

# PARKINSON'S DISEASE

— current and future aspects of drug treatment

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Deadly nightshade berries: all parts of the deadly nightshade plant contain antimuscarinic alkaloids

*The treatment of Parkinson's disease focuses on controlling symptoms and managing the complications of the drugs used. The second part of this month's special feature discusses current strategies and looks at some possible future developments that could potentially stop the degenerative process*

For nearly a century, extracts from the poisonous plant, deadly nightshade (*Atropa belladonna*) provided the only effective treatment for sufferers of Parkinson's disease. Although not the mainstay of treatment these days, antimuscarinic agents still have a place in therapy, though more modern compounds are used rather than the atropine ingested from the deadly nightshade plant.

This article provides an overview of the approaches to treating the condition as well as giving an insight to potential pharmacological developments that could be seen in the future. A number of pharmaceutical care issues are addressed and the roles pharmacists may have in improving the quality of care for patients suffering with Parkinson's disease are discussed.

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## DRUG TREATMENTS

Ideally, drug therapy should stop the degenerative process (neuroprotection), rescue dying neurones and replace or at least help to restore function in damaged pathways. Current treatment strategies, however, focus on control of symptoms and prevention or treatment of complications of the drugs used.<sup>1</sup> At the present time there is insufficient data to recommend any specific regimen for neuroprotection.<sup>2,3</sup>

Controversies surround the treatment of early Parkinson's disease, including when to initiate therapy and which drug to use first.<sup>4</sup> Treatment should be started when functional disability substantially affects the activities of daily living.

Individualising and tailoring drug regimens to the requirements of the patient is important. Factors influencing initial treatment choice include age-related co-morbidities (eg, cognitive impairment and cardiovascular disease) and the severity and nature of symptoms. Patients and their carers should be involved in the decision-making process. Profiles of the different drugs used to manage symptoms are dis-

cussed below (see Panel 1, p17, for dosage information).

**Levodopa** Levodopa is metabolised to dopamine and remains the mainstay of treatment for Parkinson's disease.<sup>1,4</sup> It provides effective symptomatic treatment in 80 per cent of patients.<sup>4</sup> It is given in combination with a peripherally acting dopa-decarboxylase inhibitor (carbidopa or benserazide) that does not cross the blood/brain barrier hence inhibiting the peripheral conversion of levodopa to dopamine. The combination preparations have helped reduce the amount of levodopa required and reduced side effects such as nausea, vomiting and hypotension.<sup>4,5</sup>

Levodopa helps improve bradykinesia (slowness in movement), hypokinesia (diminished movements) and rigidity more than tremor. Low doses should be used initially, and gradually increased by small increments with the aim of increasing mobility but keeping side effects to a minimum.<sup>5</sup>

Unfortunately, serious adverse effects may limit the use of levodopa as first-line treatment. Paradoxically, it commonly produces dyskinesias (involuntary movements) in 30 to 40 per cent of patients after four years and

