

## **The treatment of Parkinson's disease**

Parkinson's disease (PD) is a chronic and progressive movement disorder that is characterized by motor impairments including limb tremors, muscle rigidity, bradykinesia, akinesia and postural instability. These motor deficits are primarily regarded to arise from a progressive degeneration of dopamine neurons and the consequent loss of DA in the motor circuits of the brain.

Currently, no treatments in clinical use prevent PD progression. Since the 1960's, treatments have been wholly symptomatic, involving a range of approaches to restore or replace the dopamine that is lost. Levodopa (L-DOPA) is currently the gold standard for PD as it is the most effective therapy in treating the symptoms of the disease. However, its effectiveness is limited as long term use over 5-10 years is associated with the development of motor complications, known as L-DOPA-induced dyskinesias, in up to 80% of patients. As a result there are a number of possible alternative therapies that can be used as an adjunct to L-DOPA or as a monotherapy. We outline a number of these below.

### **Dopamine agonists**

The next most effective class of drugs following L-DOPA are the dopamine agonists. These drugs exert their therapeutic effect by directly activating dopamine receptors, bypassing the presynaptic synthesis of dopamine. Some dopamine receptor agonists used in the treatment of PD include bromocriptine, ropinirole, pramipexole and cabergoline, and have been shown to improve parkinsonian symptoms such as bradykinesia, rigor and tremor. Each can be used as monotherapy in mild, early PD or as an additional drug for moderate to severe disease. Dopamine agonists are longer-acting than L-DOPA and can be taken once daily. However, they are associated with more nonmotor side effects such as nausea and vomiting, hallucinations, low blood pressure, edema, and impulse control disorders.

### **Monoamine and COMT inhibitors**

Monoamine oxidase (MAO) is an enzyme that exists in two forms, MAO-A and MAO-B, and plays a role in the metabolic breakdown of dopamine. MAO inhibitors such as rasagiline and selegiline have been used as monotherapies in patients with early PD and as adjunctive therapies in patients receiving treatment with L-DOPA by smoothing out L-DOPA related motor fluctuations and prolonging dopamine-induced responses. Furthermore, a study conducted using the MPTP mouse model of PD demonstrated that a continuous administration of rasagiline following MPTP lesion restored the severe reduction in dopaminergic cell count, suggesting that rasagiline may have therapeutic use in stimulating the production of new dopamine cells.

Catechol O-methyltransferase (COMT) inhibitors, such as tolcapone and entacapone, are used in the treatment of PD due to the fact that, in the presence of carbidopa, a significant quantity of orally administered L-DOPA is metabolised by COMT in the gastrointestinal tract. This results in a measurable reduction in the amount of levodopa that will ultimately enter the brain.

### **Adenosine A2A antagonists**

Several therapies that target non-dopamine systems have been explored in the treatment of PD. Adenosine A2A receptor antagonists have attracted interest as potential symptomatic drugs for PD as they facilitate the release of  $\gamma$ -aminobutyric acid (GABA), thereby reducing neuronal overactivity and restoring balance between the output pathways of the motor circuit. Based on encouraging rodent studies, the adenosine A2A receptor antagonist istradefylline has been explored in a number of human clinical trials. Many of these clinical trials have demonstrated a significant reduction in daily “off” time in patients with advanced PD. There is also exciting evidence that higher intake of caffeine, a nonselective adenosine antagonist, has been shown in a number of studies to have a protective effect on development of PD in diverse populations.

### **Deep Brain Stimulation**

Deep brain stimulation (DBS) has developed during the past 20 years as a remarkable treatment option for several different disorders, including PD, and involves the surgical implantation of a device that sends electrical impulses to specific regions of the brain. Advances in technology and surgical techniques have essentially replaced the early ablative procedures in the pre-levodopa era of treatment. In the last decade, numerous studies have confirmed the major impact of this procedure on the symptoms of PD, with DBS improving “off” time by 5-6 hours, allowing a substantial reduction in medications in many patients or in elimination of dyskinesias entirely. DBS is now the preferred surgical procedure to treat advanced PS and is more effective at treating motor disability and improving quality of life in PD patients with motor fluctuations than best medical therapy. Whilst the exact mechanisms of DBS is not fully understood, the success of these procedures has led to application of these techniques to multiple other conditions such as epilepsy, headache, restless legs syndrome, and Alzheimer’s disease.

### **Future Therapeutics: Gene Therapy**

Current translational research is focused on the development of novel disease-modifying therapies, including those utilising gene therapeutic approaches to either compensate for the loss of dopamine or to protect the dopamine neurons. The earliest attempts at PD gene therapy utilised a variety of cell and tissue transplants, which met with some success as a subset of patients experienced palliative relief for many years. However, one of the biggest obstacles for implant therapy is the acquisition of tissue. The arrival of viral vector technology revolutionized the gene therapy field as it provided a method for the efficient delivery of genetic material without the need for human transplant tissue or cells. Adeno-associated virus (AAV) has been the most commonly utilized vector thus far due to its ease of use and safety profile. A number of potential gene therapy targets such as tyrosine hydroxylase, glutamic acid decarboxylase (GAD), glial-derived neurotrophic factor (GDNF), and neurturin have been investigated, with many already in clinical trials.

**Conclusion**

Parkinson's disease is the second most common neurodegenerative disease following Alzheimer's. As the life expectancy in industrialized countries increases, the economic burden of PD continues to rise, resulting in a dramatic need for effective treatments. Despite numerous advances in the medical and surgical treatment of PD, no treatment yet exists that halts or reverses the disease. Therefore the quest for novel treatments, and ultimately a cure, continues.