Review

Treatment interventions for Parkinson's disease: an evidence based assessment

Olivier Rascol, Christopher Goetz, William Koller, Werner Poewe, Cristina Sampaio

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[1] 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.[1] 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[2] 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.[1]

Lancet 2002; **359:** 1589–98

Clinical Investigation Centre and the Department of Clinical Pharmacology, INSERM U 455, Toulouse University Hospital, 31073 Toulouse Cedex, FRANCE (Prof O Rascol MD); **Department of Neurological Sciences, Rush Presbyterian St Luke's Medical Centre, Chicago, USA** (Prof C Goetz MD); **Neurological Department, University of Miami, Miami** (Prof W Koller MD); **Department of Neurology, University of Innsbruck, Innsbruck, Austria** (Prof W Poewe MD); **and Institute of Pharmacology and Therapeutics, Faculty of Medicine of Lisbon, Lisbon, Portugal** (Prof C Sampaio MD)

Correspondence to: Prof Olivier Rascol (e-mail: rascol@cict.fr)

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.[3] 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,[4] and two types of indirect dopamine transmission enhancers, mono-amineoxidase-B (MAO-B) and catechol-O-methyltransferase (COMT) inhibitors.[5,6] Among non-dopaminergic medications there are several anticholinergics,[7] although amantadine is the only drug widely available for antiglutamatergic effects.[8]

For personal use. Only reproduce with permission from The Lancet Publishing Group.

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%][2] 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%][2] 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 sufficient 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

RCT=randomised controlled trial.

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.[9] 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.[12]

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 [^{18}F]-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,[15] selegiline,[15] 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

For personal use. Only reproduce with permission from The Lancet Publishing Group.

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

Drugs	**Promote dopamine synthesis**	**Activate specific receptors**	**Prolong dopamine availability**	**Prolong Levodopa bioavailabilty**
Dopaminergic	*Levodopa+ dopa-decarboxylase inhibitor*	*Dopamine agonists*	*MAO-B inhibitors*	*COMT inhibitors*
		Apomorphine† Bromocriptine Cabergoline Dihydroergocriptine Lisuride Pergolide Piribedil Pramipexole Ropinirole	Selegiline	Entacapone Tolcapone‡
Antiglutamatergic		Amantadine§		
Anticholinergic		Benztropine Biperiden Orphenadrine Procyclidine Trihexyphenidyl		
Surgery	**Lesion**	**Deep brain stimulation**	**Transplantation**	
	Thalamotomy Pallidotomy Subthalamic nucleotomy	Thalamus Pallidum Subthalamic nucleus	Fetal mesencephalic cells	
Rehabilitation procedures				
		Physical therapy Occupational therapy Speech therapy		

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.

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.

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,

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

	Efficacious*	**Likely efficacious***	**Insufficient evidence***
Medications	Standard levodopa† Controlled release levodopa†	Bromocriptine‡ Lisuride‡	Apomorphine¶ Cabergoline¶ Piribedil¶
	DHEC† Pergolide† Pramipexole† Ropinirole†	Anticholinergics‡ Amantadine‡	Entacapone§¶ Tolcapone§
	Selegiline†		
Surgery	..	..	All interventions¶
Rehabilitation	..	..	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. ¶Investgational.

For personal use. Only reproduce with permission from The Lancet Publishing Group.

four were judged efficacious because they improved parkinsonism significantly more than did placebo: dihydroergocryptine (DHEC),[24] pergolide,[25] pramipexole,[26] and ropinirole.[27] The same was true for selegiline.[14,15,28]

Lisuride,[29] bromocriptine,[30] amantadine,[31] and anticholinergics[32] were not tested against placebo in high quality randomised controlled trials but, because they consistently produced improvement compared with baseline, they are classified as likely efficacious. No surgical intervention has ever been assessed as monotherapy in untreated Parkinson's disease, and for other interventions conflicting results or inadequate details preclude conclusions.

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,[33] cabergoline,[34] 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 apomorphine[44] 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 levodopa-treated patients on lisuride maintained more 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 pallidal 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.