## Panel 1: Classes of drugs currently available to treat the symptoms of Parkinson's disease

Drug	Available as	Usual adult dose	Place in therapy
<i>Levodopa</i>			
● Levodopa	500mg tablets	125mg to 500mg in divided doses	Combination therapy
● Co-beneldopa (levodopa with benserazide)	“62.5”, “125” and “250” capsules; “62.5” and “125” dispersible tablets (Madopar)	3 to 8 “125” capsules or dispersible tablets daily in divided doses	Monotherapy or in combination therapy
● Co-careldopa (levodopa with carbidopa)	“125” modified release capsules (Madopar CR)	3 to 12 capsules daily in divided doses	
	“62.5”, “110” and “275” tablets (Sinemet); “125” tablets (Sinemet-Plus); “125” modified release tablets (Half Sinemet CR); “250” modified release tablets (Sinemet CR)	2 to 8 “Plus” tablets or equivalent in divided doses 2 to 8 “CR” tablets in divided doses	Monotherapy or in combination therapy
<i>Dopamine agonists</i>			
● Bromocriptine	1mg and 2.5mg tablets; 5mg and 10 mg capsules	Initially, 1-1.25mg at night, increasing gradually to a usual range of 10- 40mg daily in three divided doses	Monotherapy or with levodopa therapy
● Cabergoline	1mg, 2mg and 4mg tablets	Initially 1mg daily, increasing at one or two week intervals to 2-6mg daily	With levodopa therapy
● Lisuride (lysuride)	200µg tablets	Initially, 200µg at bedtime, increasing weekly to a maximum dose of 5mg daily in 3 divided doses	Monotherapy or with levodopa therapy
● Pergolide	50µg, 250µg and 1mg tablets (starter packs available)	Initially, 50µg daily, increasing gradually to a usual maintenance dose of 3mg daily in 2 or 3 divided doses	Monotherapy or with levodopa therapy
● Pramipexole	88µg, 180µg and 700µg tablets	Initially 264µg daily in 3 divided doses and then increased every 5 to 7 days to a maximum of 3.3mg daily in 3 divided doses	Monotherapy or with levodopa therapy
● Ropinirole	250µg, 500µg, 1mg, 2mg and 5mg tablets (starter packs available)	Initially, 750µg daily in 3 divided doses, increasing at weekly intervals to a usual range of 3-9mg daily	Monotherapy or with levodopa therapy
<i>Antimuscarinics</i>			
● Benzatropine	1mg/ml injection	1-2mg by intramuscular or intravenous injection	Monotherapy or in combination therapy
● Biperiden	2mg tablets	Initially, 1mg twice daily, increasing gradually to 3-12mg daily in divided doses	Monotherapy or in combination therapy
● Orphenadrine	50mg tablets; 25mg/5ml and 50mg/5ml oral solutions	150-400mg daily in divided doses	Monotherapy or in combination therapy
● Procyclidine	5mg tablets; 2.5mg/5ml and 5mg/5ml oral syrup	Initially 2.5-5mg three times daily, increasing gradually if necessary to a maximum dose of 30mg daily	Monotherapy or in combination therapy
● Trihexyphenidyl (benzhexol)	2mg and 5mg tablets; 5mg/5ml oral syrup	Initially 1mg daily, increasing gradually to 5-15mg daily in 3 or 4 divided doses	Monotherapy or in combination therapy
<i>MAO-B inhibitors</i>			
● Selegiline	5mg and 10mg tablets; 10mg/5ml oral liquid	10mg in morning or 5mg at breakfast and 5mg at midday	Monotherapy (early disease) or with levodopa therapy
<i>COMT inhibitors</i>			
● Entacapone	200mg tablets	200mg with each dose of levodopa to a maximum dose of 2g daily	With levodopa therapy
<i>Others</i>			
● Amantadine	100mg capsules; 50mg/5ml oral syrup	Initially, 100mg daily, increasing to 100mg twice daily	Usually used in combination therapy
● Apomorphine	10mg/ml injection (subcutaneous or infusion)	Maximum total daily dose of 100mg daily	Monotherapy or in combination therapy

“MAO-B” is monoamine oxidase, type B; “COMT” is catechol-O-methyltransferase.

the percentage of individuals affected by levodopa complications may be as high as 70 to 80 per cent, particularly in younger patients.<sup>2</sup> In due course, levodopa invariably causes motor fluctuations, such as the "wearing off" and "on-off" phenomena. This is characterised by fluctuations in performance with normal performance during the "on" period and weakness and akinesia during the "off" period. There is usually a slow improvement in the patient's response to levodopa during the first six to 18 months which is usually maintained for about two years before a slow decline occurs.<sup>4</sup>

Adjusting the dose and frequency of levodopa, and considering the use of controlled-release and dispersible preparations, would normally be the first steps taken to help control motor fluctuations and dyskinesias.<sup>2,4</sup> Failing this, adjunctive or alternative therapy would need to be considered.<sup>5</sup>

**Dopamine agonists** A number of direct dopamine receptor agonists have been developed and licensed over the years. The ergot derivatives bromocriptine, cabergoline, lisuride and pergolide, and the newer non-ergot drugs pramipexole and ropinirole, are the currently marketed oral agents.<sup>1</sup> In contrast to levodopa, dopamine agonists act directly on dopamine receptors without need for storage and metabolism in the afferent neurone.<sup>5</sup> Several studies have been carried out with cabergoline,<sup>6</sup> pergolide,<sup>7</sup> pramipexole<sup>8</sup> and ropinirole<sup>9</sup> which show that although dopamine agonists have slightly less efficacy than levodopa, they control the disease with a lower incidence of dyskinesias. Therefore, dopamine agonists are increasingly being used as monotherapy, especially for younger patients, enabling a delay in starting levodopa. They can also be used in patients whose symptoms may be attributed to atypical parkinsonism rather than Parkinson's disease.<sup>2</sup> Furthermore, as adjunctive therapy, dopamine agonists may increase the "on" time and allow lower doses of levodopa to be used. However, suggestions that dopamine agonists slow the progression of Parkinson's disease or have direct neuroprotective effects have not been demonstrated in clinical practice.<sup>3,10</sup>

Careful dose titration is important because dopamine agonists are associated with more neuropsychiatric side effects than levodopa, (eg. confusional states and hallucinations). These may limit the use of dopamine agonists in elderly patients with cognitive impairment. Therefore, levodopa with a dopa-decarboxylase inhibitor is still preferable for Parkinson's disease patients who have cognitive impairment.

