Updated guidelines for the management of Parkinson's disease

The Parkinson's Disease Consensus Working Group
Kailash Bhatia, David J Brooks, David J Burn, Carl E Clarke, Donald G Grosset, Douglas G MacMahon, Jeremy Playfer, Anthony HV Schapira, David Stewart, Adrian C Williams

New data on diagnosis, drug therapy, surgery and psychosocial concerns have emerged since the publication of the 1998 Guidelines for the Management of Parkinson's Disease. This article reviews new data and addresses issues left unanswered in the previous guidelines.

The Parkinson's Disease Consensus Working Group: **Dr Kailash Bhatia** is Consultant in the University Department of Clinical Neurology, Institute of Neurology, London, **Professor David J Brooks** (Chairman) is Harnett Professor of Neurology, Imperial College School of Medicine, Hammersmith Hospital, London W12 0NN, **Dr David J Burn** is Consultant in the Department of Neurology at the Regional Neurosciences Centre, Newcastle General Hospital, Newcastle Upon Tyne, **Dr Carl E Clarke** is Reader in Clinical Neurology in the Department of Neurology, City Hospital NHS Trust and University of Birmingham, Birmingham, **Dr Donald G Grosset** is Consultant Neurologist at the Institute of Neurological Sciences, Glasgow,

Continued on next page

The Parkinson's Disease Consensus Working Group first presented their views on the management of Parkinson's disease (PD) in June 1998 (Bhatia et al, 1998). Since then, there have been a number of initiatives to provide health-care professionals in the UK with guidance on the management of PD (Muller et al, 1997; Olanow and Koller, 1998; Albanese et al, 1999; Thomas et al, 1999).

Our UK-specific paper discussed issues pertinent to the state of knowledge at that time, based on published evidence and the clinical expertise of the working group (Bhatia et al, 1998). In the intervening 2 years, there have been numerous publications in the worldwide literature pertaining to PD and, in the light of these new data and extended experience of the working group, it is now timely to provide an update for UK-based health-care professionals. The publication of a brief guide to assist primary care teams in dealing with PD (Parkinson's Disease Society, 1999) is one example of a recent initiative that has been well received by the general practice community in the UK.

This short guide, which is based on a four-stage paradigm for the clinical management of PD — diagnosis, maintenance, complex management and palliative care (MacMahon and Thomas, 1998), provides clear, practical advice on developing a team-based approach to PD. However, the aim of the present article is to provide more comprehensive guidelines for patient care. Unless otherwise indicated below, we continue to endorse the views and suggestions presented in the 1998 guidelines publication (Bhatia et al, 1998). Like the previous guidelines, these, on the whole, reflect the personal views of the consensus working group on the management of PD following a systematic review of the 1998 guidelines and the new data.

METHOD

During the preparatory phase of the 1998 guidelines, there was a lack of published evidence on certain aspects of PD management and this is still true for the present version. Thus, it has been necessary for the working group to continue to agree on a 'best practice' framework for the care of patients with PD. The difficulties of implementing consensus recommendations are not underestimated, and it remains our view that it must be carried out at a local level, according to needs and priorities (see later discussion).

As a first step in reviewing new information on PD, a systematic search of the worldwide literature from 1998 to date was performed on the Medline, Embase, Cinahl and Cochrane Library databases. To ensure comprehensive literature retrieval, search strategies were constructed in accordance with accepted practice using keywords or thesaurus terms to cover diagnosis, drug treatments, surgical treatments, neuroprotection and patient-focused care strategies. The output from the literature search was distributed to selected members of the working group, who reviewed the material provided.

The second step involved convening the working group with the purpose of discussing the relative importance of the published evidence. It should be noted that the working group's discussion of the evidence was based on personal professional judgment and expertise gained from the everyday management of patients with PD. These discussions were not, therefore, derived from an analysis or systematic review of the retrieved documents.

At the meeting, the working group highlighted evidence and experience that had influenced their practice and that, by consensus agreement, should be incorporated in the updated recommendations. From these recommendations, a draft manuscript was prepared and discussed at a second working group meeting approximately 1 month later. The purpose of the second meeting was to agree and finalize the wording of the management guidelines that form the core of this paper.

THE DIAGNOSIS OF PD

PD remains a clinical diagnosis. The disease is characterized by bradykinesia with tremor and/or rigidity, gait abnormality and balance impairment. In the UK, the PD Society Brain Bank criteria are used for diagnosis (Meara et al, 1999), but PD is an area that could benefit from the development of further robust diagnostic criteria. The diagnosis should be reconsidered if atypical features develop and/or the response to treatment is less than optimal, although some proven Lewy body cases never respond well to L-dopa. Acute L-dopa and apomorphine challenge tests are of limited value (Clarke and Davies, 2000) in most cases and there continues to be a theoretical risk of priming dyskinesias with the L-dopa challenge (Bédard et al, 1997). Additionally, L-dopa and apomorphine challenges have the lowest sensitivity in de novo patients (Clarke and Davies, 2000).

Imaging techniques (positron emission tomography (PET) and single photon emission computed tomography (SPECT)) have greatly enhanced the understanding of the disease, but their routine use for the diagnosis of PD is not recommended. Certain imaging techniques (e.g. (3-fluoropropyl)-2beta-carboxymethoxy-3beta-(4-iodophenyl)tropane SPECT) can be helpful when there is uncertainty between the diagnosis of parkinsonian syndromes and non-parkinsonism (particularly essential tremor) (Benamer et al, 2000).

Three key papers that considered the diagnostic accuracy of PD were identified:

1. Using data from the Deprenyl and Tocopherol Antioxidative Therapy for Parkinson's Disease (DATATOP) study in the USA, the evolution of the clinical diagnosis in 800 patients with early PD was prospectively followed up for 6 years by experts in PD (Jankovic et al, 2000). Reassessment criteria included: investigator's confidence in the diagnosis of PD, presence of atypical clinical features, findings of imaging studies, response to L-dopa, and results of post-mortem examinations. Of the 800 patients enrolled, 8.1% did not have PD on reassessment, according to the study criteria
2. Gelb and colleagues in the USA proposed a clinical diagnostic classification based on a comprehensive review of the literature regarding the sensitivity and specificity of the cardinal motor signs of PD (bradykinesia, rigidity, tremor and postural instability) (Gelb et al, 1999). They proposed three levels of diagnostic confidence: definite, probable and possible. Possible and probable PD was classified according to clinical criteria alone, whereas postmortem neuropathological confirmation was required for the diagnosis of definite PD
3. Another study assessed the accuracy of diagnosing parkinsonism and PD in the UK in a community-based group of subjects receiving antiparkinsonian medication (Meara et al, 1999). Using recommended diagnostic criteria, parkinsonism was confirmed in 74% of 402 cases, whereas only 53% of these patients were felt to have clinically 'probable' PD. Misdiagnoses included essential tremor, Alzheimer's disease and vascular pseudo-parkinsonism. The investigators recommended early referral of those suspected of having parkinsonism for specialist assessment.

Dr Douglas G MacMahon is Consultant at the Cornwall Healthcare NHS Trust and Senior Lecturer at the University of Plymouth, **Dr Jeremy Playfer** is Consultant Physician at the Royal Liverpool University Hospital, Liverpool, **Professor Anthony HV Schapira** is Professor of Clinical Neurosciences in the University Department of Clinical Neurosciences, Royal Free and University College Medical School, UCL, London, **Dr David Stewart** is Consultant at the Victoria Infirmary, Glasgow, **Professor Adrian C Williams** is Consultant in the Department of Neurosciences, Queen Elizabeth Hospital, Birmingham

Correspondence to: Professor DJ Brooks

KEY POINTS

Diagnosis of Parkinson's disease

- The cardinal features of Parkinson's disease with the most diagnostic use include resting tremor, bradykinesia, rigidity and an asymmetric onset. A response to L-dopa is not universal.
- Patients with suspected Parkinson's disease should be referred to a specialist in movement disorders for assessment.
- If atypical features develop and/or response to treatment is less than optimal, the diagnosis should be reconsidered. Acute L-dopa and apomorphine challenge tests are not recommended for routine use in the diagnosis of Parkinson's disease.
- Imaging is not recommended for routine use in the diagnosis of Parkinson's disease. However, a specific form of single photon emission computed tomography can be helpful if there is doubt between the diagnosis of parkinsonian syndromes and non-parkinsonism, particularly essential tremor.
- The diagnosis of Parkinson's disease requires regular review to ensure its accuracy. Specialists should review the diagnosis of Parkinson's disease as part of an overall review of their Parkinson's disease patient-management plans.

TREATMENT OF PD

L-dopa

As noted previously (Bhatia et al, 1998), L-dopa in combination with a peripheral decarboxylase inhibitor is an effective symptomatic treatment for PD.

However, physicians should use L-dopa cautiously because of its association with disabling motor fluctuations and dyskinesias in longer-term treatment, especially at higher doses. These are not avoided even if de novo patients are treated with controlled-release preparations. There remains a theoretical risk of a pro-oxidant effect with L-dopa, as there may be enhanced free radical formation in PD patients (Martignoni et al, 1999), but convincing evidence in vivo is lacking.

The complications of L-dopa therapy can be avoided or at least delayed by achieving symptomatic relief with other drugs, such as dopamine agonists, amantadine and anticholinergics.