Panel 4: **Symptomatic interventions for the treatment of parkinsonism as adjunct therapies in patients with Parkinson's disease and on levodopa**

	Efficacious*	Likely efficacious*	Insufficient evidence*
Medications	Controlled release levodopa†	Apomorphine§ Lisuride¶	DHEC** Piribedil** Ropinirole**
		Amantadine¶	
	Bromocriptine† Cabergoline† Pergolide† Pramipexole†	Anticholinergics¶	Seligiline**
	Entacapone† Tolcapone‡		
Surgery	..	Unilateral Pallidotomy‖ Subthalamic DBS‖ Globus pallidus DBS‖	All other surgical interventions**
Rehabili–tation	..	..	All interventions**

DHEC=dihydroergocriptine. *See panel 1 for definitions. †Clinically useful (safety=acceptable risk without specialised monitoring). ‡Despite its efficacy, tolcapone is not clinically useful for the treatment of parkinsonism because of safety concerns (unacceptable risk of liver toxicity). §Possibly useful (safety=acceptable risk with trained referring staff for subcutaneous pump infusions management). ¶Possibly useful (safety=acceptable risk without specialised monitoring). ‖Possibly useful (safety=acceptable risk with special surgical expertise and monitoring). **Investigational.

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.[56–59] Findings of some randomised controlled trials show that hallucinations are more frequent with dopamine agonists than levodopa,[22,60] with no differences among agonists.[61] 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.[62] Diarrhoea is associated with COMT inhibitors and hepatotoxicity with tolcapone.[6] 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.

For personal use. Only reproduce with permission from The Lancet Publishing Group.

Ropinirole[61] and pramipexole[33] showed greater efficacy than bromocriptine, but the relevance of this finding remains uncertain. No efficacy difference was reported between tolcapone and bromocriptine.[62]

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, the evidence is based on few studies with patients at different stages of disability, so it is difficult to conclude when such interventions might be recommended.

Symptomatic treatment of motor complications

Motor complications are frequent and disabling after several years of treatment with levodopa.[65] 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.

Parallel randomised controlled trials usually compare intervention with placebo (or bromocriptine for motor fluctuations). Most assessments of motor fluctuations are based on reports from patient diaries, summarising whether individuals were on (good effect) or off (poor response).[66] Dyskinesia rating scales were also used.[67] Patients enrolled to assess orally active medications were generally less severely affected than those enrolled to assess surgery or apomorphine. Panel 5 shows interventions used for the treatment of motor fluctuations and dyskinesias.

Motor fluctuations

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.[33,35,68–71] Results of one randomised comparison of unilateral pallidotomy versus continued medical management,[46] 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.[45,72] 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.[73–76] 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.[46,77] 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.[53,78]

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.

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**

	Efficacious*	**Likely efficacious***	**Insufficient evidence***
Medication	Pergolide (MF)† Pramipexole (MF)† Ropinirole (MF)†	Apomorphine (MF)§ Bromocriptine (MF)¶ Cabergoline (MF)¶	Controlled release Levodopa‖ DHEC‖ Lisuride‖ Piribedil‖
	Entacapone (MF)† Tolcapone (MF)‡		Selegiline‖
	Amantadine (D)†		Anticholinergics‖
Surgical intervention	..	Unilateral pallidotomy (MF)**	All other interventions‖
Rehabilitation	..	..	All interventions‖

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). ‖Investigational. **Possibly useful (safety=acceptable risk with special surgical expertise and monitoring).

For personal use. Only reproduce with permission from The Lancet Publishing Group.

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-physiological 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.[79] 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-naive patients.

Large randomised controlled trials identified three efficacious dopamine agonists: cabergoline,[80] ropinirole,[60] and pramipexole.[22] Bromocriptine[81–85] 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.[86,87] 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,[22,60] 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-naive patients with Parkinson's disease**

	Efficacious*	Likely efficacious*	Non-efficacious*	Insufficient data*
Medication	Cabergoline† Pramipexole† Ropinirole†	Bromocriptine‡	Controlled release levodopa§	Apomorphine¶ Dihydroergocriptine¶ Lisuride¶ Pergolide¶ Piribedil¶ Selegiline¶ Entacapone¶ Tolcapone¶ Amantadine¶ Anticholinergics¶
Surgery	..	..	..	All interventions¶
Rehabilitation	..	..	..	All interventions¶

*See panel 1 for definitions. †Clinically useful (safety=acceptable risk without specialised monitoring). ‡Possibly useful (safety=acceptable risk without specialised monitoring). §Not useful. ¶Investigational.

For personal use. Only reproduce with permission from The Lancet Publishing Group.