Additionally, the ergot-derived dopamine receptor agonists can cause serious adverse effects such as pulmonary fibrosis. There have been several cases of sudden onset of sleepiness with pramipexole and ropinirole. These concerns have now been extended to

other dopaminergic therapies. Therefore patients should be informed of this and advised to exercise caution if driving or operating machines while on these drugs.

**Antimuscarinics** The antimuscarinic drugs, trihexiphenidyl, benztropine, biperiden, orphenadrine and procyclidine, exert their effect by restoring the cholinergic-dopaminergic balance. Their role is limited due to the effects on cognition, urinary retention and glaucoma<sup>5</sup> making them unsuitable for use in the elderly. They reduce tremor but have little effect on rigidity and bradykinesia and therefore may be useful in patients with mild symptoms where tremor predominates. There is no evidence for benefit in later disease.

In practice, trihexiphenidyl is the most frequently used antimuscarinic drug, orphenadrine being used for mild symptoms. The UK Parkinson's Consensus Group suggests that antimuscarinics should be used sparingly and at the lowest effective dose.<sup>4</sup>

**Amantadine** Amantadine has mild beneficial effects on the symptoms of Parkinson's disease. It has dopamine releasing and anticholinergic properties, as well as blocking glutamate N-methyl-D-aspartate (NMDA) receptors.<sup>1</sup> It can improve akinesia and rigidity but has only mild effects on tremor. Side effects such as ankle oedema, psychosis, confusion, urinary retention and livedo reticularis (skin discolourations) can occur.

Amantadine is generally of limited value because only a small proportion of patients derive much benefit from it and tolerance to its effects can occur.

**MAO-B inhibitors** Selegiline is a monoamine-oxidase-B inhibitor that selectively inhibits the oxidative metabolism of levodopa and endogenous dopamine. It has been suggested that it might delay the need for levodopa.<sup>4</sup> However, the use of this drug has declined over the years due to several controversies surrounding it. The safety of its use was questioned by one study<sup>11</sup> which suggested an increased mortality when used in combination with levodopa. Also, even though there has been considerable interest in the possible role of selegiline as a neuroprotective agent, there is no convincing evidence that shows it delays disease progression.

**Catechol-O-methyltransferase inhibitors** When levodopa is taken alone, 99 per cent is metabolised peripherally; adding a dopa-decarboxylase inhibitor reduces that figure to 90 per cent, which still leaves most of the ingested drug unavailable to the brain. Peripheral conversion to 3-O-methyl-dopa by catechol-O-methyltransferase (COMT) also reduces the amount of levodopa available to reach the brain.<sup>1</sup> Two drugs that

inhibit this enzyme have been developed and both have shown that the effective period from each dose of levodopa can be extended, with improved "on" time.<sup>5</sup> Tolcapone which was the first one to be introduced worked both in the brain and peripherally. However, it had to be withdrawn from the market following several fatalities due to liver toxicity.<sup>5</sup> Currently the only available COMT inhibitor is the peripherally acting entacapone. Liver function tests do not need to be carried out routinely on patients taking entacapone. The drug should be considered as adjunctive therapy for patients who experience "end-of-dose" deterioration with levodopa therapy.

The side effects are primarily of levodopa enhancement, and therefore the dose of levodopa usually needs to be reduced by about 10 to 30 per cent. A dose of 200mg entacapone is given with each dose of levodopa and dopa-decarboxylase inhibitor therapy to a maximum of 2g daily. Some neurologists prefer to start with a lower dose and titrate upwards. A combination product of levodopa, carbidopa and entacapone (Stalevo®) has recently been launched. Even though it may be unsuitable to initiate patients on this product because of the loss of dosing flexibility, it maybe an option for stabilised patients to aid compliance.

