Parkinson's disease: when should you initiate treatment?

A range of effective drug treatments are available for Parkinson's disease (PD). However, long-term treatment is associated with the development of motor complications in a proportion of patients. The traditional view has been that deferring the initiation of therapy may be beneficial in patients with milder symptoms. However, recently, this view has been challenged as evidence has emerged that therapies given early in the disease course may have a beneficial effect in slowing disease progression.

Dr Jonathan Evans **SpR in Neurology, Norfolk and Norwich University Hospital, Norwich NR4 7UY**
Dr Paul Worth* **Consultant Neurologist and Honorary Senior Lecturer, Norfolk and Norwich University Hospital, Norwich NR4 7UY**
* **email** **paul.worth@nnuh.nhs.uk**

Parkinson's disease (PD) is a common neurodegenerative disorder of unknown aetiology that typically presents in late-middle age or old age. Clinically, PD is diagnosed by the identification of characteristic motor features: the asymmetric onset of a bradykinetic-rigid syndrome, with resting tremor in a proportion of patients. Pathologically it is defined by loss of dopaminergic neurons from the substantia nigra pars compacta (SNpc) of the midbrain, with alpha-synuclein positive Lewy bodies seen in surviving neurons.[1] The dominant early clinical features of the disorder are the consequence of loss of these SNpc dopaminergic neurons.

PD cannot currently be cured, but a number of effective symptomatic therapies exist. Most of the drugs currently available act primarily on the dopaminergic system and include levodopa (L-dopa; routinely combined with a dopa decarboxylase inhibitor), dopamine agonists, monoamine oxidase type B (MAOB) inhibitors and catechol-O-methyl transferase (COMT) inhibitors.[2]

When L-dopa was first introduced over 40 years ago, it revolutionised the treatment of PD.[3] However, the long-term use of L-dopa results in the development of motor complications in a significant proportion of patients, including levodopa-induced dyskinesias (LIDS) and motor fluctuations.[4] These complications, which are not unique to L-dopa and are seen also with other dopamimetic agents, are presumed to result from adaptive changes that occur in the striatum as a consequence of non-physiological stimulation of dopaminergic receptors. In many cases, motor complications – in particular LIDS – limit the physician's opportunities to treat PD symptoms optimally. The association between L-dopa use and LIDS is often the reason why initiation of treatment is delayed.[5]

There is a major unmet need for PD therapies that slow progression of the disease as well as provide symptomatic relief. The search for such "disease-modifying" agents has been the holy grail of PD therapeutics over the last 20 years. However, separating symptomatic and putative disease-modifying effects is not straightforward.[6] It has been claimed, based on clinical trial data, that some of the current treatment options have disease-modifying effects – possibly equating to neuroprotection. The most recent claim has been for the MAOB inhibitor rasagiline.[7] If such effects do exist, then initiating therapy at the earliest opportunity would be the logical way to maximise any benefit to surviving nigral neurons.

Faced with these opposing lines of evidence, the clinician is potentially faced with a dilemma in deciding when to start treatment in PD. The conventional wisdom has been that treatment should be delayed until symptoms significantly limit the patient's ability to function, either in their occupation or socially.[8] A "watch and wait" approach is advocated for patients with milder symptoms. Therefore, this approach is more likely to be adopted for those whose symptoms predominate on their nondominant side or those not in employment. However, if early treatment has an effect on the natural history of the disease, be it beneficial or detrimental, then this view is challenged. In this article, we outline the arguments for and against delaying treatment.

The case for deferring treatment

Although generally well tolerated, all dopaminergic therapies have the potential to cause side effects. Nausea and anorexia are common following initial treatment, particularly with L-dopa, but these effects usually habituate over two to three weeks. Postural hypotension is also reasonably common.

Neuropsychiatric effects, including somnolence and hallucinosis, are not uncommon (particularly in older people), and are most frequently seen with dopamine agonists. Additionally, dopamine agonists are associated with the development of impulse control disorders, including pathological gambling and hypersexuality, in susceptible individuals and patients should be counselled regarding these potential side effects.[9]

The side effects of treatment are readily reversible. The clinician should use the potential side effects of a drug to guide their choice of treatment rather than use them to guide their decision about when to initiate treatment. A more pressing consideration regarding treatment initiation is the association between dopaminergic therapies and motor complications, which are generally irreversible.