Panel 7: **Symptomatic treatments for non-motor features of Parkinson's disease**

	Efficacious*	Likely efficacious*	Insufficient evidence*
Mental dysfunction			
Dementia	..	..	Rivastigmine,†† donepezil,†† tacrine,†† galantamine††
Drug-induced psychosis	Clozapine†	..	Quetiapine,†† olanzapine,†† risperidone,†† zotepin,†† odensatron††, rivastigmine,†† donepezil,†† tacrine,†† galantamine††
Depression	..	..	Tricyclic antidepressants,†† MAO-inhibitors,†† serotonin-reuptake-inhibitors††, electroconvulsive therapy††
Autonomic dysfunction			
Orthostatic hypotension	..	..	Midodrine,§†† fludrocortisone,†† dihydroergotamine,¶†† etilefrine,†† indomethacine,†† yohimbine††
Urinary dysfunction	..	..	Oxybutinine,‖†† tolterodin,‖†† flavoxate,‖†† Propiverine,‖†† Prazosin‖††
Gastrointestinal dysfunction			
Constipation	..	..	Cisapride**
Drug-induced nausea	..	Domperidone‡	Metoclopramide††

*See panel 1 for definitions. †Clinically useful (safety=acceptable risk without specialised haematological monitoring). ‡Possibly useful (safety=acceptable risk without specialised monitoring). §Studies in mixed populations with neurogenic hypotension of various causes including some patients with Parkinson's disease. ¶Studied in non-neurogenic hypotension outside Parkinson's disease. ‖No study in Parkinson's disease populations. **Not useful because of safety concerns with unacceptable risk (severe cardiac arrythmia).

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[82] or added late when necessary.[22,60,85] 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.[88] 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.[89]

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.[90] 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.[91] It is frequently impossible to reduce 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[92,93] and a third compared clozapine with olanzapine.[94] 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.[95] 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.[94] Quetiapine might be another promising candidate, but no data from randomised trials are yet available.[96] 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.[97] 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

For personal use. Only reproduce with permission from The Lancet Publishing Group.

nortriptyline with placebo[98] and the other comparing moclobemide with moclobemide plus selegiline.[99] 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 and without 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.[100] 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 from randomised trials in patients with Parkinson's disease is seen in the arena of autonomic dysfunction. No single trial, studying the effect of any antihypotensive agent in a homogeneous 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, etilefrine and fludrocortisone—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 randomised controlled trials. The same is true for neurogenic bladder disturbances. Trials to assess the efficacy of the anticholinergic agents oxybutynin or tolterodine have not specifically included patients with Parkinson's disease. There are no randomised controlled trials of sildenafil or apomorphine for male erectile dysfunction. Although constipation, urinary frequency, and erectile dysfunction are commonly treated in patients with Parkinson's disease with drugs that have shown efficacy in non-parkinsonian populations, there is a clear need for properly designed trials to assess their safety and efficacy in patients with Parkinson's disease.

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 stronger 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.

Contributors

The five authors all actively participated in all aspects of writing the review—ie, literature search, selection of papers, analysis of selected papers, establishment of conclusions, and writing of the report.

Conflict of interest statement

O Rascol, C Goetz, W Poewe, and C Sampaio act as independent consultants for different pharmaceutical companies involved in the marketing and development of antiparkinsonian medications, and receive honorarium from them. W Koller has received honoraria for speaking from Pharmacia, Novartis, GlaxoSmithKline, and Medtronic Corporation. C Sampaio's research group at Lisbon School of Medicine receives unrestricted grants from different pharmaceutical companies involved in marketing and development of antiparkinsonian and antidystonia medications. She has also been involved in clinical trials, testing antiparkinsonian drugs sponsored by pharmaceutical companies and as a CPMP member at EMEA has participated in regulatory assessment of antiparkinsonian drugs.

Acknowledgments

We thank all our colleagues who have worked as members of the MDS Evidence Based Assessement Project on interventions for the treatment of Parkinson's Disease to produce the extensive MDS report that will be published as a Supplement of the Journal Movement Disorders:[1] M F Brin (New York, USA), C Brefel-Courbon (Toulouse, France), T Eichhorn (Marburg, Germany), J Ferreira (Lisbon, Portugal), C Goetz (Chicago, USA), R Katzenschlager (London, UK), W Koller (Miami, USA), A J Lees (London, UK), P LeWitt (Detroit, USA), A Lozano (Toronto, Canada), E Luginger (Innsbruck, Austria), Y Mizuno (Tokyo, Japan), J Nutt (Portland, USA), W Oertel (Marburg, Germany), C W Olanow (New York, USA), P Pastor (Barcelona, Spain), S Pearlman (New York, USA), W Poewe, (Innsbruck, Austria), O Rascol (Toulouse, France), C Sampaio (Lisbon, Portugal), K Seppi (Insbruck, Austria), S Spieker (Marburg, Germany), and E Tolosa (Barcelona, Spain).

The MDS Evidence Based Assessement Project on interventions for the treatment of Parkinson's Disease was supported by unrestricted educational grants to MDS from: Dupont, Hoffman LaRoche, Medtronic, Novartis, Orion, Pharmacia, SmithKline Beecham (GlaxoSmithKline), and Watson Laboratories. The sponsors of the study had no role in study design, data collection, data analysis, data interpretation, or in writing the report.