**Apomorphine** Apomorphine, a specialist-initiated drug, is a potent stimulator at both D1 and D2 class dopamine receptors. It can be helpful in stabilising patients experiencing unpredictable "off" periods with levodopa treatment or other dopaminergic drugs.

Intermittent injections can be useful as "rescue" therapy particularly for patients who have two or three "off" periods a day, and can relieve associated dystonia and pain. In those requiring multiple injections, or who are unable to anticipate "off" periods and inject in time, a continuous infusion may be preferred.<sup>4</sup> The practical problems associated with apomorphine are its lack of oral bioavailability, short half-life and high incidence of peripheral side effects especially nausea and vomiting.<sup>12</sup> Therefore it is essential to establish patients on domperidone (a peripheral D2-receptor blocker) for at least two days before starting apomorphine.

## SHORTFALLS OF DRUGS

The most effective drug treatment currently available is levodopa combined with a peripheral dopa-decarboxylase inhibitor. Although significant clinical benefit is obtained in many patients, it is by no means a universal success and often causes troublesome side effects. Claims that treatment with any of the existing drugs slow disease progression or repair neuronal degeneration should be viewed with scepticism.

It is not surprising therefore that much

effort is being put in to finding more effective drug treatments. The main gain however has been some reduction in problems associated with drug therapy, rather than any substantial improvements in treating the condition. Developments to date may enable delaying the use of levodopa and therefore postponing problems with dyskinesias, and providing agents which are effective as adjunctive therapy. Research in these areas (eg, manipulating dopaminergic pathways continues – see Panel 2), but other approaches are also being investigated.

## — FUTURE DEVELOPMENTS

With growing insight into the pathology of Parkinson's disease, and further ideas from biochemical, epidemiological and genetic studies, new therapeutic targets are being identified. It is hoped at least some of these will result in the development of better drugs. Furthermore, as our understanding of neurodegenerative processes increases, the chance of finding ways to inhibit or reverse these becomes greater. Therapy which achieves this could conceivably slow or even halt the progression of Parkinson's disease. Cell transplantation and genetic engineering also offer avenues to be explored in the quest for better therapies.

**Neuronal protection or regeneration** The precise aetiology of Parkinson's disease resulting in degeneration of the nigro-striatal dopamine pathway has not been established. However a number of changes have been shown to occur which may contribute to the process.<sup>13</sup> Post-mortem studies of patients with Parkinson's disease show increased levels of iron and MAO-B activity, inflammatory processes, glutamatergic excitotoxicity and reduced expression of trophic factors. There is also evidence of oxidative stress, and levels of endogenous antioxidants such as reduced glutathione are found to be depleted at post-mortem.

Studies carried out in animals with chemically induced Parkinson's disease show that neuroprotection is achieved with iron chelating agents, antioxidants, MAO-B inhibitors, glutamate antagonists and trophic factors, all of which support ideas of what factors are involved as suggested by the post-mortem studies cited above. There has been little success so far in translating these theories and the results from animal studies into clinically useful therapies. However much effort is being focused on compounds with antiglutamate properties (eg, riluzole, currently used in motor neurone disease) and antioxidant agents. Targeted delivery of trophic factors is also being explored.

Animal studies have shown that CEP-1347 can regenerate damaged neurones. This has led to the hope that neuronal loss occurring in Parkinson's disease may be slowed. CEP-1347 blocks the JNK (c-Jun N-terminal kinase) signalling pathway which is thought to be responsible for neurodegeneration. Work with non-steroidal anti-inflammatory drugs has shown these agents have neuroprotective effects in animals in which parkinsonism has been artificially induced. It is believed this benefit results from decreasing the over-excitation of neurones that otherwise causes them to die.

Other potential options are neurotrophic proteins, which prevent premature death of nerve cells and may therefore reduce progression. The big problem is getting the proteins through the blood-brain barrier. In addition, ubiquinone (co-enzyme Q10) may have valuable properties in neurodegenerative diseases where there is impairment of mitochondrial function or excessive oxidative damage because it serves as an electron acceptor for complexes I and II of the mitochondrial electron transport chain.

**Transplantation** The transplanting of embryonic dopamine cells has shown some success in improving the "off" symptoms of Parkinson's disease.<sup>14</sup> It is possible that transplantation in the early stages of the disease could prevent progression. Whether earlier intervention would achieve this and alter the clinical course of the disease is unknown. Implanting neuronal tissue from pigs in areas of the brain that have degenerated has produced reduction in symptoms in some patients. Studies with human retinal cells contained in a small implantable capsule (Spheramine) are currently underway. Implantation of Spheramine into the putamen may result in production of dopamine.