Dopamine agonists

Dopamine agonists are an appropriate option for many new-onset PD patients. They provide effective symptomatic relief, using L-dopa supplementation when required, while diminishing the frequency of complications over a 2–5-year period (Rinne et al, 1998a; Parkinson Study Group, 2000; Rascol et al, 2000). Chronological age alone is not a barrier to the use of dopamine agonists (Shulman et al, 2000); however, pathological markers of biological age such as cognitive impairment or hallucinations, as well as comorbidity that includes depression, cardiovascular and neuropsychiatric disorders, are relative contraindications. When the treatment decision between L-dopa and dopamine agonist treatment is made, it is important that all factors, including lifestyle and occupation, are considered and that all affected individuals are consulted, including patient, carer and health-care professional. A number of important clinical trials with ropinirole, pramipexole and cabergoline have now been published (*Table 1*).

Neuroprotection: Recent in-vitro data have provided evidence to suggest that dopamine agonists may have a neuroprotective effect, delaying the need for L-dopa. However, the issue of neuroprotection with the drugs currently in use for PD still requires clarification. A characteristic of PD development in the early stages is increased oxidative stress, so it would be ideal if PD pharmacotherapies contained neuroprotective substances. Preclinical work has shown that dopamine agonists, monoamine oxidase B inhibitors and N-methyl-D-aspartate receptor agonists all have a neuroprotective effect on dopamine cell cultures (Riederer et al, 2000).

Cost-effectiveness: The avoidance of dyskinesia and the increased cost of treatment that follows its onset may support a cost-efficacy argument for dopamine agonists (Dodel et al, 1998). There is evidence from a US study that the higher cost of pramipexole was offset by being more effective than baseline therapy in patients with early and advanced PD (Hoerger et al, 1998). Larger studies with prospective health economics analyses are required to confirm these data.

TABLE 1.
Dopamine agonists as monotherapy in early Parkinson's disease

Drug	Reference	Description	Main outcomes
Ropinirole	Rascol et al (2000)	Five-year, prospective, randomized, double-blind study comparing the safety and efficacy of ropinirole and L-dopa in 268 patients with early PD. Open-label L-dopa was supplemented if symptoms were inadequately controlled by the study medication	Hazard ratio for remaining free of dyskinesia was 2.82 (95% CI = 1.78–4.44) (regardless of L-dopa supplementation), a significant difference (P<0.001) in favour of ropinirole. Cumulative incidence of dyskinesia at 5 years was lower with ropinirole than L-dopa (36/177 *vs* 40/88 patients), irrespective of whether patients received L-dopa supplements. No difference between groups in the change in ADL
	Korczyn et al (1999)	Three-year, prospective, double-blind, parallel-group comparison of ropinirole and bromocriptine in 335 patients with early PD	Ropinirole-treated patients had a mean improvement in UPDRS motor score of 31% compared with 22% in the bromocriptine group (P=0.086) and a significantly better UPDRS ADL score (treatment difference 1.46 points, P=0.029)
Pramipexole	Parkinson Study Group (2000)	Randomized, multicentre, double-blind, controlled trial to compare initial treatment of pramipexole with that of L-dopa in 301 patients with early PD	Initial pramipexole treatment resulted in significantly less development of wearing off, dyskinesias, or on-off motor fluctuations (28%) compared with L-dopa (51%) (HR = 0.45; 95% CI = 0.30–0.66; P<0.001)
Cabergoline	Rinne et al (1998a)	A multicentre, randomized, double-blind, 3–5-year trial to assess cabergoline alone or in combination with L-dopa in 412 patients with early PD	Both treatments improved motor disability. The development of motor complications was significantly less frequent in the cabergoline group than in L-dopa recipients (22% *vs* 34%; P<0.02). Relative risk of developing motor complications was more than 50% lower with cabergoline than with L-dopa

ADL = activities of daily living; CI = confidence interval; HR = hazard ratio; PD = Parkinson's disease; UPDRS = Unified Parkinson Disease Rating Scale

Dopamine agonists as adjunct therapy: There have been no important developments in the use of dopamine agonists as adjunct therapy to L-dopa since the previous guidelines. The following studies have been published in the past 2 years: ropinirole (Lieberman et al, 1998), pramipexole (Wermuth, 1998; Kunig et al, 1999; Pinter et al, 1999) and cabergoline (Ulm and Schuler, 1999). All of these studies have been the subject of Cochrane reviews, which are now available in the Cochrane Library.

Safety issues: Somnolence is a side effect of all dopaminergic therapy, including L-dopa, and is an underinvestigated area (Pirker and Happe, 2000). Somnolence and sleep episodes have been observed in patients taking high doses of dopamine agonists or with lower doses in combination with other dopaminergic agents or potentially sedating drugs, particularly during the titration phase. It is thought there may be a different threshold for the antiparkinsonian effects of dopamine agonists and sedation caused by dopamine agonist administration (Olanow et al, 2000), possibly because of differences in affinity for dopamine receptor subtypes (Pirker and Happe, 2000). Large, well-controlled epidemiological studies are required to identify the risk factors for sleep episodes in PD patients (Ferreira et al, 2000). Sleep disturbances in PD are common and are often overlooked during routine assessment. Patients at risk of sleep disturbances and drug-induced sleep episodes may be identified by taking a careful history, which may be supplemented with a sleep questionnaire (e.g. Epworth scale) (Schapira, 2000).

A study of eight male PD patients without prior history of sleep disturbances reported the development of sudden, overwhelming sleepiness while driving in patients who were taking pramipexole or ropinirole. This sleepiness resulted in the patients falling asleep while driving and having automobile accidents (Frucht et al, 1999). Physicians should therefore ensure that all patients beginning treatment with these drugs are warned about this possible side effect, and should specifically ask them whether they drive. The working group supports the Driver and Vehicle Licensing Agency recommendations on driving while suffering from PD (DVLA, 2000). Individuals with PD must inform the DVLA of their condition and are required to complete a medical questionnaire, which requests patient permission for the DVLA to contact the patient's doctor and specialists for medical reports. Patients should only drive if they satisfy the requirements of this agency. The DVLA states that all patients should also inform their car insurance company that they have PD.

Catechol-O-methyltransferase inhibitors

Catechol-O-methyltransferase (COMT) inhibitors are an effective option for PD and are an adjunct to L-dopa therapy. Safety is still a concern with tolcapone therapy because of reports of hepatotoxicity and its licence remains suspended in Europe (Olanow, 2000). Entacapone therapy has not been associated with hepatotoxicity and monitoring is not required.

Two 6-month studies (Nordic Multicenter Entacapone COMT Trials; NOMECOMT, and Safety and Efficacy of Entacapone Study Assessing Wearing-Off; SEESAW) have indicated the potential beneficial effects of entacapone (*Table 2*). A study comparing tolcapone with bromocriptine supplementing L-dopa reported no significant differences in on-off time and motor disability but found that tolcapone was easier to titrate and caused fewer hallucinations and less nausea than bromocriptine (Tolcapone Study Group, 1999).

Other treatments

Selegiline: Selegiline monotherapy provides limited symptomatic benefit in the treatment of PD. However, selegiline should not be used in

TABLE 2.
Entacapone in Parkinson's disease

Reference	Description	Main outcomes
Rinne et al (1998b)	171 parkinsonian patients with wearing-off-type motor fluctuations participated in a 6-month, randomized, placebo-controlled, double-blind, parallel-group study	Patients' home diaries indicated that entacapone increased the mean 'on' time significantly (9.3 ± 2.2 to 10.7 ± 2.2 h; $P<0.01$) and correspondingly decreased the 'off' time. The daily L-dopa dose was reduced significantly in the entacapone group ($P<0.01$), the difference between groups being 102 mg
Parkinson Study Group (1997)	205 parkinsonian patients with motor fluctuations participated in a 6-month, randomized, placebo-controlled, double-blind, parallel group multicentre trial	Patients' home diaries completed at 30-minute intervals showed that entacapone increased average baseline 'on' time (60.5%) by 5 percentage points, with a greater effect in patients with a smaller per cent baseline 'on' time (<55%)

patients with orthostatic hypotension because of the risk of confusion and falls. There is no definite evidence of a neuroprotective effect with selegiline. The original DATATOP study (Parkinson Study Group, 1989) demonstrated that selegiline was L-dopa sparing in de novo cases. This, however, may well have been confounded by the mild symptomatic effect of this agent. In support of this viewpoint, the extension study showed a similar level of complications after 4 years in early and late users of selegiline (Parkinson Study Group, 1996).

A second double-blind, placebo-controlled study of selegiline in de novo PD patients has also shown that selegiline significantly delayed the need for L-dopa therapy (P=0.028; Palhagen et al, 1998). In a randomized, prospective, placebo-controlled, double-blind, multicentre trial (selegiline plus L-dopa; SELEDO), selegiline and placebo were added to existing L-dopa therapy in 116 patients with early PD (Przuntek et al, 1999). The median time to reach the primary end point (time at which a ≥50% increase in L-dopa dose was necessary) was 4.9 years in the selegiline group and 2.6 years in the placebo group (log-rank test, P=0.027), again demonstrating that selegiline is L-dopa sparing.

The UK Parkinson's Disease Research Group found excess mortality in patients treated with combined L-dopa and selegiline that was not explained by revised diagnosis, autonomic or cardiovascular events, or drug interactions (Ben-Shlomo et al, 1998). The study was an open, randomized trial that reclassified the cause of death of PD patients. These results were supported by an analysis of medical records of 12 621 patients from the UK General Practice Research Database (Thorogood et al, 1998). Data from patients who had received a prescription for an antiparkinsonian drug were assessed and a non-significant 11% increase (95% confidence interval = 0–23%) in the risk of death associated with taking selegiline either alone or in combination with L-dopa was found. It has been suggested that the excess deaths may be a result of orthostatic hypotension (Churchyard et al, 1999). The working group, therefore, advise caution, especially when postural hypotension is evident.