LIDS comprise dystonic and choreiform movements, which may range in severity from mild and barely noticeable to significantly disabling. The pathophysiology of LIDs is not completely understood.[10] The risk of developing LIDS is related to the dose and to the duration of dopaminergic treatment.[4,11] Younger age at onset may be an independent risk factor, possibly due to increased neuronal plasticity,[12] but this may be confounded as younger patients have a longer disease course.

The risk of dyskinesias is highest with L-dopa therapy, but whether this is a class effect or simply due to its superior potency when compared with other dopaminergic therapies is unclear.[13] After 4–6 years of L-dopa monotherapy, approximately 40% of patients develop LIDS.[14] The use of a dopamine agonist as initial therapy may delay the onset of LIDS, with the trade-off being a slight reduction in motor symptom control.[15] However, virtually all PD patients will eventually require L-dopa, and this increases their risk of developing motor complications even when L-dopa is delivered with a dopamine agonist.[16]

When mild, LIDS do not have a significant impact upon quality of life.[17] But in patients with more advanced disease, LIDS make a major contribution to the burden of

the disease.[18] In patients with a low dyskinesia threshold, it might be difficult to treat with sufficient levels of dopaminergic therapy to achieve optimum relief of their motor symptoms.[11]

Although LIDS and motor fluctuations cannot be cured, they can be managed and ameliorated using a number of different approaches.[10] These include drug delivery strategies designed to produce a more continuous profile of dopaminergic stimulation, such as via subcutaneous or intrajejunal infusion, which have been shown to be effective in advanced disease.[19,20]

One question of obvious interest is whether a similar strategy that uses a more continuous drug delivery method to recapitulate the physiological profile of dopamine delivery to the striatum might avert or delay motor complications if used in early stage disease. Currently available "sustained-release" oral preparations of L-dopa do not appear to offer any such advantages.[21] Regular oral therapy with an L-dopa preparation combined with the COMT inhibitor entacapone leads to a plasma profile very close to that of a continuous L-dopa infusion.[22] However in the STRIDE-PD study, the use of the combined preparation Stalevo in early disease paradoxically resulted in higher rates of motor complications compared with standard therapy.[23] The transdermally delivered dopamine agonist rotigotine has been shown to achieve continuous dopaminergic stimulation in animal models,[24] but there is currently insufficient prospective data to draw any conclusions about whether this will translate into a reduction in LIDS in clinical practice.

The case for early treatment

Measuring disease progression in PD is not straightforward. At present, we do not have biomarkers that are sufficiently sensitive to index the evolution of the disease.[25] Clinical assessments using well validated rating scales, such as the Unified Parkinson's disease Rating Scale (UPDRS), are the most widely used outcome measures in both clinical trials and naturalistic studies.

As there were no studies of the natural history of PD during the pre-treatment era, the clinical manifestations of natural disease evolution are largely masked by treatment. But data from the placebo arms of clinical trials give some insight into the rate of progression of untreated PD during the early stages. Such studies indicate that the disease evolves rapidly in its early stages, with changes in UPDRS scores equivalent to 6-8% of the maximum score per annum.[26,27] This is supported by the results of neuroimaging and pathological studies.[28] It also indicates that a particular "window of opportunity" does exist early in the disease for delivering putative neuroprotective therapies.

The DATATOP study represented the first attempt to test neuroprotection in PD.[29] It showed the MAOB inhibitor selegiline to be superior to placebo at delaying the need for L-dopa, but the symptomatic effect of selegiline may alone explain this result.[30] Two studies have compared dopamine agonists with L-dopa using neuroimaging dopamine changes as a marker of PD progression in early disease. While both CALM-PD-CIT (pramipexole)[31] and REAL-PET (ropinirole)[32] reported reduced rates of progression with the trial drug, this was confounded by drug-related differences in the regulation of the pre-synaptic dopamine markers targeted by the imaging ligand.[6]