**Genetic engineering** Recent studies of early-onset Parkinson's disease have shown that an excess of the alpha-synuclein gene resulting from abnormal multiplication may cause the condition. Modifying

### Panel 2: Potential drugs for the future, acting on dopaminergic pathways

Drug	Class
Etilevodopa	Ethyl ester of levodopa
Rotigotine (SPM-962)	Dopamine-2 selective agonist
Sumanitrole	Dopamine-2 selective agonist
SLV-308	Dopamine-2 partial agonist
Adrogolide (ABT-431)	Dopamine-1 selective agonist
Dinapsoline	Dopamine-1 selective agonist
BAM-1110	Dopamine-1 selective agonist
Rasagiline*	Monoamine oxidase-B inhibitor
NIL-A	Adenosine A2a antagonist
LY40187	Adenosine A2a antagonist
SLV318	Adenosine A2a antagonist
Brasofensine†	Dopamine re-uptake inhibitor

\*Unlike selegiline, rasagiline does not metabolise to methamphetamine, and so the likelihood of sleep problems is reduced. †Development may be further delayed because of toxicity concerns. Adenosine A2a antagonists block output neurones in the striatum

the genetic code of certain cells (eg, from the skin) to create dopamine-producing cells may open another approach to effecting treatments for Parkinson's disease.

It is clear that the transplantation of dopaminergic embryonic tissue, gene therapy, the use of nerve growth factors and neuroprotective treatments form an exciting range of new strategies which may lead to useful advances in the treatment (or possibly cure) of Parkinson's disease.

## THE PHARMACIST'S ROLE

In addition to the recognition of "holy grail" therapies for Parkinson's disease being yet unproven or yet to be discovered, it is also widely accepted that neither the benefits of current treatments have been maximised, nor the harms minimised. As the disease progresses, treatment regimens invariably become more complex for all involved, health care professionals, patients and their carers. Current treatments are also associated with many adverse effects. Patients often do not receive optimal treatment and the result is poor symptom control, decreased quality of life and increased risk of secondary complications (eg, falls). Pharmacists have a key role in maximising the health gains available from current treatments. As yet, the contribution by pharmacists in both primary and secondary care has generally been minimal. This is changing, and must change in order for patients to experience the maximum benefits of present and future treatments.

Patients have limited access to physicians with specialist knowledge in Parkinson's disease. This often results in patients receiving sub-optimal treatment. For example, one community-based study found a diagnostic error rate of up to 50 per cent.<sup>15</sup> Another study comparing the prescribing patterns of UK general practitioners with that of specialists in Parkinson's disease, found that GPs consistently "under-dosed" patients when prescribing dopamine agonists.<sup>16</sup> Unfortunately, 44 per cent of GPs do not have ongoing access to specialist Parkinson's disease physicians for advice on dosing or dose titration. Where guidance was available it was also less than adequate, with only 60 per cent of specialists providing the GPs with a long-term treatment plan.<sup>17</sup> There is a clear potential here for pharmacists with a specialist knowledge and interest in Parkinson's disease to support GPs, their patients and carers. In fact, the effectiveness of providing a network of specially trained community pharmacists to do this is the subject of a nation-wide pilot study beginning in July 2004.<sup>18</sup> This project has already gained a high level of support from patients and GPs alike.

There is also a need to develop specialist Parkinson's disease services in secondary care. A recent survey of neurologists and geriatricians showed that only 23 per cent

ran specialist Parkinson's disease clinics and only 46 per cent provide treatment reviews for their patients more frequently than every six months.<sup>19</sup> Hospital pharmacists can improve this situation by becoming a more prominent member of the multidisciplinary Parkinson's disease team and supporting the treatment review process. They can provide "holistic drug therapy reviews" individualised for each patient. Pharmacists can initiate modifications to drug choice and formulation as well as dosage regimens for Parkinson's disease or other concurrent illnesses. Pharmacists should be the natural foremost contact point for patients or their carers for all matters relating to drug therapy, providing ongoing support to patients and advice regarding side effects. Pharmacists should also proactively review their patients' response to treatment on a regular basis. This could involve regular meetings with patients to discuss their progress and review their "symptoms diary". Such reviews could lead to the pharmacists advising and initiating changes to an existing regimen.