For personal use. Only reproduce with permission from The Lancet Publishing Group.

References

1 Goetz CG, Koller WC, Poewe W, et al. Management of Parkinson's disease: an evidence-based review. *Mov Disorders* (in press).

2 Dixon RA, Munro JF, Silcocks RP. Checklists for critical appraisal: the evidence based medicine workbook—critical appraisal for clinical problem solving. Oxford: Butterworth Heinemann Medical, 1997.

3 DeLong MR. Primate models of movement disorders of basal ganglia origin. *Trends Neurosci* 1990; **13:** 281–85.

4 Rascol O, Ferreira JJ, Thalamas C, Galitzki M, Montastruc JL. Dopamine agonists: their role in the management of Parkinson's disease. *Adv Neurol* 2001; **86:** 301–09.

5 Johnson S, Sandler M. The pharmacology of selegiline. *Rev Contemp Pharmacol* 1992; **9:** 51–65.

6 Kaakkola S. Clinical pharmacology, therapeutic use and potential of COMT inhibitors in Parkinson's disease. *Drugs* 2000;**59:** 1233–50.

7 Lang AE, Blair RDG. Anticholinergic drugs and amantadine in the treatment of Parkinson's disease. In: Calne DB, ed. Handbook of experimental pharmacology, volume 88: drugs for the treatment of Parkinson's diseases. Berlin Heidelberg: Springer-Verlag, 1989.

8 Greenamyre JT, O'Brien CF. N-methyl-D-aspartate antagonists in the treatment of Parkinson's disease. *Arch Neurol* 1991; **48:** 977–81.

9 Lang AE. Surgery for Parkinson disease: a critical evaluation of the state of the art. *Arch Neurol* 2000; **57:** 1118–25.

10 Bjorklund A. Cell replacement strategies for neurodegenerative disorders. *Novartis Found Symp* 2000; **231:** 7–15.

11 Morrish PK, Rakshi JS, Bailey DL, Sawle GV, Brooks DJ. Measuring the rate of progression and estimating the preclinical period of Parkinson's disease with (18)fluorodopa-PET. *J Neurol Neurosurg Psychiatry* 1998; **64:** 314–19.

12 Mizuno Y, Mori H, Kondo T. Potential of neuroprotective therapy in Parkinson's disease. *CNS Drugs* 1994; **1:** 45–56.

13 Chan PLS, Holford NHG. Drug treatment effects on disease progression. *Annu Rev Pharmacol Toxicol* 2001; **41:** 625–59.

14 Parkinson Study Group. Effect of deprenyl on the progression of disability in early Parkinson's diseases. *N Engl J Med* 1989; **321:** 1364–71.

15 Parkinson Study Group. Effects of tocopherol and deprenyl on the progression of disability in early Parkinson's disease. *N Engl J Med* 1993; **328:** 176–83.

16 Olanow CW, Hauser RA, Gauger L, et al. The effect of deprenyl and levodopa on the progression of Parkinson's disease. *Ann Neurol* 1995; **38:** 771–77.

17 Murer MG, Raisman-Vozari R, Gershanik O. Levodopa in Parkinson's disease. Neurotoxicity issue laid to rest? *Drug Safety* 1999; **21:** 339–52.

18 Fahn S, Elton R, and the members of the UPDRS Development Committee. Unified Parkinson's disease rating scale. In: Fahn S, Marsden CD, Calne DB, Goldstein M, eds. Recent development in Parkinson's Disease, volume 2. New York: Macmillan Publishing, 1987: 153–63.

19 Cotzias GC, Papavasiliou PS, Gellene R. Modification of parkinsonism: chronic treatment with levodopa. *N Engl J Med* 1969; **280:** 337–45.

20 Parkinson'Disease Research Group in the United Kingdom. Comparisons of therapeutic effects of levodopa, levodopa and selegiline, and bromocriptine in patients with early, mild Parkinson's disease: three year interim report. *BMJ* 1993; **307:** 469–72.

21 Rascol O, Brooks DJ, Brunt ER, et al. Ropinirole in the treatment of early Parkinson's disease: a 6-month interim report of a 5-year levodopa-controlled study. *Mov Disord* 1998; **13:** 39–45.

22 Parkinson Study Group. Pramipexole versus levodopa as initial treatment for Parkinson's disease: a randomized controlled trial. *JAMA* 2000; **284:** 1931–38.