In contrast, a meta-analysis of five long-term, prospective, randomized trials of selegiline in patients with untreated PD found no increase in mortality associated with selegiline treatment whether or not patients also received L-dopa (Olanow et al, 1998). However, this analysis did not include the UK Parkinson's Disease Research Group trial (Ben-Shlomo et al, 1998). Further work is needed to clarify the role of selegiline in view of the recent availability of a buccally absorbed formulation of the drug, the dose reduction to 1.25 mg, and the effect that these may have on its metabolism. A large pragmatic trial to this effect has recently started in the UK (PD med).

Amantadine: Amantadine may have a role as an antidyskinetic agent in advanced PD. Most studies with amantadine have been small-scale trials and have provided inadequate evidence of the drug's use in PD.

In a recent, 1-year, double-blind, placebo-controlled, crossover study, amantadine was found to have an antidyskinetic effect against L-dopa-induced motor complications in 17 patients with PD (Metman et al, 1999). The beneficial effects of amantadine on motor response complications were maintained for at least 1 year after initiation of treatment.

Anticholinergics: Recent data have provided strong evidence that anticholinergic therapy exacerbates psychiatric problems in patients with PD, and this is not restricted to elderly patients (Mason and Sagar, 1997; Sarter and Bruno, 1998; Hindle, 1999). For this reason, anticholinergic therapy should rarely be used. Drug treatment guidelines for the long-term management of PD provide information to help health-care professionals make treatment decisions. A recent set of German guidelines has suggested that young patients should be treated with selegiline and/or a dopamine agonist, and that in the tremor dominance type, budipine or a dopamine agonist should be used (Reichmann et al, 2000). Budipine, however, is not available in the UK.

KEY POINTS
Role of drug treatment of Parkinson's disease

- Dopamine agonists are recommended as alternative first-line treatment options to L-dopa in appropriate patients.
- Entacapone is a useful adjunct in L-dopa-treated patients experiencing fluctuating treatment responses. Early therapy with entacapone can reduce the frequency of dosage of L-dopa and lead to smoother plasma levels.
- For those Parkinson's disease patients taking L-dopa, the dose should be kept as low as possible.
- Few recent, good-quality studies are available to provide updated recommendations on other antiparkinsonian drugs such as selegiline, amantadine and apomorphine.
- There is no evidence of hepatotoxicity with entacapone.
- The effectiveness of antidepressants in patients with comorbid depression or of antipsychotics in patients with psychosis is underinvestigated.
- Dopamine agonists may have a neuroprotective activity although in-vivo evidence is required to confirm this.
- Selegiline should not be used in patients with orthostatic hypotension, confusion or at risk of falling.

SURGERY

There have been a large number of study reports on the surgical treatment of PD since the publication of the first guidelines in 1998 (Bhatia et al, 1998; *Tables 3–9*). A systematic literature review by the Therapeutics and Technology Assessment Committee of the American Academy of Neurology, leading to the development in 1999 of American guidelines (Hallett and Litvan, 1999), included papers published up to and including 1998 and resulted in recommendations similar to the 1998 guidelines. For ease of evaluation, the working group included this review, together with papers published in 1999 and up to June 2000, in the current guidelines. For analysis, the retrieved publications were subdivided into the four surgical procedures that had undergone the most rigorous investigation. These were thalamotomy, pallidotomy, subthalamic nucleus (STN) stimulation, and globus pallidus internus (GPi) stimulation.

Because of a sparsity of publications at that time, the merits of several surgical issues were left unresolved by the 1998 guidelines. These issues included the long-term effects of thalamotomy *vs* thalamic stimulation, the long-term outcome of pallidotomy, the safety of bilateral pallidal stimulation alone and in comparison with bilateral STN stimulation, the long-term outcome of bilateral STN stimulation and STN lesions, and the comparative worth of STN lesions and STN stimulation. A primary purpose of the new guidelines was to address these unresolved issues.

Thalamotomy

In a study evaluating the long-term outcome of unilateral thalamotomy in 44 patients treated between 1977 and 1996 (Moriyama et al, 1999; *Table 3*), the positive effects of thalamotomy, such as significant reduction in tremor and rigidity and reduced L-dopa requirements, were maintained for a mean of 8.8 years, confirming the reliability of the procedure over time. Although improvements in activity of daily living (ADL) were also reported, unilateral thalamotomy had limited effects on akinesia, and its progression eventually resulted in further deterioration in ADL. This procedure is therefore likely to be of greatest benefit to those patients whose disability is caused mainly by tremor and rigidity.

Limited data are available on bilateral thalamotomy. However, in the same study, 9 patients underwent bilateral thalamotomies at a mean interval of 56 months. Five of these patients benefited from the second thalamotomy, but a high incidence of bulbar complications was observed.

Thalamic stimulation

Thalamic stimulation has been shown to be effective and relatively safe in reducing parkinsonian tremor and associated disability (*Table 4*). Surgical complications appear to be infrequent and efficacy is not reduced after 1 year (Koller et al, 1997; Limousin et al, 1999b).

Thalamotomy *vs* thalamic stimulation

Both thalamotomy and thalamic stimulation are effective against tremor. A comparison of the two techniques (Schuurman et al, 2000; *Table 5*)

TABLE 3.
Unilateral thalamotomy

Reference	Description	Main outcomes
Moriyama et al (1999)	Evaluation of long-term outcome for 53 patients with idiopathic Parkinson's disease treated by stereotactic thalamotomy	Significant reduction of tremor and rigidity of the contralateral extremities persisted throughout the follow-up period (mean 8.8 years) in 44 patients who underwent unilateral thalamotomy

TABLE 4.
Thalamic stimulation

Reference	Description	Main outcomes
Limousin et al (1999b)	Multicentre study to evaluate the efficacy and morbidity of thalamic stimulation in 110 patients with PD	Thalamic stimulation was shown to be an effective and relatively safe treatment for disabling tremor
Koller et al (1997)	Multicentre trial of unilateral high-frequency stimulation of the ventral intermedius nucleus of the thalamus in 29 patients with essential tremor and 24 patients with PD using a blinded assessment at 3 months	A significant reduction in both essential and parkinsonian tremor occurred contralaterally with stimulation. Patients reported a significant reduction in disability. Measures of function were significantly improved in patients with essential tremor
Ondo et al (1998)	Efficacy and tolerability of unilateral thalamic deep brain stimulation for patients with medically refractory essential tremor and the tremor associated with PD	PD patients demonstrated an 82% reduction ($P<0.0001$) in contralateral tremor and significant improvement in disability and global impressions. There was, however, no meaningful improvement in other motor aspects of the disease

PD = Parkinson's disease

TABLE 5.
Thalamotomy vs thalamic stimulation

Reference	Description	Main outcomes
Schuurman et al (2000)	Sixty-eight patients (45 with Parkinson's disease, 13 with essential tremor, and 10 with multiple sclerosis) were randomly assigned to undergo thalamotomy or thalamic stimulation	Thalamic stimulation and thalamotomy are equally effective for the suppression of drug-resistant tremor, but thalamic stimulation has fewer adverse effects and results in a greater improvement in function

showed that although equally effective in tremor, thalamic stimulation gave better functional benefit and appeared to be safer than thalamotomy, being associated with fewer side effects and complications. This was at additional cost and the need for review and adjustment. Further studies are needed to evaluate this procedure in the longer term.