With the advent of supplementary prescribing, the possibilities for pharmacist involvement are increasing. One way forward would be to develop specialist Parkinson's disease pharmacists (SPDP), who would support and work closely with neurologists. SPDPs would see outpatients in their own clinics where they would initiate, modify and review treatments. Similar services would be provided to inpatients. Through training and experience they would have proven competence in diagnosing and assessing the severity of Parkinson's disease and related illnesses. Additionally, they would develop and command expertise in the diagnosis and management of adverse drug reactions relating to CNS drugs and CNS side effects. The SPDP would manage and have responsibility for patients as well as being actively involved in research and clinical trials.

## REFERENCES

1. Titner R, Jankovic J. Treatment options for Parkinson's disease. *Current Opinion Neurology* 2002;15:467-76.
2. Schapira AHV. Disease-modifying strategies and challenges in Parkinson's disease (Interactive breakout sessions). *Neurology* 2002;61(Suppl):556-63.
3. Albin RL, Frey KA. Initial agonist treatment of Parkinson's disease (A critique). *Neurology* 2003;60:390-4.
4. Hudson S, Macphree G, Muir E, Thomson F, Stirton J. Parkinson's disease. *Pharmaceutical Journal* 2001;267:600-12.
5. MacMahon D. Current drug treatment of Parkinson's disease. *Prescriber* 2002;13:21-42.
6. Rinne UK, Braclo F, Chouza C, Dupont E, Gershanik O, Marti Masso JF et al. Early treatment of Parkinson's disease with cabergoline delays the onset of motor

7. Oertel WH. Pergolide vs L-dopa (PELMORT). *Movement Disorder* 2000;15(Suppl):4.
8. Parkinson's study group. Pramipexole vs levodopa as initial treatment for Parkinson's disease: a randomised controlled trial. *Journal of the American Medical Association* 2002;284:1931-1938.
9. Rascol O, Brooks DJ, Korczyn AD, De Deyn PP, Clark CE, Lang AE. A five year study of the incidence of dyskinesia in patients with early Parkinson's disease who are treated with ropinirole or levodopa. 056 Study Group. *New England Journal of Medicine* 2002;342:1484-91.
10. Schapira AHV. Neuroprotection in PD - A role for dopamine agonists? *Neurology* 2003;61(Suppl):534-41.
11. Shoulson I and the Parkinson Study Group. Deprenyl and tocopherol antioxidative therapy of parkinsonism (DATATOP). *Acta Neurol. Scandinavica* 1989;80(Suppl 126):171-75.
12. Priano L, Albani G, Brioschi A, Guastamacchia G, Calderoni S, Lopiano L et al. Nocturnal anomalous movement reduction and sleep microstructure analysis in parkinsonian patients during 1-night transdermal apomorphine treatment. *Neurological Sciences* 2003;24:207-8.
13. Mandel S, Grunblatt E, Riederer P, Gerlach M, Levites Y, Youdim MB. Neuroprotective strategies in Parkinson's disease: an update on progress. *CNS Drugs* 2003;17:729-62.
14. Freed CR, Leehey MA, Zawada M, Bjugstad K, Thompson L, Breeze RE. Do patients with Parkinson's disease benefit from embryonic dopamine cell transplantation? *Journal of Neurology* 2003;250(Suppl):44-6.
15. Meara J, Bhowmick BK, Hobson P. Accuracy of diagnosis in patients with presumed Parkinson's disease. *Age and Ageing* 1999;28:99-102.
16. Dose of dignity. Current prescribing patterns. Available at [www.doseofdignity.co.uk/hcp/overview/current\\_prescribing\\_patterns.html](http://www.doseofdignity.co.uk/hcp/overview/current_prescribing_patterns.html) (accessed 9 December 2003).
17. Dose of dignity. Management role of the primary care team. Available at [www.doseofdignity.co.uk/hcp/overview/management.html](http://www.doseofdignity.co.uk/hcp/overview/management.html) (accessed 9 December 2003).
18. Medicines Partnership Community Pharmacy Parkinson's Disease Medicines Support Service Pilot. Available at [www.medicines-partnership.org/projects/parkinsons-pilot](http://www.medicines-partnership.org/projects/parkinsons-pilot) (accessed 9 December 2003).
19. British Geriatrics Society. Factors influencing modern treatment of Parkinson's disease. Available at [www.pdsection.org.uk/spring\\_research.htm](http://www.pdsection.org.uk/spring_research.htm) (accessed 9 December 2003).