23 Koller WC, Hutton JT, Tolosa E, et al. Immediate-release and controlled-release carbidopa/levodopa in PD: a 5-year randomized multicenter study. *Neurology* 1999; **53:** 1012–19.

24 Bergamasco B, Frattola L, Muratorio A Piccoli F, Mailland F, Parnetti L. Alpha-dihydroergocryptine in the treatment of de novo parkinsonian patients: results of a multicentre, randomised, double-blind, placebo-controlled study. *Acta Neurol Scand* 2000; **101:** 372–80.

25 Barone P, Bravi D, Bermejo-Pareja F, et al. Pergolide monotherapy in the treatment of early Parkinson's disease: a randomized, controlled study. *Neurology* 1999; **53:** 573–79.

26 Shannon KM, Bennett JP, Friedman JH, et al. Efficacy of pramipexole, a novel dopamine agonist, as monotherapy in mild to moderate Parkinson's disease. *Neurology* 1997; **49:** 724–28.

27 Adler CH, Sethi KD, Hauser RA, et al. Ropinirole for the treatment of early Parkinson's disease. *Neurology* 1997; **49:** 393–99.

28 Parkinson Study Group. Impact of deprenyl and tocopherol treatment of Parkinson's disease in DATATOP subjects not requiring levodopa. *Ann Neurol* 1996; **39:** 29–36.

29 Rinne UK. Lisuride, a dopamine agonist in the treatment of early Parkinson's disease. *Neurology* 1989; **39:** 336–39.

30 Staal-Schreinemachers AL, Wesseling H, Kamphuis DJ, Burg WVD, Lakke JPWF. Low dose bromocriptine therapy in Parkinson's disease: double-blind, placebo-controlled study. *Neurology* 1986; **36:** 291–93.

31 Butzer JF, Silver DE, Sans AL. Amantadine in Parkinson's disease: a double-blind, placebo-controlled, crossover study with long-term follow-up. *Neurology* 1975; **25:** 603–06.

32 Cooper JA, Sager HJ, Doherty SM, Jordan N, Tidswell P, Sullivan EV. Different effects of dopaminergic and anticholinergic therapies on cognitive and motor function in Parkinson's disease. *Brain* 1992; **115:** 1701–25.

33 Guttman M, and the international Pramipexole-Bromocriptine study group. Double-blind comparison of pramipexole and bromocriptine treatment with placebo in advanced Parkinson's disease. *Neurology* 1997; **49:** 1060–65.

34 Hutton JT, Koller WC, Ahlskog JE, et al. Multicenter, placebo-controlled trial of cabergoline taken once daily in the treatment of Parkinson's disease. *Neurology* 1996; **46:** 1062–65.

35 Olanow CW, Fahn S, Muenter M, et al. A multicenter double-blind placebo-controlled trial of pergolide as an adjunct to Sinemet in Parkinson's disease. *Mov Disord* 1994; **9:** 40–47.

36 Pinter MM, Pogarell O, Oertel WH. Efficacy, safety and tolerance of the non-ergoline dopamine agonist pramipexole in the treatment of advanced Parkinson's disease: double-blind, placebo-controlled, randomized, multicenter study. *J Neurol Neurosurg Psychiatry* 1999; **66:** 436–41.

37 Waters CH, Kurth M, Bailey P, et al. Tolcapone in stable Parkinson's disease: efficacy and safety of long-term treatment. *Neurology* 1997; **49:** 665–71.

38 Adler CH, Singer C, O'Brien C, et al. Randomized, placebo-controlled study of tolcapone in patients with fluctuating Parkinson's disease treated with levodopa-carbidopa. *Arch Neurol* 1998; **55:** 1089–95.

39 Rinne UK, Larsen JP, Siden A, et al. Entacapone enhances the response to levodopa in parkinsonian patients with motor fluctuations. *Neurology* 1998; **51:** 1309–14.

40 Goetz CG, Tanner CM, Shannon KM, Carroll VS, Klawans HL. Controlled release long-acting levodopa/carbidopa combination in Parkinson's disease patients with and without motor fluctuation. *Neurology* 1988; **38:** 1143–45.

41 Feldman RG, Mosbach PA, Kelly MR, Thomas CA, Saint-Hilaire MH. Double-blind comparison of standard Sinemet and Sinemet CR in patients with mild-to-moderate Parkinson's disease. *Neurology* 1989; **39:** 96–101.

42 Wallace W, Tourtelotte WW, Potvin AR. Parkinson's disease: Cogentin with Sinemet, a better response. *Prog Neuro Psychopharmacol Biol Psychiatry* 1982; **6:** 51–55.

43 Savery F. Amantadine and a fixed combination of levodopa and carbidopa in the treatment of Parkinson's disease. *Dis Nerv Syst* 1977; **38:** 605–08.