The ADAGIO study used a novel "delayed start" trial design in comparing rasagiline with placebo in early, untreated PD.[7] Patients on rasagiline 1 mg showed an improvement in their UPDRS scores consistent with a symptomatic benefit. However, patients randomised to the "delayed-start" arm never caught up with those initiated on the trial drug; even with treatment their UPDRS scores were consistently higher, indicating more motor impairment. While the authors interpreted this as evidence for a disease-modifying effect, this has subsequently been disputed.[33]

One of the most informative treatment trials in PD in recent years, the ELLDOPA study was originally designed to test the hypothesis that L-dopa might exert a toxic effect upon dopaminergic neurons in vivo.[34] Patients with PD of less than two years duration were randomised either to placebo or to one of three doses of carbidopa-levodopa (up to 600 mg/day). After 40 weeks of treatment, patients were assessed both by UPDRS and Beta-CIT neuroimaging after a two week washout period. As expected, during the treatment phase, patients taking the active drug showed a dose-related improvement in their UPDRS scores compared with those taking placebo. Furthermore, this improvement was sustained in all three treatment groups even after the washout period. Various interpretations of this unexpected result have been suggested. These include: that L-dopa exerts a prolonged symptomatic effect,[35] which lasts longer than two weeks; and that L-dopa itself has a disease-modifying effect in PD, possibly by supporting intrinsic physiological compensatory mechanisms within the basal ganglia.[36] To add a further degree of complexity, the neuroimaging arm of the study showed the opposite result. This result was a greater decrease in Beta-CIT signal in the treated groups, the significance of which remains unclear.

Therefore, the idea that L-dopa, generally regarded as

the archetypal "symptomatic" therapy, has a modifying effect upon the natural history of PD appears plausible. This is supported by evidence from longitudinal natural history studies indicating that progression of disability has slowed markedly in the treatment era.[37,38] Furthermore, L-dopa has improved both the quality of life and life expectancy of PD patients.[39, 40]

The interpretation of the existing clinical trial data depends upon how the concept of disease modification is viewed. If, as Sampaio et al suggest, a "disease-centred" view (which requires evidence for an effect upon the pathophysiology of the disorder and consequent slowing of disease progression) is adopted, then no PD therapy has yet shown such an effect.[41] Alternatively, if a "patient-centred" view is adopted and the focus is instead on the ability of a treatment to achieve long-lasting delay in the progression of disability, then there is good evidence that L-dopa at least is disease modifying in this sense. Increasingly, patient-rated measures, such as quality-of-life scores, are being incorporated as outcome measures in clinical trials. The results of studies, such as PD-MED,[42] are likely to provide further insights into the effect of early treatment upon the patient's experience of the disease.

The limitations of existing therapies

PD is not purely a motor disorder, and a range of non-motor symptoms (eg, cognitive and psychiatric dysfunction, disturbance of homeostatic function, and autonomic impairment) are common.[43] Furthermore, Lewy body pathology is restricted neither to the SNpc nor to dopaminergic neurons.[44] Involvement of other loci in the brainstem and cerebral cortex appears to be more important in the pathophysiology of these non-motor features, which are generally poorly responsive to dopaminergic replacement.[45]

Cognitive impairment, in particular, makes a significant contribution to the disease burden in PD. Up to a third of patients show impairment in at least one neuropsychological domain at the time of diagnosis[46] and, followed longitudinally, the rate of dementia is around five times that of non-PD controls.[47] Increased age is the strongest risk factor for dementia,[48] and cognitive impairment has been shown to be the single greatest predictor of impaired quality of life in PD.[49] Put into context, the elderly PD patient (and an arbitrary designation of >75 has been suggested[5]) is likely to be at higher risk of cognitive complications than complications related to long-term treatment.

Furthermore, not all PD motor symptoms respond equally to dopaminergic therapy. Axial symptoms, such as postural instability and gait dysfunction, are relatively refractory to standard treatments, probably because they result from degeneration in non-dopaminergic systems.[50] As the disease progresses, these symptoms frequently become the dominant clinical feature.[51] It is therefore important to recognise that, though effective at treating the core motor features of the disorder, dopaminergic replacement has limitations — particularly in advanced disease.

