

Parkinson's Disease Therapy – When to Start and What to Choose

a report by

Andrew J Lees

Director, Reta Lila Weston Institute of Neurological Studies, University College London, and

Professor of Neurology, National Hospital for Neurology and Neurosurgery

DOI:10.17925/ENR.2008.03.02.34

Parkinson's disease (PD) is a neurodegenerative disorder that, at least in the early stages, is predominantly characterised by a loss of nigrostriatal dopaminergic function, and the presence of bradykinesia is a *sine qua non* for diagnosis. As the disease progresses, additional non-motor symptoms sometimes emerge. The natural history of the disorder varies markedly from patient to patient, and attempts to delineate clinical subtypes have been made (tremor-dominant, axial and bulbar forms). Treatment decisions take into account individual disabilities and the patient's age (biological and chronological), occupation and lifestyle.

Accurate diagnosis is an essential pre-requisite for providing advice on prognosis and planning of disease management. Several assessment tools are available for providing semi-quantitative measures of disease progression, including: the Unified Parkinson's Disease Rating Scale (UPDRS), the current gold standard for motor assessment; the Mini Mental State Examination (cognitive); the Geriatric Depression Scale (GDS15); and the Parkinson's Disease Questionnaire-39 (PDQ39) (quality of life [QoL]). Staging of PD using the Hoehn and Yahr (H&R) scale has also proved to be a useful and simple marker of disease progression.

The recognition of numerous non-motor symptoms in even the early stages of PD has prompted the Movement Disorders Society (MDS) to revise the UPDRS scale to include non-motor and QoL elements. Professor Christopher Goetz from Rush University Medical Center in Chicago is chairing the study group, and a publication appeared in the December 2008 issue of *Movement Disorders*.

Timing of Treatment

There are a number of guidelines regarding the optimal time-frame for onset of therapy and treatment choices for PD patients, but most of these are not supported by robust evidence-based literature. In the UK, the National Institute of Clinical Excellence (NICE) has developed recommendations for the management and pharmacotherapy of PD in primary and secondary care.¹ The NICE guidelines recommend pharmacotherapy once motor symptoms begin to impair the patient's

functional ability. Useful practice parameters are also available from the Quality Standards Subcommittee of the American Academy of Neurology (AAN).²

Evidence-based reviews by the MDS also offer some guidance of when to initiate therapy, as do the European Federation of Neurological Societies (EFNS) guidelines, although the EFNS document is not widely used outside Europe. Other algorithms for the treatment and management of patients with PD have also been published, but these

The recognition of numerous non-motor symptoms in even the early stages of Parkinson's disease has prompted the Movement Disorders Society to revise the UPDRS scale to include non-motor and quality of life elements.

can be criticised on the grounds of pharmaceutical industry sponsorship.^{3,4} Ultimately, although some guidance for the initial treatment of PD is available, the question of when to start treatment and with what drug remains largely a decision for the treating physician.^{1,5}

The optimal time-frame for onset of therapy has remained controversial since levodopa became routinely available in 1969. One view supports early treatment, exemplified by the substantial improvements observed in *de novo* patients treated with levodopa and reduced mortality.⁶⁻⁹ It has even been suggested that early treatment could offer some neuroprotection to active dopaminergic neurons and facilitate compensatory neuroplasticity.¹⁰

An opposing view developed throughout the 1980s and 1990s, when concerns regarding levodopa neurotoxicity and levodopa-related motor complications led to the adoption by many neurologists of a 'watch and wait' strategy: delaying the onset of levodopa therapy until symptoms substantially impaired a patient's functional ability.^{11,12} More recently, proponents of early treatment have taken advantage of the improved dyskinesia profile of dopamine agonists, particularly for young-onset PD patients. Recently, a study by Grosset et al. called for a re-evaluation of the policy of delaying treatment in *de novo* PD patients. In this PD-Life study, Grosset et al. showed a trend towards improvement in self-reported health status scores after PD pharmacotherapy was initiated. This first-time report was an observational study of the effect of anti-PD drug treatment, such that



Andrew J Lees is Director of the Reta Lila Weston Institute of Neurological Studies at University College London, and a Professor of Neurology at the National Hospital for Neurology and Neurosurgery in London. He is Director of the Queen Square Brain Bank for Neurological Disorders and the Sara Koe PSP Research Centre. Professor Lees is also Associate Director of the UK Dementias and Neurodegenerative Diseases Research Network and Chairman of the Clinical Studies Group on Parkinson's

Disease. He is Past President of the Movement Disorders Society (MDS) and former Co-Editor in Chief of the journal *Movement Disorders*.

