trials will permit modifications of conclusions in this on-going effort, especially those relating to recent interventions. The few trials identified with the older medications, such as anticholinergics, amantadine, and the first generation of dopamine agonists, were done in times when technical solutions to plan such trials had not yet developed. Since then, those drugs have come off patent, and there is no present financial interest in understanding them better. Consequently, conclusions on efficacy are better substantiated for recently marketed drugs than for older ones, though the strength of conclusions might not reflect true clinical differences. Conversely, years of experience with an older agent offers greater reliability with respect to safety than does the short follow-up of recent agents. Throughout this review, conclusions were more focused on proof of efficacy than safety, because reviewing randomised controlled trials is not the best method to study side-effects, especially the less frequent ones.

The amount of evidence was sufficient to conclude that several interventions were efficacious. Frequently, when an intervention was not classified as having an established efficacy, the primary limitation was the absence of enough data from clinical trials to clearly judge. One important finding of the project was to identify the numerous situations where data remained insufficient to conclude. For example, the lack of evidence with respect to everyday practice routine interventions, like rehabilitation, the treatment of depression, dementia, or dysautonomia, is striking. There are nearly no data for comparisons between interventions. If choices among equivalent therapeutic options will always remain a matter of clinical expertise and individual preferences, a lot remains to be done to identify which options are equivalent. Similarly, there is a lack of data to assess the potential interest of simultaneous or successive combinations of different interventions. There are insufficient data on long-term outcomes and mortality. We hope that, by pointing out these insufficiencies, we will encourage the scientific community to do the appropriate investigations to correct such lacunas.
References