44 Dewey RB, Hutton JT, LeWitt PA, Factor SA. A randomised double-blind placebo-controlled trial of subcutaneously injected apomorphine for parkinsonian off-stat events. *Arch Neurol* 2001; **58:** 1385–92.

45 Allain H, Destee A, Petit H, et al. Five-year follow-up of early lisuride and levodopa combination therapy versus levodopa monotherapy in de novo Parkinson's disease. *Europ Neurology* 2000; **44:** 22–30.

46 De Bie RM, de Haan RJ, Nijssen PC, et al. Unilateral pallidotomy in Parkinson's disease: a randomized, single-blind, multicenter trial. *Lancet* 1999; **354:** 1665–69.

47 Lindvall O, Widner H, Rehncrona S, et al. Transplantation of fetal dopamine neurons in Parkinson's disease: one-year clinical and neuropsychological observations in two patients with putaminal implants. *Ann Neurol* 1992; **31:** 155–65.

48 Spencer DD, Robbins RJ, Naftolin F, et al. Unilateral transplantation of human fetal mesencephalic tissue into the caudate nucleus of patients with Parkinson's disease. *N Engl J Med* 1992; **327:** 1541–48.

49 Kopyov OV, Jacques DS, Lieberman A, Duma CM, Rogers RL. Outcome following intrastriatal fetal mesencepahalic grafts for Parkinson's patients is directly related to the volume of grafted tissue. *Exp Neurol* 1997; **146:** 536–45.

50 Freed CR, Greene PE, Breeze RE, et al. Transplantation of embryonic dopamine neurons for severe parkinson's disease. *N Engl J Med* 2001; **344:** 710–19.

51 Jankovic J, Cardoso F, Grossman RG, Hamilton WJ. Outcome after stereotactic thalamotomy for parkinsonian, essential and other types of tremor. *Neurosurgery* 1995; **37:** 680–86.

52 Schuurman PR, Bosch DA, Bossuyt PM, et al. A comparison of continuous thalamic stimulation and thalamotomy for suppression of severe tremor. *N Engl J Med* 2000; **342:** 461–68.

53 Burchiel KJ, AndersonVC, Favre J, Hammerstad JP. Comparison of pallidal and subthalamic nucleus deep brain stimulation for advanced Parkinson's disease: results of randomized, blinded pilot study. *Neurosurgery* 1999; **45:** 1375–82.

For personal use. Only reproduce with permission from The Lancet Publishing Group.