E: ales@ion.ucl.ac.uk

only limited conclusions can be drawn about the relative merits of levodopa versus dopamine agonist treatment. Other limitations include the incompleteness of longitudinal follow-up and the low number of patients remaining drug-naïve at second follow-up.¹³

Treatment Choices

Levodopa

During the early phases of PD, there is a good sustained response to levodopa treatment – the so-called ‘honeymoon’ period – which may last for up to five years. As treatment continues, the disease advances

Interestingly, it is only relatively recently that the efficacy of levodopa has been compared with that of other agents.

and a diminished response to levodopa, or ‘wearing off’, occurs, often coupled with the appearance of treatment-related motor disturbances such as dyskinesia and neuropsychiatric side effects such as hallucinations, delusions and confusion.

Levodopa remains the most effective agent for the management of PD.¹⁴ Interestingly, it is only relatively recently that the efficacy of levodopa has been compared with that of other agents. In the PELMOPET monotherapy study, the dopamine agonist pergolide was compared with levodopa in previously untreated early PD. Results showed that symptomatic relief was significantly greater in patients receiving levodopa; however, the authors conclude that both levodopa and pergolide are suitable options for initial PD therapy.¹⁵ Lees et al. showed the long-term effectiveness of three different initial regimens in patients with early and mild PD. Compared with patients randomised to the bromocriptine treatment arm, patients initially randomised to levodopa had slightly better disability scores throughout the first years of therapy at the expense of a slightly higher incidence of motor complications.¹⁶ The ELLDOPA trial by Fahn et al. found no clinical evidence that levodopa accelerates disease progression.¹⁷ Even more recent evidence suggests that levodopa may in fact delay symptomatic disease progression, with disease benefits sustained beyond the early phases.¹⁷ Nonetheless, despite the lack of *in vivo* evidence that levodopa is neurotoxic, many clinicians prefer to hold back levodopa treatment by several months or years in order to delay or prevent levodopa-induced complications.

Dopamine Agonists

Non-ergot-derived dopamine agonists such as pramipexole, ropinirole, rotigotine patch and apomorphine injections are used widely as monotherapy and adjuvants to levodopa in PD. The older drug bromocriptine and other ergot-derived agonists such as pergolide and cabergoline are now rarely used due to an increased risk of fibrotic valvular heart and lung disease.^{18–20} A recent study by Moller et al. suggests a possible antidepressant action of pramipexole and beneficial effect on tremor when used as an adjuvant therapy to levodopa compared with placebo in advanced PD.²¹

Monoamine Oxidase-B Inhibitors

In addition to a levodopa-sparing role, some observational studies have claimed that the monoamine oxidase-B (MAO-B) inhibitor selegiline has a neuroprotective effect.^{22,23} The ADAGIO study, one of the largest conducted in PD, randomised patients with very early PD in order to compare the effects of early versus later initiation of rasagiline.²⁴ The rationale for the delayed start was to try to avoid symptomatic²⁴ confounding effects when testing putative neuroprotective therapy. Benefits were seen with early treatment in the 1mg but not the 2mg active rasagiline arms.

The benefit of early treatment in the 1mg/day early treatment group confirmed the findings from the earlier TEMPO trial.¹⁸ The Parkinson Study Group authors concluded that the effects of rasagiline on the progression of disability in patients with PD cannot be fully explained by its symptomatic effect and may be due to a disease-modifying activity of the drug.²⁵ This has led to the recommendation by some opinion leaders that this class of drugs could be started soon after diagnosis. Both the TEMPO and ADAGIO trials showed that early start with mildly disabled patients immediately after diagnosis conferred mild lasting benefit at one year over patients started six months later. However, there are a number of possible interpretations, and it would be ill-advised to assume that the trial necessarily shows that rasagiline slows disease progression.