TABLE 6.
Unilateral pallidotomy

Reference	Description	Main outcomes
de Bie et al (1999b)	Evaluation of the effects of unilateral pallidotomy in patients with PD in 26 patients who also had disabling dyskinesias, painful and/or disabling dystonia, and/or pain	Stereotactic unilateral pallidotomy can improve symptoms and disability in the 'off' phase. In the 'on' phase, dyskinesias disappeared at the side contralateral to the procedure
de Bie et al (1999a)	Efficacy of unilateral pallidotomy in a randomized, single-blind, multicentre trial in 37 patients	Unilateral pallidotomy is an effective treatment in patients with advanced PD who have an unsatisfactory response to pharmacological treatment
Eskandar et al (2000)	Seventy-five patients underwent unilateral pallidotomy	Significant improvements in 'off'-period scores for the activities of daily living portion of the UPDRS, motor scores, total 'on' time, L-dopa-induced dyskinesias, and contralateral tremor
Favre et al (2000)	Patients' perspective on their results after undergoing unilateral or bilateral pallidotomy	According to visual analogue scale scores, unilateral pallidotomy significantly improved dyskinesias ($P<0.05$). The procedure also improved night sleep, muscle pain, freezing, overall 'on', overall 'off', and the duration of 'off' periods, but worsened the volume of the voice and articulation, increased drooling, and reduced concentration
Honey et al (1999)	Twenty-one patients suffering from PD were followed prospectively for 1 year after they had undergone a unilateral pallidotomy	Significant reduction in overall pain scores at 6 weeks ($P<0.001$) and 1 year ($P=0.001$) following pallidotomy
Jankovic et al (1999)	Unilateral posteroventral pallidotomy on L-dopa-induced dyskinesias in 42 patients followed for up to 9 months	The mean UPDRS scores for L-dopa-related disability and pain decreased from 1.95 to 0.74 ($P<0.0001$) and from 1.02 to 0.17 ($P<0.0001$) respectively
Junque et al (1999)	Fifteen consecutive patients with PD were assessed neuropsychologically before and after unilateral posteroventral pallidotomy	In the 3-month follow-up, learning, memory, and speed returned to the pre-surgical level, but verbal fluency remained below the baseline
Kimber et al (1999)	Seventeen patients were assessed post-surgically for mechanisms of improvement in bradykinesia	Improvements in bradykinesia are related to mechanisms other than pallidothalamocortical connectivity and may be the result of greater efficacy of external cues after withdrawal of the abnormal pallidal discharge
Limousin et al (1999a)	Effect of posteroventral pallidotomy on movement preparation and execution in 27 parkinsonian patients	Movement time measured during unwarned simple and choice reaction time tasks was improved for the contralesional hand. Movement times also improved for isometric and isotonic ballistic movements. Repetitive, distal, and fine movements were not improved
Martinez-Martin et al (2000)	Eleven patients with PD and motor complications refractory to medical therapy underwent unilateral pallidotomy	Pallidotomy significantly improved quality of life in patients with advanced PD
Pal et al (2000)	Fifteen patients (part of an original cohort of 24 patients) underwent posteroventral pallidotomy for motor fluctuations and disabling dyskinesias 3 years previously. Evaluation scales included UPDRS, Goetz dyskinesia scale, and Purdue pegboard test	When compared with baseline scores, the reduction in limb dyskinesias and off-state tremor scores persisted on the side contralateral to the pallidotomy at the end of 3 years. However, all other early benefits disappear and ADL continues to worsen as the disease progresses
Samii et al (1999)	Results of a 2-year post-pallidotomy follow-up study in 20 patients	Improvements in dyskinesia and tremor on the side contralateral to pallidotomy are preserved, while the initial improvements in most other deficits disappear
Samuel et al (1998)	Assessment of the effects of unilateral ventral medial pallidotomy in 26 patients with medically intractable PD and marked drug-induced dyskinesias. Patients were assessed preoperatively and at 3 months and 1 year postoperatively	Contralateral dyskinesias were most significantly reduced postoperatively (67%, $P=0.0001$); however, ipsilateral and axial dyskinesias also improved. Median 'off'-motor UPDRS score and contralateral rigidity also improved significantly and there were improvements in contralateral tremor and bradykinesia scores. Responses were generally maintained up to 1 year
Schmand et al (2000)	Assessment of neuropsychological functioning in 19 patients with advanced PD after randomization to unilateral pallidotomy	No significant differences over time were found between pallidotomy and control groups, with the exception of a decrease of verbal fluency in the left-sided pallidotomy group
Schrag et al (1999)	Twenty-two patients with advanced PD followed-up more than 1 year after unilateral pallidotomy	The reduction of contralateral dyskinesias (median 67%) at 3 months was slightly attenuated after 1 year to 55% (both $P<0.001$ compared with baseline)
Yokoyama et al (1999)	Pre- and postoperative cognitive function was evaluated in 25 patients with PD who underwent unilateral posteroventral pallidotomy	Cognitive dysfunction in patients with PD relates to advancement of Hoehn and Yahr stage, but unilateral pallidotomy is not associated with significant long-lasting cognitive deficits

ADL = activities of daily living; PD = Parkinson's disease; UPDRS = Unified Parkinson Disease Rating Scale

Pallidotomy

Pallidotomy has so far been the most widely reported surgical procedure for the treatment of advanced PD (*Table 6*). As mentioned in the 1998 guidelines, the main effect of pallidotomy is to improve contralateral dyskinesias (Lang et al, 1997). Some improvement in other parkinsonian features also occurs. One study reported improvements in movement times for isometric and isotonic ballistic movements, although motor initiation was unaffected (Limousin et al, 1999a).

Motor execution tasks in 'off' periods were improved, but motor preparation tasks and distal, fine and repetitive movements were no better than pre-surgical levels (Jankovic et al, 1999; Kimber et al, 1999; Limousin et al, 1999a). Few studies have addressed the neuropsychological aspect of unilateral pallidotomy and, although decreased verbal fluency was found with left pallidotomy in one study (Schmand et al, 2000), the suggestion is that this procedure is not associated with significant long-lasting cognitive defects (Yokoyama et al, 1999). Additional long-term studies are required.

Data on the long-term outcome of pallidotomy are limited. A 1-year follow-up study (Schrag et al, 1999) in 22 patients with advanced PD reported that post-surgical reductions in contralateral dyskinesias were most responsive to this procedure and that this benefit was maintained over the 12 months of study. However, pallidotomy had a less pronounced effect on ipsilateral and axial dyskinesias. Both the Unified Parkinson Disease Rating Scale (UPDRS) and ADL scores showed modest improvement compared with baseline and this was also maintained throughout the year. These results confirm similar data from an earlier study (Samuel et al, 1998).

Two-year follow-up data from 20 patients who had undergone pallidotomy (Samii et al, 1999) showed similar results. Reductions in contralateral dyskinesias and 'off'-state tremor were maintained over the 2-year period, but ipsilateral dyskinesia, axial dyskinesia, 'off'- or 'on'-state Perdue Pegboard Test, 'off'-state ADL, and 'off'-state gait and postural stability remained at baseline levels, while 'on'-state ADL scores worsened by 75%. Improvements in contralateral dyskinesia and tremor scores were maintained in 15 patients whose progress was followed for a further year (Pal et al, 2000).

Another study (Baron et al, 2000) assessed the outcome of unilateral pallidotomy in 10 patients with advanced PD after 4 years of follow-up. Improvements in contralateral tremor, akinesia, and drug-induced dyskinesias were sustained in most patients over this time period, although the UPDRS motor examination scores returned to baseline levels within 3 or 4 years. Despite disease progression, most patients undergoing this procedure continued to report quality of life (QoL) scores above preoperative levels.

There is little new information regarding bilateral pallidotomy and this omission is probably because of the risks associated with this procedure. A recent study (Favre et al, 2000) indicates that simultaneous bilateral pallidotomy can reduce all the key symptoms of Parkinson's disease (i.e. akinesia, tremor, and rigidity) and the side effects of L-dopa treatment (i.e. dyskinesias) and is more effective than unilateral pallidotomy with regard to tremor, rigidity, and dyskinesias. However, in addition to previously described motor and visual field deficits, bilateral simultaneous pallidotomy may be followed by emotional, behavioural and cognitive deficits, such as depression, obsessive-compulsive disorders and loss of psychic autoactivation-abulia, as well as disabling corticobulbar dysfunction and apraxia of eyelid opening. These side effects make this type of surgery undesirable, even though significant improvement in motor deficits can be achieved (Ghika et al, 1999).

Deep brain stimulation of GPi

There is little new information on deep brain stimulation of the GPi. However, the study of Vingerhoets and colleagues (1999; *Table 7*) confirmed that pallidal stimulation does give relief of the motor symptoms of PD. In this study, where neuropsychological assessment had been performed, older patients and those needing high preoperative levels of L-dopa were found to be more vulnerable to cognitive decline than other patients who showed no change in this parameter.

TABLE 7.
Unilateral globus pallidus internus stimulation

Reference	Description	Main outcomes
Baron et al (2000)	Non-blinded Core Assessment Program for Intracerebral Transplantations protocol assessments in 10 of 15 patients for 4 years following surgery	Four years after unilateral pallidotomy, most patients continue to experience a quality of life above preoperative levels
Vingerhoets et al (1999)	Twenty non-demented patients with PD were neuropsychologically assessed 2 months before and 3 months after unilateral pallidal stimulation	Left or right pallidal stimulation for the relief of motor symptoms in PD seems relatively safe, although older patients and patients needing high preoperative doses of L-dopa seem to be more vulnerable to cognitive decline

PD = Parkinson's disease

TABLE 8.
Bilateral globus pallidus internus *vs* subthalamic nucleus stimulation

Reference	Description	Main outcomes
Burchiel et al (1999)	A randomized, blinded comparison of GPi and STN stimulation in advanced PD	Pallidal and STN stimulation appear to be safe and efficacious for the management of advanced PD
Hammerstad et al (2000)	Follow-up of Burchiel et al (1999). 30-month follow-up of 6 PD patients	UPDRS motor scores

GPi = globus pallidus internus; PD = Parkinson's disease; STN = subthalamic nucleus; UPDRS = Unified Parkinson Disease Rating Scale

TABLE 9.
Unilateral subthalamic nucleus stimulation

Reference	Description	Main outcomes
Limousin et al (1997)	Investigation in 12 parkinsonian patients of the difference between the effect of STN and GPi stimulation on movement-related activity. Unilateral stimulation of the contralateral STN (6 patients) or GPi (6 patients) was performed	Demonstrated the importance of STN input in the control of non-primary motor areas

GPi = globus pallidus internus; STN = subthalamic nucleus

KEY POINTS

Recommendations for surgical treatment of Parkinson's disease

- Additional randomized controlled trials are necessary.
- Unilateral thalamotomy can be considered for asymmetric, medically intractable tremor. Bilateral thalamotomy is not appropriate because of significant associated bulbar side effects.
- Unilateral thalamic stimulation is as effective as thalamotomy for reducing tremor, but produces increased functional benefit. Bilateral thalamic stimulation is effective for bilateral tremor and has less risk of producing the side effects observed with bilateral thalamotomy.
- Unilateral pallidotomy often provides dramatic relief of dyskinesia, but this effect is predominantly unilateral. Long-term follow up (up to 4 years) has shown that the antidyskinesic effects persist, but that other features of Parkinson's disease, such as bradykinesia and rigidity, return owing to the progression of the condition.
- There are no new data on bilateral pallidotomy, and this may be because of the significant side effects associated with this procedure.
- Bilateral subthalamic nucleus (STN) stimulation has proved to be highly effective in relieving most features of Parkinson's disease, including 'off'-period dystonia. However, studies reporting a large number of cases have yet to appear in the literature. Bilateral STN stimulation may be the procedure of choice for non-demented patients who initially respond well to L-dopa but, on average 10–12 years after the onset of Parkinson's disease, are fluctuating with dyskinesias and are under consideration for apomorphine or have tried it unsuccessfully in practice despite good responses to test doses.
- Bilateral globus pallidus internus stimulation can also be effective, but appears to be marginally less effective than STN stimulation in reversing parkinsonism.