54 Deep-brain stimulation for Parkinson's disease study group. Deep-brain stimulation of the subthalamic nucleus or the pars interna of the globus pallidus in Parkinson's disease. *N Engl J Med* 2001; **345:** 956–63.
55 Limousin P, Speelman JD, Gielen F, Janssens M. Multicentre European study of thalamic stimulation in parkinsonian and essential tremor. *J Neurol Neurosurg Psychiatry* 1999; **66:** 289–96.
56 Frucht S, Rogers JD, Greene PE, Gordon MF, Fahn S. Falling asleep at the wheel: motor vehicle mishaps in persons taking pramipexole and ropinirole. *Neurology* 1999; **52:** 1908–10.
57 Ferreira JJ, Galitzky M, Montastruc JL, Rascol O. Sleep attacks and Parkinson's disease treatment. *Lancet* 2000; **355:** 1333–34.
58 Ferreira JJ, Thalamas C, Montastruc JL, Castro-Caldas A, Rascol O. Levodopa monotherapy can induce "sleep attacks" in Parkinson's disease patients. *J Neurol* 2001; **248:** 426–27.
59 Tracik F, Ebersbach G. Sudden daytime sleep onset in Parkinson's disease: polysomnographic recordings. *Mov Disorders* 2001; **16:** 500–06.
60 Rascol O, Brooks DJ, Korczyn AD, et al. A five-year study of the incidence of dyskinesia in patients with early Parkinson's disease who were treated with ropinirole or levodopa. *N Engl J Med* 2000; **342:** 1484–91.
61 Korczyn AD, Brooks DJ, Brunt ER, et al. Ropinirole versus bromocriptine in the treatment of early Parkinson's disease: 6-month interim report of a 3-year study. *Mov Disord* 1998; **13:** 46–51.
62 Tolcapone Study Group. Efficacy and tolerability of tolcapone compared with bromocriptine in levodopa-treated parkinsonian patients. *Mov Disord* 1999; **14:** 38–44.
63 Todman DH, Oliver WA, Edwards RL. Pleuropulmonary fibrosis due to bromocriptine tratment for Parkinson's disease. *Clin Exp Neurol* 1990; **27:** 79–82.
64 Mondal BK, Suri S. Pergolide-induced retroperitoneal fibrosis. *Int J Clin Pract* 2000; **54:** 403.
65 Jankovic J, Tolosa E, eds. Parkinson's disease and movement disorders. Baltimore: Williams and Wilkins, 1998.
66 Hausser RA, Friedlander J, Zesiewicz TA, et al. A home diary to assess functional status in patients with Parkinson's disease with motor fluctuations and dyskinesia. *Clin Neuropharmacol* 2000; **23:** 75–81.
67 Goetz CG. Rating scales for dyskinesia in Parkinson's disease. *Mov Disord* 1999; **14** (suppl 1)**:** 48–53.
68 Rascol O, Lees AJ, Senard JM, Pirtosek Z, Montastruc JL, Fuell D. Ropinirole in the treatment of levodopa-induced motor fluctuations in patients with Parkinson's disease. *Clin Neuropharmacol* 1996; **19:** 234–45.
69 Lieberman A, Olanow CW, Sethi K, et al. A multicenter trial of ropinirole adjunct treatment for Parkinson's disease. *Neurology* 1998; **51:** 1057–62.
70 Kurth MC, Adler CH, Hilaire MS, et al. Tolcapone improves motor function and reduces levodopa requirement in patients with Parkinson's disease with the "wearing-off" phenomenon: a double-blind, placebo-controlled, multicenter trial. *Neurology* 1997; **48:** 81–87.
71 Ruottinen HM, Rinne UK. Entacapone prolongs levodopa response in a one-month double-blind study in parkinsonian patients with levodopa related fluctuations. *J Neurol Neurosurg Psychiatry* 1996; **60:** 36–40.
72 OstergaardL, Werdelin L, Odin P, et al. Pen injected apomorphine against off phenomena in late Parkinson's disease: a double blind, placebo controlled study. *J Neurol Neurosurg Psychiatry* 1995; **58:** 681–87.
73 Verhagen-Metman L, Del Dotto P, van den Munckhof P, Fang J, Mouradian MM, Chase TN. Amantadine as treatment for dyskinesias and motor fluctuations in Parkinson's disease. *Neurology* 1998; **50:** 1323–26.
74 Verhagen-Metman L, Del Dotto P, LePoole K, Konitsiotis S, Fang J, Chase TN. Amantadine for levodopa-induced dyskinesias: a 1-year follow-up study. *Arch Neurol* 1999; **56:** 1383–86.
75 Snow BJ, MacDonald L, Mcauley D, Wallis W. The effect of amantadine on levodopa-induced dyskinesias in Parkinson's disease: a double-blind, placebo-controlled study. *Clin Neuropharmacol* 2000; **23:** 82–85.
76 Luginger E, Wenning GK, Bosch S, Poewe W. Beneficial effects of amantadine on levodopa-induced dyskinesia in Parkinson's disease. *Mov Disorders* 2000; **15:** 873–78.
77 Shannon KM, Penn RD, Kroin JS, et al. Stereotactic pallidotomy for the treatment of Parkinson's disease: efficacy and adverse effects at 6-months in 26 patients. *Neurology* 1998; **50:** 434–38.
78 Colzi A, Turner K, Lees AJ. Continuous subcutaneous waking day apomorphine in the long term treatment of levodopa induced interdose dyskinesia in Parkinson's disease. *J Neurol Neurosug Psychiatry* 1998; **64:** 573–76.
79 Olanow CW, Schapira AHV, Rascol O. Continuous dopamine-receptor stimulation in early Parkinson's disease. *Trends Neurosci* 2000; **23** (suppl)**:** S117–26.