Anticholinergics/Catechol O-Methyltransferase Inhibitors/Amantadine

These agents are more commonly used to augment levodopa therapy. Anticholinergic agents such as trihexyphenidyl were the very first efficacious treatment used for PD. Most of the clinical data are old, but this does not mean they should be discounted. Anticholinergics are mainly reserved for a very specific group of younger patients with severe tremor and dystonic contortions of the feet. Although this group constitutes a very small percentage (<2%) of all new PD patients, anticholinergics can be an extremely effective treatment for

During the early phases of Parkinson's disease, there is a good sustained response to levodopa treatment – the so-called ‘honeymoon’ period – which may last for up to five years.

these patients. The added benefit is that anticholinergic agents are very cheap. Amantadine is more widely used, and shows weak to modest beneficial effects. Amantadine may be helpful for fatigue, and can reduce levodopa-induced dyskinesias.

Catechol-O-methyltransferase (COMT) inhibitors such as entacapone and tolcapone improve delivery of levodopa to the brain and as such prolong its symptomatic efficacy. Since 2003 a triple combination of levodopa, carbidopa and entacapone has been available for use in PD patients experiencing wearing-off. It is currently being investigated in early PD patients, with data from two double-blind trials available (FIRST STEP) or soon to be available (Stalevo Reduction in Dyskinesia Evaluation [STRIDE-PD]), as well as the recently published QUEST-AP trial.²⁶

Levodopa versus Dopamine Agonists

Levodopa has been used as a comparator in many trials evaluating dopamine agonists in early PD. The Comparison of the Agonist Pramipexole with Levodopa on Motor Complications of PD (CALM-PD)

It would be ill-advised to assume that the trial necessarily shows that rasagiline slows disease progression.

study, conducted by the Parkinson Study Group, investigated initial treatment with pramipexole versus levodopa in early PD patients.²⁷ Data from this study were used to compare the effect of pramipexole versus levodopa on disease-specific QoL. At 24 months, the levodopa treatment group showed improved QoL scores compared with the pramipexole group.²⁷

Results from a 10-year follow-up trial from the Parkinson's Disease Research Group of the UK (PDRG-UK) showed that treatment with the dopamine agonist bromocriptine does not reduce mortality or motor disability, and the initially reduced frequency in motor complications was not sustained.²⁸ Katzenschlager et al. concluded that there were no long-term advantages to initiating treatment with bromocriptine compared with levodopa in early PD.²⁸ Furthermore, the greater proclivity for dopamine agonists to cause psychotoxicity and cognitive side effects, including confusion, balance disturbances and visual hallucinations, has also limited their routine use, especially in the elderly.²⁹ Given this situation, results from the STRIDE-PD are eagerly awaited as they may tilt the scale in favour of levodopa, if indeed the

new optimised levodopa regimen Stalevo™ (levodopa/carbidopa/entacapone) is proved to delay the time to onset of dyskinesia compared with standard levodopa in PD patients requiring initial levodopa treatment.

Summary

Accurate diagnosis is a prerequisite to effective therapy. At least 10% of cases in the early stages of disease are misdiagnosed by neurologists, leading to inappropriate therapy in some cases. The explanation of the diagnosis to the patient is also very important and should not be hurried. If symptoms are severe enough to have an impact on the patient's QoL, there would be nothing lost by initiating pharmacotherapy within the first year after diagnosis. Treatment options, including relative efficacy and possible side effects, must be discussed frankly in order to reach concordance about the most appropriate initial treatment. A fear lingers among physicians and patients about starting treatment with levodopa. It is therefore important to assuage concerns about permanent or damaging side effects or a finite period of usefulness and to discuss impartially the pros and cons of all available therapies. If a patient were

At least 10% of cases in the early stages of disease are misdiagnosed by neurologists, leading to inappropriate therapy in some cases.

to ask 'What would you do if you were me?' my personal view is that if the patient has moderate disability, whatever age, I would recommend they start therapy on low doses of a levodopa-based therapy (no more than 300mg a day for the first two years). ■