Conclusion

A key principle in the modern management of PD is to individualise treatment strategies, including the decision about when to initiate treatment, according to the circumstances of the patient. In a number of cases, perhaps the majority, this decision is straightforward as the patient's symptoms are sufficiently severe at the time of diagnosis to mandate treatment. In others, symptoms are mild or have little apparent effect on day-to-day function, and the issues covered in this review are intended to frame a discussion with such patients about when treatment should be initiated.

Guided by the evidence that we have reviewed in this article, there is an emerging consensus in the PD community that early treatment, initiated at the time of diagnosis or shortly thereafter, is the correct approach.[36] Delaying treatment means that the potential benefits which may accrue as a result of early treatment, either in terms of symptom reduction or, potentially, disease-modifying effects, are missed or reduced.

Strategies to minimise the longer term risks of motor complications should also be employed where appropriate. In practice, the use of a dopamine agonist or MAOB inhibitor as the initial therapy in patients who are younger, have little co-morbidity or have mild symptoms is advocated, and various algorithms have been suggested to guide the clinician in this choice.[52]

Two further points are worthy of comment. First, as the risk of LIDS is related most strongly to total dopaminergic exposure, and patients early in their disease course are likely to respond to small doses of medication, the incremental increase in risk from early treatment is likely to be small. Secondly, neurodegeneration in PD is inexorable and disease progression may be characterised by development of complications including loss of postural stability and cognitive impairment that are not amenable

to conventional therapies. The elderly are particularly at risk of such complications relatively early in their disease course – a phenomenon that has been termed the "compression of morbidity in PD with increased age of onset"[53] – and this would justify a more aggressive approach to the treatment of dopamine responsive symptoms, incorporating the early initiation of treatment, in this demographic group.

The results of ongoing research into the safety and efficacy of novel PD treatments, such as transdermal L-dopa preparations, and interventional therapies utilising cell-, gene- or neurotrophic factor based technologies will further inform the discussion about treatment initiation in PD.[54] Ultimately, our target must be the development of true neuroprotective therapies that will definitively resolve the issue; our focus will then shift instead towards the identification and treatment of PD in its pre-motor phase.[55]