Unilateral and bilateral STN stimulation

As described in the 1998 guidelines (Bhatia et al, 1998), STN stimulation may produce the best long-term improvements in patients with advanced PD. Studies have indicated that unilateral STN stimulation results in contralateral improvements in all aspects of 'off'-period parkinsonism, including tremor, but data are limited by the small number of patients participating (Kumar et al, 1998, 1999).

Kumar and colleagues (1999) also assessed bilateral STN stimulation and found this procedure to be particularly effective in patients with significant bilateral disability. Bilateral STN may also mildly improve 'on'-period motor function (Kumar et al, 1998) and benefit 'off'-period dystonia (Krack et al, 1999).

Dyskinesias have also been shown to improve with bilateral STN stimulation, but this is probably related to the decrease in L-dopa requirements in these patients, rather than to the effects of surgery (Benabid et al, 2000).

Deep brain stimulation of GPi *vs* STN stimulation

There are few comparative data on these surgical techniques in patients with advanced PD (*Tables 8* and *9*). One study (Burchiel et al, 1999) involved 10 patients with idiopathic PD, L-dopa-induced dyskinesias and response fluctuations, who were randomized to the implantation of GPi or STN stimulators. Results indicate that both procedures are effective for advanced PD, giving a 40% improvement in UPDRS after 12 months. Rigidity, tremor and bradykinesia also improved in both groups and no serious adverse effects were reported.

Another study (Krack et al, 1998) compared the benefits of these two procedures in patients with young-onset (<40 years) PD. In 'off'-drug phases, motor-score improvements were significantly better in STN-stimulated patients compared with those undergoing GPi stimulation and were comparable to the best L-dopa response. Rigidity and tremor improved in both groups. In 'on'-drug phases, GPi stimulation resulted in a marked improvement in L-dopa-induced dyskinesias compared with STN-stimulation ($P<0.05$). Overall results favoured STN stimulation over GPi stimulation; the former procedure is, however, more technically demanding, while the latter uses more power reducing the longevity of the batteries.

Although STN stimulation appears to be more promising than GPi stimulation, further randomized studies are needed to compare these procedures and to investigate any differences in

symptom response and the interaction of L-dopa at each site. A large pragmatic trial of STN surgery *vs* delayed surgery has just commenced in the UK (PD-SURG), which is likely to produce substantial QoL data, as well as health economic information on the true cost of the procedure.

PSYCHOSOCIAL ISSUES OF TREATING PD

There is increasing recognition of the health burden and health-care costs associated with PD. Comorbid neuropsychiatric conditions, including dementia, not only have detrimental effects upon QoL for the patients and their carers, but are also a major determinant of breakdown of home support services and transfer to institutional care, and hence a major driver of the costs, both direct and indirect.

Traditional clinical assessment tools for PD concentrate on the impairments experienced by a patient rather than their disability and handicap, but QoL is now recognized as an important measure in health care, as it incorporates the patient's own perspective of their health. QoL measures may be generic or disease specific. Generic measures include the Sickness Impact Profile (SIP), the Nottingham Health Profile (NHP) and the Short Form-36 (SF-36). All have drawbacks when applied to people with PD, such as their length (SIP), insensitivity to lower levels of ill health (NHP), and bias towards work-related questions (SF-36).

Disease-specific measures for PD include the Parkinson's Disease Quality of Life Questionnaire (PDQL) and the Parkinson's Disease Questionnaire 39 (PDQ-39). The PDQ-39 covers eight different dimensions (mobility, ADL, emotional wellbeing, bodily discomfort, stigma, social support, cognition and communication). It has validity for use among patients attending movement disorder clinics for the treatment of PD (Fitzpatrick et al, 1997) and identifies problems that are important to these patients. The PDQ-8 is a shortened version of the PDQ-39 and has also been validated.

Recent studies examining the factors that contribute to QoL in PD have repeatedly indicated that depression is a major component (Hobson et al, 1999; Karlsen et al, 1999; Findley et al, 2000; Kuopio et al, 2000; Schrag et al, 2000). For example, in the recent Global Parkinson's Disease Survey using the Beck Depression Inventory (BDI), over 58% of the observed variation in QoL could be explained by depression. Significantly, depression assessed using the BDI was underreported by the patients themselves (Findley et al, 2000). Other less significant determinants of QoL include disability, postural instability, self-reported insomnia and cognitive impairment (Hobson et al, 1999; Karlsen et al, 1999; Schrag et al, 2000).

Depression

Assessing the prevalence of depression in PD is problematic owing to symptom overlap and, in particular, somatic symptoms. Estimates of the frequency of depression associated with PD range between 20 and 90%. The disparity relates mainly to methodological differences, notably patient selection and the tool(s) used to assess depression. Clinic-based studies have found generally higher frequencies, while community-based studies have yielded lower figures, which are sometimes only marginally higher than the prevalence of depression in the general population.

One review of 14 studies suggested that depression affects approximately 46% of patients with PD (Gotham et al, 1986). The extent of depression is higher in PD than in other chronic diseases and there is no correlation with the severity or duration of PD. Clinical features include a greater frequency of dysphoria, irritability, sadness, suicidal ideation and anxiety, but there is a reduced frequency of guilt and self-blame, delusions and hallucinations, and actual suicide compared with endogenous depression (Gotham et al, 1986).

The most suitable screening tools for depression in PD are probably the Geriatric Depression Scale, the Hospital Anxiety and Depression Scale and the Centre for Epidemiologic Studies Depression Scale (Beekman, 1999). These scales are easy to administer and are relatively unaffected by overlap with symptoms of physical illness. All three have well-established cut-off points for probable depression. Once diagnosed, the monitoring of depression may best be carried out using the Montgomery-Åsberg Depression Rating Scale or the Hamilton Rating Scale (Beekman, 1999). The BDI has been used in a number of studies to assess depression in PD. The validity of this scale as a diagnostic measure of depression in PD has not been established. Indeed, it may measure distress rather than depression in disabled people (Wade, 1992).

Treatment of depression in PD

Currently, depression is undertreated and there are no clear guidelines on the management of depression in PD. Furthermore, there have been no adequately conducted double-blind trials of

antidepressant treatment in PD (Allain et al, 2000). Treatment options include counselling, antidepressant drugs, and, in extreme depression, electroconvulsive therapy.

Few studies have evaluated efficacy and tolerability of antidepressant drugs in PD. The most widely prescribed are the tricyclic antidepressants (TCAs) and selective serotonin reuptake inhibitors (SSRIs). TCAs have variable anticholinergic, sedative and hypotensive adverse effects. In the appropriate patient, both anticholinergic and sedative effects may actually be beneficial, although in the elderly patient TCAs are generally best avoided. SSRIs can theoretically worsen parkinsonism, although in practice this rarely occurs. Drugs in this class should not be co-prescribed with selegiline if possible because of the risk of precipitating the so-called 'serotonin syndrome' (overall frequency 0.24%, serious in 0.04%) (Richard et al, 1997).

There is anecdotal evidence that some SSRIs may make parkinsonism worse (Richard and Kurlan, 1997), particularly in de novo patients. Paroxetine has been associated with inducing or aggravating movement disorders more than other agents in this class (Jiminez-Jiminez et al, 1994) but more recent work refutes this claim (Tesei et al, 2000). It should be restated that electroconvulsive therapy has an important role in those cases refractory to antidepressant drugs, and may have a beneficial effect on the motor dysfunction as well as the psychological state.

Dementia

Prevalence figures for dementia in PD vary, but a recent community-based study reported that 44% of patients over the age of 60 years fulfilled established criteria (Hobson and Meara, 1999). Risk factors include older age (Ebmeier et al, 1990; Stern et al, 1993), older age at onset of PD (Ebmeier et al, 1990; Biggins et al, 1992), longer duration of disease (Biggins et al, 1992) and psychotic reactions to L-dopa (Stern et al, 1993).

Around 20% of patients on long-term dopaminergic therapy manifest visual hallucinations, confusion or paranoid delusions. Monoamine oxidase B inhibitors, anticholinergics and dopamine agonists have a high risk of precipitating or exacerbating hallucinations and confusion. In the PD patient with neuropsychiatric symptoms, the first therapeutic decision should be to review the patient's antiparkinsonian medication and, if necessary, to gradually withdraw these drugs.

Treatment of psychosis in PD

When neuropsychiatric symptoms occur in the patient with PD, management of the motor dysfunction becomes more complex. The best outcome will invariably be a compromise between a relatively mobile but psychotic patient and a non-psychotic but immobile one. The emergence of psychosis is an ominous sign, being a strong predictor of institutionalization (Goetz and Stebbins, 1993) and increased mortality (Starkstein et al, 1990).

The most important practice point in the management of a PD patient with neuropsychiatric features is caution in (or preferably avoidance of) the use of neuroleptic medications, which are the mainstay of antipsychotic treatment in other patient groups. Neuroleptic sensitivity reactions can precipitate severe parkinsonism, impair consciousness levels, and induce autonomic disturbances reminiscent of neuroleptic malignant syndrome (McKeith et al, 1992). Acute dopamine D_2 receptor blockade is thought to mediate these effects. Atypical and novel antipsychotics, such as risperidone and olanzapine, can have unpredictable motor effects in patients with PD (Friedman and Factor, 2000). A newer agent, quetiapine, is currently under investigation, but only one paper has been published on this drug (Fernandez et al, 2000). The role of cholinesterase inhibitors (including rivastigmine and donepezil) in the management of the PD patient with psychotic symptoms and evidence of cognitive impairment is also currently being evaluated.