- National Institute for Health and Clinical Excellence. Parkinson's Disease: Diagnosis and management in primary and secondary care. London: NICE 2006. Available at: www.nice.org.uk/nicemedia/pdf/cg035niceguideline.pdf (accessed November 2008).
- Miyasaki JM, Martin W, Suhowersky O, et al., Practice parameter: Initiation of treatment for parkinson's disease: An evidence-based review: Report of the quality standards subcommittee of the American Academy of Neurology, *Neurology*, 2002;58:11–17.
- Bhatia K, Brooks DJ, Burn DJ, et al., Updated guidelines for the management of parkinson's disease, *Hosp Med*, 2001;62:456–70.
- Olanow CW, Watts RL, Koller WC, An algorithm (decision tree) for the management of parkinson's disease (2001): Treatment guidelines, *Neurology*, 2001;56:S1–S88.
- Montgomery EB, Slowing parkinson's disease progression: Recent dopamine agonist trials, *Neurology*, 2004;62:343, author reply 343–5.
- Markham CH, Diamond SG, Evidence to support early levodopa therapy in parkinson disease, *Neurology*, 1981;31:125–31.
- Markham CH, Diamond SG, Long-term follow-up of early dopa treatment in parkinson's disease, *Ann Neurol*, 1986;19:365–72.
- Diamond SG, Markham CH, Hoehn MM, et al., Effect of age at onset on progression and mortality in parkinson's disease, *Neurology*, 1989;39:1187–90.
- Hoehn MM, The natural history of parkinson's disease in the pre-levodopa and post-levodopa eras, *Neurol Clin*, 1992;10:331–9.
- Reichmann H, Initiation of parkinson's disease treatment, *J Neurol*, 2008;255(Suppl. 5):57–9.
- Fahn S, Bressman SB, Should levodopa therapy for parkinsonism be started early or late? Evidence against early treatment, *Can J Neurol Sci*, 1984;11:200–205.
- Fahn S, Cohen G, The oxidant stress hypothesis in parkinson's disease: Evidence supporting it, *Ann Neurol*, 1992;32:804–12.
- Grosset D, Taurah L, Burn DJ, et al., A multicentre longitudinal observational study of changes in self reported health status in people with parkinson's disease left untreated at diagnosis, *J Neurol Neurosurg Psychiatry*, 2007;78:465–9.
- Lees A, Drugs for Parkinson's disease, *J Neurol Neurosurg Psychiatry*, 2002;73(6):607–10.
- Oertel WH, Wolters E, Sampaio C, et al., Pergolide versus levodopa monotherapy in early parkinson's disease patients: The pelmopet study, *Mov Disord*, 2006;21:343–53.
- Lees AJ, Katzenschlager R, Head J, Ben-Shlomo Y, Ten-year follow-up of three different initial treatments in de-novo pd: A randomized trial, *Neurology*, 2001;57:1687–94.
- Fahn S, Oakes D, Shoulson I, et al., Levodopa and the progression of parkinson's disease, *N Engl J Med*, 2004;351:2498–2508.
- Zanettini R, Antonini A, Gatto G, et al., Valvular heart disease and the use of dopamine agonists for parkinson's disease, *N Engl J Med*, 2007;356:39–46.
- Van Camp G, Flamez A, Cosyns B, et al., Treatment of parkinson's disease with pergolide and relation to restrictive valvular heart disease, *Lancet*, 2004;363:1179–83.
- Rezak M, Current pharmacotherapeutic treatment options in parkinson's disease, *Dis Mon*, 2007;53:214–22.
- Moller JC, Oertel WH, Koster J, et al., Long-term efficacy and safety of pramipexole in advanced parkinson's disease: Results from a european multicenter trial, *Mov Disord*, 2005;20:602–10.
- Pallhagen S, Heinonen E, Hagglund J, et al., Selegiline slows the progression of the symptoms of parkinson disease, *Neurology*, 2006;66:1200–1206.
- Olanow CW, Attempts to obtain neuroprotection in parkinson's disease, *Neurology*, 1997;49:S26–33.
- Olanow CW, Hauser R, Jankovic J, et al., A randomized, double-blind, placebo-controlled, delayed start study to assess rasagiline as a disease modifying therapy in parkinson's disease (the adagio study): Rationale, design, and baseline characteristics, *Mov Disord*, 2008.
- Parkinson Study Group, A controlled, randomized, delayed-start study of rasagiline in early parkinson disease, *Arch Neurol*, 2004;61:561–6.
- Fung VS, Herawati L, Wan Y, Quality of life in early parkinson's disease treated with levodopa/carbidopa/entacapone, *Mov Disord*, 2008.
- Parkinson Study Group, A randomized controlled trial comparing pramipexole with levodopa in early parkinson's disease: Design and methods of the CALM-PD study. Parkinson study group, *Clin Neuropharmacol*, 2000;23:34–44.
- Katzenschlager R, Head J, Schrag A, et al., Fourteen-year final report of the randomized pdrg-uk trial comparing three initial treatments in pd, *Neurology*, 2008;71:474–80.
- Lees A, Alternatives to levodopa in the initial treatment of early parkinson's disease, *Drugs Aging*, 2005;22:731–40.