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Drugs for Parkinson's disease: Levodopa is still the gold standard

Parkinson's disease (PD) is a global affliction which occurs in all ethnic groups and socioeconomic classes, with estimated incidences ranging from 16–19 per 100,000 people per year and crude prevalence rates as high as 160 per 100,000 people per year (WHO/WFN 2004). It was recently estimated that there were over 1 million PD patients in Western Europe and the USA in 2005, and this number was expected to double by 2030 with accompanying dramatic rises in the numbers in developing countries (Dorsey et al 2007). Patients have both disabling motor symptoms and distressing non-motor features like depression and anxiety. Pharmacotherapy for PD has been available since the 1950s in the form of anticholinergic drugs, which are of limited efficacy and carry a high burden of gastrointestinal and neuropsychiatric side effects (Katzenschlager 2007). More effective treatment arrived in the early 1960s with the first clinical trials of levodopa (Birkmayer and Horneykiewicz 1961), and there are now many different formulations and variants on the levodopa theme (Lundqvist 2007) as well as a plethora of selective dopamine agonists of the ergoline and nonergoline type (Pinder 2007). The only exception to the dopamine theme has been selegiline, an irreversible inhibitor of monoamine oxidase type B (MAO-B), which finds use in both PD and major depressive disorder (Lee and Chen 2007).

In this issue of Neuropsychiatric Disease and Treatment, a number of issues concerning the drug treatment of PD are reviewed. Nayak and Henchcliffe (2008) discuss the merits of the newly approved MAO-B inhibitor, rasagiline, which shares with selegiline a potential for neuroprotective effects but does lack the latter's amphetamine and methamphetamine metabolites. Time will tell whether rasagiline is a worthy addition to the PD armamentarium, but early clinical results are very promising. Thus, rasagiline as monotherapy has proved effective, safe and well tolerated in early PD, while large trials in advanced PD suggest that when given adjunctively with levodopa it can significantly decrease 'off' time. Many PD patients suffer 'on' and 'off' periods during ongoing dopaminergic pharmacotherapy, when their motor symptoms either respond or return, the 'off' being attributed to the deep troughs in delivery of levodopa to the brain arising from the short plasma half-life of conventional levodopa formulations. Indeed the 'off' time with its associated motor complications has led to both physician caution and patient reluctance to use levodopa, and its various combinations with dopa decarboxylase inhibitors (DDCI), as the initial treatment for newly diagnosed early PD (Antonini et al 2008; Brooks 2008). Dopamine agonists have become, almost by default, the drugs of choice for front-line treatment of early PD. However, a number of large, well controlled, long-term clinical trials have consistently demonstrated the substantial superiority of the symptomatic control offered by conventional levodopa formulations compared with dopamine agonists. Levodopa remains the gold standard of PD therapy (Lundqvist 2007; Antonini et al 2008; Brooks 2008).

Levodopa is metabolized via two peripheral pathways before it can reach the brain, one to dopamine involving the enzyme dopa decarboxylase (DDC) and the other to 3-O-methyldopa involving another enzyme catechol-O-methyltransferase (COMT). Inhibitors of DDC such as carbidopa have long been available and were introduced many years ago into PD treatment in combination with levodopa (Antonini et al 2008; Brooks 2008). COMT inhibition is a more recent target, and two agents have been introduced, tolcapone (Antonini et al 2008) and entacapone (Brooks 2008), as add-on

therapies to conventional levodopa and levodopa/carbidopa combinations. Both agents seem to significantly increase 'on' time in PD patients who are experiencing reemergence of motor symptoms, they afford greater functionality than conventional levodopa and combinations alone, and they are generally well tolerated. It is suggested that patients who experience motor fluctuations despite ongoing treatment with conventional levodopa, dopamine agonists or MAO-B inhibitors should receive a trial with a COMT inhibitor and certainly before levodopa infusion or neurosurgery are considered as last resort strategies.

Many PD patients experience neuropsychiatric illnesses such as anxiety and depression. Depression is particularly difficult to diagnose in PD patients because of the overlap of many of the cognitive, motor and somatic symptoms (Looi et al 2005; Frisina 2008). PD patients, even when suffering from affective disturbances, are more likely to complain about their burden of motor disability. Nevertheless, depression seems to occur in about 30%–40% of PD patients, of whom only one-fifth receive any form of antidepressant treatment. In this issue, Frisina and her colleagues (2008) discuss the health risks, etiology, and treatment options for depression in PD patients. It seems that conventional treatments are effective, and they recommend a multidisciplinary approach combining pharmacotherapy, psychotherapy, and psychoeducation.

PD is a complex disease but there are many therapeutic possibilities to relieve the burden of both the motor and some of the nonmotor symptoms. All of the current pharmacotherapies are symptomatic, and only neurosurgery goes to the heart of the neuropathology. However, most PD patients can be reliably maintained on a judiciously tailored and regularly monitored set of medications. Advances in our understanding of the pathogenesis of the disease, particularly the rapidly expanding field of PD genetics, may lead to more specific and potentially disease modifying modalities in the future. Whatever, on the basis of current and extensive evidence in clinical trials and despite its many shortcomings, levodopa in its several forms remains the gold standard of efficacy and effectiveness in PD therapeutics.

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