A pragmatic personalised approach to treatment initiation in Parkinson disease

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Over the past 50 years, symptomatic therapy for Parkinson's disease has involved the use of levodopa, with the subsequent licencing of dopamine agonists and monoamine oxidase B inhibitors (MAOBIs). Dopaminergic therapy significantly improves motor performance, reducing bradykinesia, rigidity, and tremor, and enhancing both quality of life and life expectancy. For some years there has been a debate regarding the timing of the introduction and sequencing of these drugs. In a comprehensive Review,[1] de Bie and colleagues seek to clarify these issues; their recommendations are worthy of support, but also some nuancing.

The timing of treatment initiation has evolved from the traditional view of delaying until symptoms are sufficiently severe as to cause substantial impairment of daily function or quality of life, to a more contemporary view for earlier initiation.[2] The notion that the patient has impaired quality of life at diagnosis is not new,[3] and in part is reflected by the clinical features required to make the diagnosis. There are several factors that need to be considered in determining the most appropriate time for drug initiation in Parkinson's disease, including age, co-morbidities, occupation, severity of symptoms, likely adverse event profile, patient preference, and financial implications. Newly diagnosed patients form a heterogeneous group for whom the timing and nature of drug initiation should be a personalised process. The decision should be an informed joint decision between physician and patient, and one in which the latter has a critical role. The newly diagnosed patient should be provided with understandable background information on Parkinson's disease, written material, sources for patient contact groups, and general advice regarding exercise, diet, and sleep, etc. Their views should be sought on whether they would like to begin treatment with dopaminergic medication. So that they may make an informed decision, it is important to describe the nature of the therapy and to dispel some of the myths that are well covered in the Review.[1] The patient must understand there is no specific advantage to delaying treatment and understand the distinct advantages in terms of improving stiffness, pain, slowness, and tremor.

Some patients might want to delay treatment initiation, and the physician should respect this decision, although also use their judgement gently to advise the patient against this course of action if it is apparent that their symptoms are clinically significant. If the patient declines treatment, follow-up should be in 3 months to enable further discussion and clarification of the management strategy. For those who wish to begin drug therapy, as highlighted in the Review,[1] there are certain patient features that are relative contraindications (eg, use of anti-depressants and MAOBIs, although not absolute; a history of impulse control features; confusion and hallucinations; and the use of dopamine agonists). As a generalisation, elderly people are probably better started on levodopa irrespective of other considerations. Drug adherence is an important issue—Parkinson's disease patients prefer once daily medication to thrice daily,[4] and the mode of administration (once daily pramipexole or ropinirole tablets or rotigotine patch) should be discussed with those suitable for MAOBIs or dopamine agonists.

MAOBIs remain a good option for those who have generally mild Parkinson's disease—these are once a day drugs that are generally well tolerated. Patients will typically be back to baseline clinical disability in 9–12 months. Dopamine agonists provide effective and prolonged relief as once daily tablets or patches, and are well tolerated in most people if titrated slowly. As highlighted by de Bie and colleagues,[1] there are specific behavioural changes that can develop in the short or longer term that require regular discussion and exclusion at each visit. Pramipexole has been shown to be effective in improving depressive symptoms.[5] Levodopa is the most effective treatment for relieving motor disability and dopaminergic features, and all patients with Parkinson's disease will require this therapy at some point. It is usually initiated as a thrice daily oral preparation, although longer half-life

preparations are becoming available. The main limitation for levodopa is the emergence of wearing off and dyskinesia, generally at a rate of 10% per annum, although these complications can appear in a substantial proportion within 1 year at high doses.[6] Female and young-onset (<45 years) patients with Parkinson's disease are particularly susceptible to the development of these motor complications. Dose and duration of levodopa are also likely to be relevant risk factors for motor complications.[7,8] Dyskinesias when they first appear are usually non-troublesome, but later begin to complicate therapy leading to complex dose fractionation schedules, inadequate control, and the consideration of parentral medical therapy (apomorphine or Duodopa infusions) or surgery (deep brain stimulation).

Many physicians take a pragmatic approach with initiation of once daily MAOBIs or dopamine agonists in suitable patients, adding the alternate when symptoms require. This approach allows the patient to take medication in a simple and effective manner. Levodopa is then often added and patients can be well controlled for several years on this combination with relatively low dose levodopa. Such a strategy requires regular follow up and both the patient and physician being alert to potential complications. MAOBIs and dopamine agonists are licensed as adjunctive therapy to levodopa, allowing a reverse strategy of initiating levodopa (eg, 100mg thrice daily), and subsequently adding a MAOBI or dopamine agonist as required.

There is no convincing evidence that any of the above drugs either accelerate or slow neurodegeneration in Parkinson's disease. For the most part, they do not address the non-motor aspects of Parkinson's disease.[9] These aspects remain the two most important areas of unmet need in Parkinson's disease—development of interventions to slow or stop progression, and treatment of the non-motor features that dominate the later period of Parkinson's disease and result in severe impairment of quality of life and the need for nursing home care.

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