Conflict of interest: none declared

References

1. Oppenheimer DR. Disease of the basal ganglia, cerebellum and motor neurons, in Greenfield's Neuropathology, JH Adams and LW Duchen, Editors. 1984, Wiley: New York. p. 699–47
2. Schapira AH. Treatment options in the modern management of Parkinson disease. *Arch Neurol* 2007; **64**: 1083–8
3. Fahn S. The history of dopamine and levodopa in the treatment of Parkinson's disease. *Mov Disord* 2008; **23** (Suppl 3): S497–08
4. Fabbrini G, Brotchie JM, Grandas F, et al. Levodopa-induced dyskinesias. *Mov Disord* 2007; **22**: 1379–89 (quiz 1523)
5. Aminoff MJ. Treatment should not be initiated too soon in Parkinson's disease. *Ann Neurol* 2006; **59**: 562–4; discussion 564–5
6. de la Fuente-Fernandez R, Schulzer M, Mak E, et al. Trials of neuroprotective therapies for Parkinson's disease: problems and limitations. *Parkinsonism Relat Disord* 2010; **16**: 365–9
7. Olanow CW, Rascol O, Hauser R, et al. A double-blind, delayed-start trial of rasagiline in Parkinson's disease. *N Engl J Med* 2009; **361**: 1268–78
8. Marsden CD, Parkes JD. Success and problems of long-term levodopa therapy in Parkinson's disease. *Lancet* 1977; **1**: 345–9
9. Dodd ML, Klos KJ, Bower JH, et al. Pathological gambling caused by drugs used to treat Parkinson disease. *Arch Neurol* 2005; **62**: 1377–81
10. Del Sorbo F, Albanese A. Levodopa-induced dyskinesias and their management. *J Neurol* 2008; **255** (Suppl 4): 32–41
11. Schrag A, Quinn N. Dyskinesias and motor fluctuations in Parkinson's disease. A community-based study. *Brain* 2000; **123**: 2297–05
12. Kostic V, Przedborski S, Flaster E, et al. Early development of levodopa-induced dyskinesias and response fluctuations in young-onset Parkinson's disease. *Neurology* 1991; **41**: 202–5
13. Metman LV, Konitsiotis S, Chase TN. Pathophysiology of motor response complications in Parkinson's disease: hypotheses on the why, where, and what. *Mov Disord*, 2000; **15**: 3–8
14. Ahlskog JE, Muenter MD. Frequency of levodopa-related dyskinesias and motor fluctuations as estimated from the cumulative literature. *Mov Disord* 2001; **16**: 448–58
15. Holloway RG, Shoulson I, Fahn S, et al. Pramipexole vs levodopa as initial treatment for Parkinson disease: a 4-year randomized controlled trial. *Arch Neurol* 2004; **61**: 1044–53
16. Rascol O, Brooks DJ, Korczyn AD, et al. A five-year study of the incidence of dyskinesia in patients with early Parkinson's disease who were treated with ropinirole or levodopa. 056 Study Group. *N Engl J Med* 2000; **342**: 1484–91
17. Marras C, Lang A, Krahn M, et al. Quality of life in early Parkinson's disease: impact of dyskinesias and motor fluctuations. *Mov Disord* 2004; **19**: 22–8
18. Pechevis M, Clarke CE, Vieregge P, et al. Effects of dyskinesias in Parkinson's disease on quality of life and health-related costs: a prospective European study. *Eur J Neurol* 2005; **12**: 956–63
19. Sage JI, Trooskin S, Sonsalla PK, et al. Long-term duodenal infusion of levodopa for mo–tor fluctuations in parkinsonism. *Ann Neurol*, 1988; **24**: 87–9
20. Stocchi F, Vacca L, Ruggieri S, et al. Intermittent vs continuous levodopa administration in patients with advanced Parkinson disease: a clinical and pharmacokinetic study. *Arch Neurol* 2005; **62**: 905-10
21. Dupont E, et al. Sustained-release Madopar HBS compared with standard Madopar in the long-term treatment of de novo parkinsonian patients. *Acta Neurol Scand* 1999; **93**: 14–20
22. Olanow CW, Obeso JA, Stocchi F. Continuous dopamine-receptor treatment of Parkinson's disease: scientific rationale and clinical implications. *Lancet Neurol* 2006; **5**: 677–87
23. Klivenyi P, Vecsei L. Novel therapeutic strategies in