The management of psychosocial issues and comorbid conditions in the PD patient is underinvestigated. Comorbid psychosis also occurs in PD patients. It is often associated with cognitive impairment and may also be associated with PD drug therapy. Psychosis in PD is underinvestigated and there are no UK treatment guidelines to aid physician decision making. The working group suggests that the treatment approach should involve the elimination of unnecessary drugs in the regimen and simplification of antiparkinsonian therapy, and only then should introduction of atypical antipsychotic agents be considered after consultation with a psychiatrist or neuropsychiatrist. Dopamine agonists should normally be avoided in these patients.

There are few data on the use of atypical antipsychotics in PD patients. In a multicentre investigation, the medical records of 172 consecutive patients treated with clozapine were reviewed (Trosch et al, 1998). Clozapine improved psychiatric symptoms of psychosis, anxiety, depression, hypersexuality, sleep distur-

bance and akathisia, and there were modest improvements in tremor, torticollis, limb dystonia and pain. Recent studies on olanzapine have concluded that it worsens parkinsonism and so should be avoided in PD (Molho and Factor, 1999; Friedman and Factor, 2000; Goetz et al, 2000). All antipsychotics should be prescribed only by specialists familiar with their use and then only in low doses.

The working group concludes that the multidisciplinary team should be alert to the possibility of depression, cognitive impairment and/or psychosis in PD patients, and will often need to seek support from a psychiatric or neuropsychiatric specialist team in their management.

MODELS OF MANAGEMENT

In the absence of well-conducted, randomized, controlled trials, management strategies lack a sound evidence base. Arrangements will necessarily vary and reflect local circumstances, but the four-stage management paradigm developed by the Primary Care Task Force for the Parkinson's Disease Society (UK) is a useful aid (Parkinson's Disease Society, 1999). The working group recognizes that principles such as specialist assessment and a multidisciplinary team approach to management are valuable.

Individual GPs will have experience of managing very few patients with PD. Most will have only three or four such patients. It is difficult, therefore, for GPs to develop the expertise that comes with the experience of managing large numbers of patients and to keep appraised of new therapeutic developments. There is now consensus that patients suspected of having PD should, where local provision allows, be referred for assessment to a movement disorders specialist (Parkinson's Disease Society, 1999). In the UK this will usually be a neurologist or geriatrician with an interest in PD. Assessment should ideally be carried out before treatment is started in order to both aid diagnosis and allow consideration of the best treatment strategy for each individual. Local development of shared care guidelines between primary and secondary care is to be encouraged.

If specialist services are not readily available, an alternative approach might be for GPs to specialize within primary care groups or to use the experience of a PD nurse specialist. The impact of PD nurse specialists is currently under investigation by Hurwitz and colleagues (1999) in a randomized, controlled trial using QoL assessments as a main end point. Nurse specialists may be community or hospital based but in all cases it is desirable that they have well-developed links with specialist movement disorder services.

PD is a progressive condition and complications emerge in many patients over time (Iansek, 1999a). Problems such as postural instability, falls, and speech and swallowing difficulties respond poorly to dopaminergic treatment (Playfer, 1997). Many patients are elderly and management is further complicated by the presence of cognitive impairment, multiple pathology and polypharmacy. Because of these issues, PD is best managed by a coordinated interdisciplinary team (Iansek, 1999b).

Core members of a multidisciplinary/interdisciplinary team include a movement disorders specialist, a nurse specialist, a physiotherapist, an occupational therapist and a speech therapist. Other relevant professionals are the dietician, the social worker, the psychiatrist and the psychologist. The team should work to agreed protocols and be alert to the psychosocial as well as the medical issues. One member, usually the nurse specialist, should have a coordinating role. Good communication is essential, both within the team and with community services. The team should engage fully with clinical effectiveness and be subject to the rules of clinical governance.

The need to provide support for carers should be recognized, particularly in the palliative stage of disease (Parkinson's Disease Society, 1999). Access to social services and respite care is an important element in helping to avoid institutional care where possible. The Parkinson's Disease Society has produced a booklet discussing the commissioning of services for PD (Thomas et al, 1999).

IMPLEMENTING GUIDELINES

There is a wealth of literature on guideline development but little on their implementation.

One study, funded by the King's Fund in 1995, assessed 17 different projects which were undertaken over 18 months with the aim of putting evidence into practice. These projects were not PD-related but helped to identify four important factors that can help to achieve an embedded change in practice. These key factors were:

- Resources (time, money, skills)
- The recognition that the proposed change would offer real benefit (savings in time or money, improved patient care and/or professional development)
- Enough of the right people, especially clinical leaders, on the team, as early as possible
- An interactive approach related to current practice (small group or face-to-face teaching).

It is important that, for the purposes of implementation, recommendations are straightforward. To this end, the working group suggests the following:

- GPs should refer PD patients early and untreated to specialists with an interest in this disease
- Specialist services should be organized into coordinated teams
- Neurologists and geriatricians should consider using alternatives to L-dopa therapy, such as dopamine agonists, in biologically younger patients
- Local implementation meetings should be held
- Communication between all parts of the PD service should be mediated and improved by the PD nurse specialists. **HM**

Conflict of interest: none.

Albanese A, Baronti F, Fuhr P et al (1999) Guidelines for diagnosis and therapy of idiopathic Parkinson's syndrome. *Schweiz Arch Neurol Psychiatr* **150:** 288

Allain H, Schuck S, Manduit N (2000) Depression in Parkinson's disease. *Br Med J* **320:** 1287–8

Baron MS, Vitek JL, Bakay R-AE et al (2000) Treatment of advanced Parkinson's disease by unilateral posterior GPi pallidotomy: 4-year results of a pilot study. *Mov Disord* **15:** 230–7

Bédard PJ, Gomez-Mancilla B, Blanchet P et al (1997) Dopamine agonists as first-line therapy of parkinsonism in MPTP monkeys. In: Olanow CW, Obeso JA, eds. *Beyond the Decade of the Brain.* Wells Medical, Tunbridge Wells: 101–13

Beekman ATF (1999) Diagnostic procedures in depression in Parkinson's disease. In: Wolters EC, Scheltens P, Berendse HW, eds. *Mental dysfunction in Parkinson's disease* II. Vol 11. Academic Pharmaceutical Productions, Utrecht: 263–71

Benabid AL, Benazzouz A, Limousin P et al (2000) Dyskinesias and the subthalamic nucleus. *Ann Neurol* **47** (Suppl 1): S189–92

Benamer TS, Patterson J, Grosset DG et al (2000) Accurate differentiation of parkinsonism and essential tremor using visual assessment of [^{123}I]-FP-CIT SPECT imaging: the [^{123}I]-FP-CIT study group. *Mov Disord* **15:** 503–10

Ben-Shlomo Y, Churchyard A, Head J et al (1998) Investigation by Parkinson's Disease Research Group of United Kingdom into excess mortality seen with combined levodopa and selegiline treatment in patients with early, mild Parkinson's disease: further results of randomised trial and confidential inquiry. *Br Med J* **316:** 1191–6

Bhatia K, Brooks DJ, Burn DJ et al (1998) Guidelines for the management of Parkinson's disease. The Parkinson's Disease Consensus Working Group. *Hosp Med* **59:** 469–80

Biggins CA, Boyd JL, Harrop FM et al (1992) A controlled longitudinal study of dementia in Parkinson's disease. *J Neurol Neurosurg Psychiatry* **55:** 566–71

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

Churchyard A, Mathias CJ, Lees AJ (1999) Selegiline-induced postural hypotension in Parkinson's disease: a longitudinal study on the effects of drug withdrawal. *Mov Disord* **14:** 246–51

Clarke CE, Davies P (2000) Systematic review of acute levodopa and apomorphine challenge tests in the diagnosis of idiopathic Parkinson's disease. *J Neurol Neurosurg Psychiatry* **69:** 590–94

de Bie R-MA, de Haan RJ, Nijssen PC et al (1999a) Unilateral pallidotomy in Parkinson's disease: a randomised, single-blind, multicentre trial. *Lancet* **354:** 1665–9

de Bie R-MA, Schuurman PR, de Haan PS, Bosch DA, Speelman JD (1999b) Unilateral pallidotomy in advanced Parkinson's disease: a retrospective study of 26 patients. *Mov Disord* **14:** 951–7

Dodel RC, Singer M, Kohne-Volland R et al (1998) The economic impact of Parkinson's disease. An estimation based on a 3-month prospective analysis. *Pharmacoeconomics* **14:** 299–312

Drivers and Vehicle Licensing Agency (2000) *At a Glance – a Guide for Medical Practitioners.* Drivers Medical Unit, DVLA, Swansea

Ebmeier KP, Calder SA, Crawford JR, Stewart L, Besson JAO, Mutch WJ (1990) Clinical features predicting dementia in idiopathic Parkinson's disease. *Neurology* **40:** 1222–4

Eskandar EN, Shinobu LA, Penney JB Jr, Cosgrove GR, Counihan TJ (2000) Stereotactic pallidotomy performed without using microelectrode guidance in patients with Parkinson's disease: surgical technique and 2-year results. *J Neurosurg* **92:** 375–83

Favre J, Burchiel KJ, Taha JM, Hammerstad J (2000) Outcome of unilateral and bilateral pallidotomy for Parkinson's disease: patient assessment. *Neurosurgery* **46:** 344–53

Ferreira J, Galitzky M, Montastruc JL, Rascol O (2000) Sleep attacks in Parkinson's disease. *Lancet* **355:** 1333–4