80 Rinne UK, Bracco F, Chouza C, et al. Early treatment of Parkinson's disease with cabergoline delays the onset of motor complications. *Drugs* 1998; **55** (suppl 1)**:** 23–30.
81 Hely MA, Morris JGL, Reid WGJ. The Sydney multicentre study of Parkinson's disease: a randomized, prospective five year study comparing low dose bromocriptine with low dose levodopa-carbidopa. *J Neurol Neurosurg Psychiatry* 1994; **57:** 903–10.
82 Montastruc JL, Rascol O, Senard JM, Rascol A. A randomised controlled study comparing bromocriptine to which levodopa was later added, with levodopa alone in previously untreated patients with Parkinson's disease: a five year follow-up. *J Neurol Neurosurg Psychiatry* 1994; **57:** 1034–38.
83 Przuntek H, Welzel D, Gerlach M, et al. Early institution of bromocriptine in Parkinson's disease inhibits the emergence of levodopa-associated motor side effects: long-term results of the PRADO study. *J Neural Transm* 1996; **103:** 699–715.
84 Gimenez-Roldan S, Tolosa E, Burguera JA, Chacon J, Liano H, Forcadell F. Early combination of bromocriptine and levodopa in Parkinson's disease: a prospective randomized study of two parallel groups over a total follow-up period of 44 months including an initial 8-month double-blind stage. *Clin Neuropharmacol* 1997; **20:** 67–76.
85 Korczyn AD, Brunt ER, Larsen JP, Nagy Z, Poewe WH, Ruggieri S. A 3-year randomized trial of ropinirole and bromocriptine in early Parkinson's disease. *Neurology* 1999; **53:** 364–70.
86 Dupont E, Anderson A, Boqs J, et al. Sustained-release Madopar HBS compared with standard Madopar in the long-term treatment of de novo parkinsonian patients. *Acta Neurol Scand* 1996; **93:** 14–20.
87 Block G, Liss C, Scott R, Irr J, Nibbelink D. Comparison of immediate-release and controlled release carbidopa/levodopa in Parkinson's disease: a multicenter 5-year study. *Eur Neurol* 1997; **37:** 23–27.
88 Mayeux R, Denaro J, Hemenegildo N, et al. A population-based investigation of Parkinson's disease with and without dementia: relationship to age and gender. *Arch Neurol* 1992; **49:** 492–97.
89 McKeith IG, Galasko D, Kosaka K, et al. Consensus guidelines for the clinical and pathological diagnosis of dementia with Lewy bodies (DLB): report of the consortium on DLB international workshop. *Neurology* 1996; **47:** 1113–24.
90 McKeith I, Del Ser T, Spano P, et al. Efficacy of rivastigmine in dementia with Lewy bodies: a randomised, double-blind, placebo-controlled international study. *Lancet* 2000; **356:** 2031–36.
91 Factor SA, Molho ES, Podskalny GD, Brown D. Parkinson's disease: drug-induced psychiatric states. *Adv Neurol* 1995; **65:** 115–38.
92 Parkinson Study Group. Low-dose clozapine for the treatment of drug-induced psychosis in Parkinson's disease. *N Engl J Med* 1999; **340:** 757–63.
93 French Clozapine Parkinson Study Group. Clozapine in drug-induced psychosis in Parkinson's disease. *Lancet* 1999; **353:** 2041–42.
94 Goetz CG, Blasucci LM, Leurgans S, Pappert EJ. Olanzapine and clozapine: comparative effects on motor function in hallucinating PD patients. *Neurology* 2000; **55:** 789–94.
95 Honigfeld G, Arellano F, Sethi J, Bianchini A, Schein J. Reducing clozapine-related morbidity and mortality: 5 years of experience with the Clozaril National Registry. *J Clin Psychiatry* 1998; **59:** 3–7.
96 Matheson AJ, Lamb HM. Quetiapine: a review of its clinical potential in the management of psychotis symptoms in Parkinson's disease. *CNS Drugs* 2000; **14:** 157–72.
97 Oertel WH, Höglinger GU, Ceracheni T, et al. Depression in Parkinson's disease: an update. *Adv Neurol* 2001; **86:** 373–83.
98 Andersen J, Aabro E, Gulmann N, Hjelmsted A, Pedersen HE. Antidepressive treatment in Parkinson's disease: a controlled trial of the effect of nortriptyline in patients with Parkinson's disease treated with L-Dopa. *Acta Neurol Scand* 1980; **62:** 210–19.
99 Steur EN, Ballering LA. Moclobemide and selegeline in the treatment of depression in Parkinson's disease. *J Neurol Neurosurg Psychiatry* 1997; **63:** 547.
100 Senard JM, Rai S, Lapeyre-Mestre M, et al. Prevalence of orthostatic hypotension in Parkinson's disease. *J Neurol Neurosurg Psychiatry* 1997; **63:** 584–89.
101 Jankovic J, Gilden JL, Hiner BC, et al. Neurogenic orthostatic hypotension: a double-blind, placebo controlled study with midodrine. *Am J Med* 1993; **95:** 38–48.
102 Low PA, Gilden JL, Freeman R, Sheng KN, McElligott MA. Efficacy of midodrine vs placebo in neurogenic orthostatic hypotension: a randomized, placebo-controlled multicenter study. *JAMA* 1997; **277:** 1046–51.
103 Lubke KO. A controlled study with Dihydergot on patients with orthostatic dysregulation. *Cardiology* 1976; **61:** 333–41.

For personal use. Only reproduce with permission from The Lancet Publishing Group.