Parkinson's disease. *Eur J Clin Pharmacol* 2010; **66**: 119–25
24. Kehr J, Hux X, Goiny M, Scheller D. Continuous delivery of rotigotine decreases extracellular dopamine, suggesting continuous receptor stimulation. J *Neural Transm* 2007; **114**: 1027–31
25. Michell AW, Lewis SJ, Foltynie T, Barker RA, et al. Biomarkers and Parkinson's disease. *Brain* 2004; **127**: 1693–705
26. Fahn S. Does levodopa slow or hasten the rate of progression of Parkinson's disease? *J Neurol* 2005; **252** Suppl 4: IV37–IV42
27. The Parkinson Study Group. Effect of lazabemide on the progression of disability in early Parkinson's disease. *Ann Neurol* 1996; **40**: 99–107
28. Maetzler W, Liepelt I, Berg D. Progression of Parkinson's disease in the clinical phase: potential markers. *Lancet Neurol* 2009; **8**: 1158–71
29. The Parkinson Study Group. Effects of tocopherol and deprenyl on the progression of disability in early Parkinson's disease. *N Engl J Med* 1993; **328**: 176–83
30. Schulzer M, Mak E, Calne DB. The antiparkinson efficacy of deprenyl derives from transient improvement that is likely to be symptomatic. *Ann Neurol* 1992; **32**: 795–8
31. Parkinson Study Group. Dopamine transporter brain imaging to assess the effects of pramipexole vs levodopa on Parkinson disease progression. *JAMA* 2002; **287**: 1653–61
32. Whone AL, Watts RL, Stoessl AJ, et al. Slower progression of Parkinson's disease with ropinirole versus levodopa: The REAL-PET study. *Ann Neurol* 2003; **54**: 93–101
33. Ahlskog JE, Uitti RJ. Rasagiline, Parkinson neuroprotection, and delayed-start trials: still no satisfaction? *Neurology* 2010; **74**: 1143–8
34. Fahn S, Oakes D, Shoulson I, et al. Levodopa and the progression of Parkinson's disease. *N Engl J Med* 2004; **351**: 2498–08
35. Hauser RA, Auinger P, Oakes D. Levodopa response in early Parkinson's disease. *Mov Disord* 2009; **24**: 2328–36
36. Schapira AH, Obeso J. Timing of treatment initiation in Parkinson's disease: a need for reappraisal? *Ann Neurol* 2006; **59**: 559–62
37. Muller J, Wenning GK, Jellinger K, et al. Progression of Hoehn and Yahr stages in Parkinsonian disorders: a clinicopathologic study. *Neurology* 2000; **55**: 888–91
38. Maier Hoehn MM. Parkinsonism treated with levodopa: progression and mortality. *J Neural Transm Suppl* 1983. **19**: 253–64
39. Uitti RJ, Ahlskog JE, Maraganore DM, et al. Levodopa therapy and survival in idiopathic Parkinson's disease: Olmsted County project. *Neurology* 1993; **43**: 1918–26
40. Rajput AH. Levodopa prolongs life expectancy and is non-toxic to substantia nigra. *Parkinsonism Relat Disord* 2001; **8**: 95–100
41. Sampaio C, Rascol O. Disease-Modifying Strategies in Parkinson's Disease, in Parkinson's disease and Movement Disorders, J. Jankovic, Editor. 2001, Lippincott, Williams and Wilkins: Philadelphia. p. 103-109
42. University of Birmingham 2010. www.pdmed.bham.ac.uk (accessed 30 September 2010)
43. Chaudhuri KR, Healy DG, Schapira AH. Non-motor symptoms of Parkinson's disease: diagnosis and management. *Lancet Neurol* 2006; **5**: 235–45
44. Braak H, Del Tredici K, Rüb U, et al. Staging of brain pathology related to sporadic Parkinson's disease. *Neurobiol Aging* 2003; **24**: 197–211
45. Ziemssen T, Reichmann H. Non-motor dysfunction in Parkinson's disease. *Parkinsonism Relat Disord* 2007; **13**: 323–32
46. Foltynie T,Brayne CE, Robbins TW, Barker RA. The cognitive ability of an incident cohort of Parkinson's patients in the UK. The CamPaIGN study. *Brain* 2004; **127**: 550–60
47. Williams-Gray CH, Foltynie T, Brayne CE, et al. Evolution of cognitive dysfunction in an incident Parkinson's disease cohort. *Brain* 2007; **130**: 1787–98
48. Aarsland D, Kurz MW. The epidemiology of dementia associated with Parkinson disease. *J Neurol Sci* 2009;
49. Schrag A. Quality of life and depression in Parkinson's disease. *J Neurol Sci* 2006; **248**: 151–7
50. Levy G, Tang MX, Cote LJ, et al. Motor impairment in PD: relationship to incident dementia and age. *Neurology* 2000; **55**: 539–44
51. Hely MA, Morris JG, Reid WG, et al. Sydney Multicenter Study of Parkinson's disease: non-L-dopa-responsive problems dominate at 15 years. *Mov Disord* 2005; **20**: 190–9
52. Schapira AH, Olanow CW. Drug selection and timing of initiation of treatment in early Parkinson's disease. *Ann Neurol* 2008; **64** (Suppl 2): S47–55
53. Levy G. The relationship of Parkinson disease with aging. *Arch Neurol* 2007; **64**: 1242–6
54. Olanow CW. Levodopa/dopamine replacement strategies in Parkinson's disease--future directions. *Mov Disord* 2008; **23** (Suppl 3): S613–22
55. Linazasoro G. A global view of Parkinson's disease pathogenesis: implications for natural history and neuroprotection. *Parkinsonism Relat Disord* 2009; **15**: 401–5