Fernandez HH, Weiner WJ, Minagar A, Shulman LM (2000) Quetiapine for L-dopa-induced psychosis in PD. *Neurology* **55:** 899

Findley L, Peto V, Pugner K, Holmes J, Baker M, MacMahon DG (2000) The impact of Parkinson's disease on quality of life: results of a research survey in the UK. *Mov Disord* **15** (Suppl 3): 179

Fitzpatrick R, Peto V, Jenkinson C, Greenhall R, Hyman N (1997) Health-related quality of life in Parkinson's disease: a study of outpatient clinic attenders. *Mov Disord*

KEY POINTS

Management issues in Parkinson's disease

- A large proportion of the health-care burden associated with Parkinson's disease arises from psychosocial issues rather than drug treatment.
- The management of psychosocial issues and comorbid conditions is underinvestigated.
- Comorbid depression in Parkinson's disease is a common problem, difficult to assess and frequently undertreated. The multidisciplinary team should be alert to the possibility of depression and/or psychosis in Parkinson's disease patients. Comorbid conditions should be assessed and treated as part of the management plan.
- There is a need for agreement between health-care specialists and their patients on what constitutes the goals of therapy.
- The use of a multidisciplinary team to manage Parkinson's disease patients is still regarded as the best practice model. The team should have a coordinated working practice that should be regularly reviewed.
- An appropriate spread of professional disciplines should be evident in the make-up of the health-care team in order to provide adequately for the wider needs of patients.
- The nurse specialist in Parkinson's disease is regarded as a key player in this team and studies are underway to assess their impact on the patients' quality of life.
- The process of implementing management guidelines is underinvestigated and is perceived as a barrier to better management of patients with Parkinson's disease.

12: 916–22
Friedman JH, Factor SA (2000) Atypical antipsychotics in the treatment of drug-induced psychosis in Parkinson's disease. *Mov Disord* **15:** 201–11
Frucht S, Rogers JD, Greene PE, Gordon MF, Fahn S (1999) Falling asleep at the wheel: motor vehicle mishaps in persons taking pramipexole and ropinirole. *Neurology* **52:** 1908–10
Gelb DJ, Oliver E, Gilman S (1999) Diagnostic criteria for Parkinson disease. *Arch Neurol* **56:** 33–9
Ghika J, Ghika-Schmid F, Fankhauser H et al (1999) Bilateral contemporaneous posteroventral pallidotomy for the treatment of Parkinson's disease: neuropsychological and neurological side effects. Report of four cases and review of the literature. *J Neurosurg* **91:** 313–21
Goetz CG, Stebbins GT (1993) Risk factors for nursing home placement in advanced Parkinson's disease. *Neurology* **43:** 2227–9
Goetz CG, Blasucci LM, Leurgans S, Pappert EJ (2000) Olanzapine and clozapine: comparative effects on motor function in hallucinating PD patients. *Neurology* **55:** 789–94
Gotham AM, Brown RG, Marsden CD (1986) Depression in Parkinson's disease: a quantitative and qualitative analysis. *J Neurol Neurosurg Psychiatry* **49:** 381–9
Hallet M, Litvan I (1999) Evaluation of surgery for Parkinson's disease: a report of the Therapeutics and Technology Assessment Subcommittee of the American Academy of Neurology. The Task Force on Surgery for Parkinson's Disease. *Neurology* **53:** 1910–21
Hammerstad J, Anderson V, Burchiel K (2000) Pallidal *vs* subthalamic nucleus stimulation for advanced PD: 30 month followup. *Mov Disord* **15** (Suppl 3): 54
Hindle JR (1999) Psychiatric problems in Parkinson's disease. *Geriatr Med* **29:** 37–43
Hobson P, Meara J (1999) The detection of dementia and cognitive impairment in a community population of elderly people with Parkinson's disease by use of the CAMCOG neuropsychological test. *Age Ageing* **28:** 39–43
Hobson P, Holden A, Meara J (1999) Measuring the impact of Parkinson's disease with the Parkinson's Disease Quality of Life questionnaire. *Age Aging* **28:** 341–6
Hoerger TJ, Bala MV, Rowland C, Greer M, Chrischilles EA, Holloway RG (1998) Cost effectiveness of pramipexole in Parkinson's disease in the US. *Pharmacoeconomics* **14:** 541–57
Honey CR, Stoessl AJ, Tsui JK, Schulzer M, Calne DB (1999) Unilateral pallidotomy for reduction of parkinsonian pain. *J Neurosurg* **91:** 198–201
Hurwitz B, Bajekal M, Jarman B (1999) Evaluating community-based Parkinson's disease nurse specialists: rationale, methodology, and representativeness of patient sample in a large randomized controlled trial. *Adv Neurol* **80:** 431–8
Iansek R (1999a) Key points in the management of Parkinson's disease. *Aust Fam Physician* **28:** 897–901
Iansek R (1999b) Interdisciplinary rehabilitation in Parkinson's disease. *Adv Neurol* **80:** 555–9
Jankovic J, Lai E, Ben Arie L, Krauss JK, Grossman R (1999) Levodopa-induced dyskinesias treated by pallidotomy. *J Neurol Sci* **167:** 62–7
Jankovic J, Rajput AH, McDermott MP, Perl DP (2000) The evolution of diagnosis in early Parkinson disease. Parkinson Study Group. *Arch Neurol* **57:** 369–72
Jiminez-Jiminez FJ, Tejeiro J, Martinez-Junquera G, Cabrera-Valdivia F, Alarcon J, Garcia-Albea E (1994) Parkinsonism exacerbated by paroxetine. *Neurology* **44:** 2406
Junque C, Alegret M, Nobbe FA et al (1999) Cognitive and behavioral changes after unilateral posteroventral pallidotomy: relationship with lesional data from MRI. *Mov Disord* **14:** 780–9
Karlsen KH, Larsen JP, Tandberg E, Maeland JG (1999) Influence of clinical and demographic variables on quality of life in patients with Parkinson's disease. *J Neurol Neurosurg Psychiatry* **66:** 431–5
Kimber TE, Tsai CS, Semmler J et al (1999) Voluntary movement after pallidotomy in severe Parkinson's disease. *Brain* **122:** 895–906
Koller W, Pahwa R, Busenbark K et al (1997) High-frequency unilateral thalamic stimulation in the treatment of essential and parkinsonian tremor. *Ann Neurol* **42:** 292–9
Korczyn AD, Brunt ER, Larsen JP, Nagy Z, Poewe WH, Ruggieri S (1999) A 3-year randomized trial of ropinirole and bromocriptine in early Parkinson's disease. The 053 Study Group. *Neurology* **53:** 364–70
Krack P, Pollak P, Limousin P et al (1998) Subthalamic nucleus or internal pallidal stimulation in young onset Parkinson's disease. *Brain* **121:** 451–7
Krack P, Pollak P, Limousin P, Benazzouz A, Deuschl G, Benabid AL (1999) From off-period dystonia to peak-dose chorea. The clinical spectrum of varying subthalamic nucleus activity. *Brain* **122:** 1133–46
Kumar R, Lozano AM, Montgomery E et al (1998) Pallidotomy and deep brain stimulation of the pallidum and subthalamic nucleus in advanced Parkinson's disease. *Mov Disord* **13** (Suppl 1): 73–82
Kumar R, Lozano AM, Sime E et al (1999) Comparative effects of unilateral and bilateral subthalamic nucleus deep brain stimulation. *Neurology* **53**: 561–6
Kunig G, Pogarell O, Moller JC, Delf M, Oertel WH (1999) Pramipexole, a nonergot dopamine agonist, is effective against rest tremor in intermediate to advanced Parkinson's disease. *Clin Neuropharmacol* **22:** 301–5
Kuopio AM, Marttila RJ, Helenius H, Toivonen M, Rinne UK (2000) The quality of life in Parkinson's disease. *Mov Disord* **15**: 216–23
Lang AE, Lozano AM, Montgomery E, Duff J, Tasker R, Hutchinson W (1997) Posteroventral medial pallidotomy in advanced Parkinson's disease. *N Engl J Med* **337:** 1036–42
Lieberman A, Olanow CW, Sethi K et al (1998) A multicenter trial of ropinirole as adjunct treatment for Parkinson's disease. Ropinirole Study Group (published erratum appears in *Neurology* (1999) **52:** 435). *Neurology* **51:** 1057–62
Limousin P, Greene J, Pollak P, Rothwell J, Benabid AL, Frackowiak R (1997) Changes in cerebral activity pattern due to subthalamic nucleus or internal pallidum stimulation in Parkinson's disease. *Ann Neurol* **42:** 283–91
Limousin P, Brown RG, Jahanshahi M et al (1999a) The effects of posteroventral pallidotomy on the preparation and execution of voluntary hand and arm movements in Parkinson's disease. *Brain* **122:** 315–27
Limousin P, Speelman JD, Gielen F, Janssens M (1999b) Multicentre European study of thalamic stimulation in parkinsonian and essential tremor. *J Neurol Neurosurg Psychiatry* **66:** 289–96
MacMahon DG, Thomas S (1998) Practical approach to quality of life in Parkinson's disease: the nurses's role. *J Neurol* **245** (Suppl 1): S19–22
Martignoni E, Blandini F, Godi L et al (1999) Peripheral markers of oxidative stress in Parkinson's disease. The role of L-DOPA. *Free Radic Biol Med* **27:** 428–37
Martinez-Martin P, Valldeoriola F, Molinuevo JL, Nobbe FA, Rumia J, Tolosa E (2000) Pallidotomy and quality of life in patients with Parkinson's disease: an early study. *Mov Disord* **15:** 65–70
Mason DL, Sagar HL (1997) The effect of initial treatment on the development of motor and cognitive complications in Parkinson's Disease: a randomized, longitudinal comparison of levodopa, dopamine agonists and anticholinergic drugs. *Neurology* **48** (Suppl 2): A369–70
McKeith I, Fairbairn A, Perry R, Thompson P, Perry E (1992) Neuroleptic sensitivity in patients with senile dementia of Lewy body type. *Br Med J* **305:** 673–8
Meara J, Bhowmick BK, Hobson P (1999) Accuracy of diagnosis in patients with presumed Parkinson's disease. *Age Ageing* **28:** 99–102
Metman LV, Del Dotto P, LePoole K, Konitsiotis S, Fang J, Chase TN (1999) Amantadine for levodopa-induced dyskinesias: a 1-year follow-up study. *Arch Neurol* **56:** 1383–6
Molho ES, Factor SA (1999) Worsening of motor features of parkinsonism with olanzapine. *Mov Disord* **14:** 1014–6
Moriyama E, Beck H, Miyamoto T (1999) Long-term results of ventrolateral thalamotomy for patients with Parkinson's disease. *Neurol Med Chir* **39:** 350–6
Muller T, Kuhn W, Przuntek H (1997) Current therapy of idiopathic Parkinson's disease. 1: diagnosis therapeutic guidelines, standard pharmacotherapy and physical therapy. *Fortschr Med* **115:** 31–4
Olanow CW (2000) Tolcapone and hepatotoxic effects. Tasmar Advisory Panel. *Arch Neurol* **57:** 263–7
Olanow CW, Koller WC (1998) An algorithm (decision tree)

for the management of Parkinson's disease: treatment guidelines. *Neurology* **50** (Suppl 2): S1–S57
Olanow CW, Myllyla VV, Sotaniemi KA et al (1998) Effect of selegiline on mortality in patients with Parkinson's disease: a meta-analysis. *Neurology* **51:** 825–30
Olanow CW, Schapira AHV, Roth T (2000) Waking up to sleep episodes in Parkinson's disease. *Mov Disord* **15:** 212–5
Ondo W, Jankovic J, Schwartz K, Almaguer M, Simpson RK (1998) Unilateral thalamic deep brain stimulation for refractory essential tremor and Parkinson's disease tremor. *Neurology* **51:** 1063–9
Pal PK, Samii A, Kishore A et al (2000) Long term outcome of unilateral pallidotomy: follow up of 15 patients for 3 years. *J Neurol Neurosurg Psychiatry* **69:** 337–44
Palhagen S, Heinonen EH, Hagglund J et al (1998) Selegiline delays the onset of disability in de novo parkinsonian patients. Swedish Parkinson Study Group. *Neurology* **51:** 520–5
Parkinson's Disease Society (1999) *Parkinson's Aware in Primary Care. A guide for primary care teams developed by the Primary Care Task Force for PDS (UK).* Parkinson's Disease Society, London: 1–4
Parkinson Study Group (1989) DATATOP: a multicenter controlled clinical trial in early Parkinson's disease. *Arch Neurol* **46:** 1052–60
Parkinson Study Group (1996) Impact of deprenyl and tocopherol treatment on Parkinson's disease in DATATOP patients requiring levodopa. *Ann Neurol* **39**: 37–45
Parkinson Study Group (1997) Entacapone improves motor fluctuations in levodopa-treated Parkinson's disease patients. *Ann Neurol* **42:** 747–55
Parkinson Study Group (2000) Pramipexole *vs* levodopa as initial treatment for Parkinson's disease: A randomized controlled trial. *JAMA* **284:** 1931–8
Pinter MM, Pogarell O, Oertel WH (1999) Efficacy, safety, and tolerance of the non ergoline dopamine agonist pramipexole in the treatment of advanced Parkinson's disease: a double blind, placebo controlled, randomised, multicentre study. *J Neurol Neurosurg Psychiatry* **66:** 436–41
Pirker W, Happe S (2000) Sleep attacks in Parkinson's disease (and author's reply). *Lancet* **356:** 597–600
Playfer JR (1997) Parkinson's disease: classical disease revisited. *Postgrad Med J* **73:** 257–64
Przuntek H, Conrad B, Dichgans J et al (1999) SELEDO: a 5-year long-term trial on the effect of selegiline in early parkinsonian patients treated with levodopa. *Eur J Neurol* **6:** 141–50
Rascol O, Brooks DJ, Korczyn AD, De Deyn PP, Clarke CE, Lang AE (2000) 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* **342:** 1484–91
Reichmann H, Sommer U, Fuchs G et al (2000) Workshop IV: drug treatment guidelines for the long-term management of Parkinson's disease. *J Neurol* **247** (Suppl 4): 40–41
Richard IH, Kurlan R, Tanner C et al (1997) Serotonin syndrome and the combined use of deprenyl and an antidepressant in Parkinson's disease. Parkinson Study Group. *Neurology* **48:** 1070–7
Richard IH, Kurlan R (1997) A survey of antidepressant drug use in Parkinson's disease. Parkinson Study Group. *Neurology* **49:** 1168–70
Riederer P, Sian J, Gerlach M (2000) Is there neuroprotection in Parkinson syndrome? *J Neurol* **247** (Suppl 4): 8–11
Rinne UK, Bracco F, Chouza C et al (1998a) Early treatment of Parkinson's disease with cabergoline delays the onset of motor complications. Results of a double-blind levodopa controlled trial. The PKDS009 Study Group. *Drugs* **55** (Suppl 1): 23–30
Rinne UK, Larsen JP, Siden A, Worm-Petersen J (1998b) Entacapone enhances the response to levodopa in parkinsonian patients with motor fluctuations. Nomecomt Study Group. *Neurology* **51:** 1309–14
Samii A, Turnbull IM, Kishore A et al (1999) Reassessment of unilateral pallidotomy in Parkinson's disease. A 2-year follow-up study. *Brain* **122:** 417–25
Samuel M, Caputo E, Brooks DJ et al (1998) A study of medial pallidotomy for Parkinson's disease: clinical outcome, MRI location and complications. *Brain* **121:** 59–75
Sarter M, Bruno JP (1998) Corticol acetylcholine, reality distortion, schizophrenia, and Lewy Body Dementia: too much or too little cortical acetylcholine? *Brain Cognition* **38:** 297–316
Schapira AHV (2000) Sleep attacks (sleep episodes) with pergolide. *Lancet* **355:** 1332–3
Schmand B, de Bie R-MA, Koning HM, De Smet JS, Speelman JD, Van Zomeren AH (2000) Unilateral pallidotomy in PD: a controlled study of cognitive and behavioral effects. *Neurology* **54:** 1058–64
Schrag A, Samuel M, Caputo E et al (1999) Unilateral pallidotomy for Parkinson's disease: results after more than 1 year. *J Neurol Neurosurg Psychiatry* **67:** 511–7
Schrag A, Jahanshahi M, Quinn N (2000) What contributes to quality of life in patients with Parkinson's disease? *J Neurol Neurosurg Psychiatry* **69:** 308–12
Schuurman PR, Bosch DA, Bossuyt PM et al (2000) A comparison of continuous thalamic stimulation and thalamotomy for suppression of severe tremor. *N Engl J Med* **342:** 461–8
Shulman LM, Minagar A, Rabinstein A, Weiner WJ (2000) The use of dopamine agonists in very elderly patients with Parkinson's disease. *Mov Disord* **15:** 664–8
Starkstein SE, Bolduc PL, Mayberg HS, Preziosi TJ, Robinson RG (1990) Cognitive impairments and depression in Parkinson's disease: a follow up study. *J Neurol Neurosurg Psychiatry* **53:** 597–602
Stern Y, Marder K, Tang M-X, Mayeux R (1993) Antecedent clinical features associated with dementia in Parkinson's disease. *Neurology* **43:** 1690–2
Tesei S, Antonini A, Canesi M, Zecchinelli A, Mariani CB, Pezzoli G (2000) Tolerability of paroxetine in Parkinson's disease: a prospective study. *Mov Disord* **15:** 986–9
Thomas S, MacMahon D, Henry S (1999) *PD Society UK Primary Care Task Force. Moving and shaping – the future. Commissioning services for people with Parkinson's Disease.* Parkinson's Disease Society Publication, London
Thorogood M, Armstrong B, Nichols T, Hollowell J (1998) Mortality in people taking selegiline: observational study. *Br Med J* **317:** 252–4
Tolcapone Study Group (1999) Efficacy and tolerability of tolcapone compared with bromocriptine in levodopa-treated parkinsonian patients. *Mov Disord* **14:** 38–44
Trosch RM, Friedman JH, Lannon MC et al (1998) Clozapine use in Parkinson's disease: a retrospective analysis of a large multicentered clinical experience. *Mov Disord* **13:** 377–82
Ulm G, Schuler P (1999) Cabergoline versus pergolide: a video-blinded, randomised multicenter cross-over study. *Aktuelle Neurol* **26:** 360–5
Vingerhoets G, van der Linden C, Lannoo E et al (1999) Cognitive outcome after unilateral pallidal stimulation in Parkinson's disease. *J Neurol Neurosurg Psychiatry* **66**: 297–304
Wade DT (1992) *Measurement in Neurological Rehabilitation.* Oxford University Press, Oxford: 264–7
Wermuth L (1998) A double-blind, placebo-controlled, randomized, multi-center study of pramipexole in advanced Parkinson's disease. *Eur J Neurol* **5:** 235–42
Yokoyama T, Imamura Y, Sugiyama K et al (1999) Prefrontal dysfunction following unilateral posteroventral pallidotomy in Parkinson's disease. *J Neurosurg* **90:** 1005–10