State-of-the-art Therapeutic Strategies in Parkinson's Disease

a report by

Paola Piccini *and* **Nicola Pavese**

Medical Research Council Clinical Sciences Centre and Division of Neuroscience,
Faculty of Medicine, Imperial College, Hammersmith Hospital

Parkinson's disease (PD) is a chronic, progressive neuro-degenerative disorder, characterised by rest tremor, bradykinesia, rigidity and postural instability.

The incidence of the disease increases with age, with the majority of patients experiencing onset after the age of 50. A significant number of patients, however, experience onset of symptoms at a younger age and in 5–7% of cases, the onset of symptoms occurs before the age of 40.[1]

The cause of the disease is still unknown, but growing evidence suggests that it may be due to a combination of environmental and genetic factors. The relative contribution of each factor might vary from one individual to another.

The clinical features of PD result from a relatively selective neuronal loss primarily involving the pigmented dopamine-producing neurons, particularly within the substantia nigra pars compacta (SNc). Neuronal loss in the SNc produces a marked deficit of dopamine content in the striatum, particularly in the dorsolateral region of the putamen, and a consequent disruption of the extensive basal ganglia circuitry, including thalamocortical and brain stem motor systems. In fact, in normal condition, the putamen receives inputs from the motor and somatosensory cortical areas and communicates with the internal segment of the globus pallidus (GPi) and the pars reticulata of the substantia nigra (SNr) through a direct inhibitory pathway and a multisynaptic indirect pathway via the pars externa of the globus pallidus (GPe) and the subthalamic nucleus (STN). Gamma-aminobutyric acid (GABA)-ergic neurons in the direct pathway, which mainly express D1 dopamine receptors and co-express the peptides substance P and dynorphin, establish a monosynaptic, inhibitory connection from the putamen to GPi/SNr. On the other hand, striatal neurons in the indirect pathway, which express mainly D2 dopamine receptors and the peptide enkephalin, send their GABAergic axons to the GPe, which in turn connects with the STN. By using glutamic acid as a neurotransmitter, the STN exerts an excitatory effect on the GPi/SNr and other brain stem nuclei connected with it.

As a result of this complex circuit, the inhibitory output from the GPi/SNr directed to the ventro-lateral thalamic nucleus and the pedunculo-pontine tegmental nucleus is effectively under a dual control mechanism, with the direct pathway reducing the neuronal firing in the GPi/SNr and the indirect pathway increasing the inhibition from the GPi/SNr onto their projection nucleus.

Dopamine is thought to modulate striatal activity, mainly by inhibiting the indirect and facilitating the direct pathways. In PD, dopamine deficiency leads to increased inhibitory activity from the putamen onto the GPe, with disinhibition of the STN whose hyperactivity for its glutamatergic action produces excessive excitation of the GPi/SNr neurons, which over-inhibit the thalamocortical and brain stem motor centres. The resulting abnormal increment in the inhibitory output activity of basal ganglia produces poverty and slowness of movement.[2] Indeed, surgery of the STN or GPi in PD patients may markedly improve all motor features and restore thalamocortical activity. In addition, levodopa (L-dopa) and apomorphine decrease neuronal firing in STN and GPi recorded during surgery.

Current therapeutic strategies for PD largely reflect the attempts to correct the pathophysiological features of the basal ganglia previously described.

Three different aspects can be considered:

- Symptomatic treatments – this approach simply aims to improve signs and symptoms of the disease by correcting the neurotransmitter imbalance within the basal ganglia circuitry. Symptomatic treatments include a variety of medications that remain the milestone of PD treatment and several surgical procedures, such as pallidotomy, thalamotomy and pallidal and subthalamic stimulation, which are reserved for more advanced stages of the disease.

- Neuroprotective treatments – recent advances in neurosciences have provided the rationale to test several putative neuroprotective agents that might slow down the progression of the disease. Results from the first clinical trials were being reported at the time of press.

- Restorative treatments – these treatments are still in an experimental phase and aim to reverse some or all of the biochemical abnormalities and the restoration of normal neuronal function to damaged cells. They include striatal implantation of foetal midbrain tissue or stem-cell-derived dopamine neurons to replace the missing dopamine cells, gene-based therapies and use of nervous system growth factors.

Symptomatic Treatments

Drugs Used in PD

Several types of medication are commonly used to treat PD and they mainly aim at either restoring dopaminergic tone or manipulating non-dopaminergic systems (i.e. blocking excessive glutamatergic or cholinergic activity). *Table 1* provides an extensive review of available and emerging drugs.

L-dopa, the amino acid precursor of dopamine, in combination with an extracerebral dopa–decarboxylase inhibitor, remains the mainstay of treatment of PD. The drug acts mainly by replenishing depleted striatal dopamine and improves bradykinesia and rigidity more than tremor. Although extremely effective in reducing symptoms, L-dopa does not slow the progression of the disease, and long-term treatment with the drug is associated with increased incidence of abnormal involuntary movements (L-dopa-induced dyskinesias) and reduction of its anti-parkinsonian effects. Dyskinesias can affect over 75% of patients within five years of starting treatment with L-dopa. Changes in the motor response to L-dopa, also called motor fluctuations, are reported by patients as a shortening of the time for which the drug is effective (wearing-off phenomenon) or a sudden unpredictable lack of efficacy, 'off' periods, during a well-established 'on' condition (on/off fluctuations). The cause of motor complications as a consequence of long-term L-dopa therapy probably has several mechanisms and includes the pulsatile nature of L-dopa administration, the severity of nigral degeneration when the therapy is started and the total dose and duration of L-dopa therapy. To avoid fluctuations in plasma L-dopa levels, sustained-release L-dopa preparations have been developed. These preparations have effectively improved the clinical management of PD patients, particularly for reducing

Table 1: Available and Emerging Drugs for PD

Enhancement of Dopaminergic Tone	
Increased synthesis of dopamine	L-dopa
Increased dopamine release	Amantadine
	Selegiline
	Nicotine
Dopamine re-uptake inhibition	Amantadine
	Selegiline
	Brasofensine
MAO-B inhibition	Selegiline
	Lazabemide
	Resagiline
COMT inhibition	Entacapone
	Tolcapone
Dopamine agonists	Ergot derivates
	Non-ergot derivates

Manipulation of Non-dopaminergic Systems	
Acetylcholine	Antimuscarinics
	Nicotine
	SIB-1508Y
Glutamate	NMDA antagonists (budipina, remacemide)
GABA	Zolpidem
	Gabapentin
Noradrenaline	L-DOPS
	MAO-A inhibitors (moclobemide)
	Alpha2 antagonists (idazoxan, efaroxan)
Adenosine	A_2A antagonists

COMT = catechol-O-metyltransferase, GABA = gamma-aminobutyric acid, L-dopa = levodopa, L-DOPS = L-threo-3,4-dihydroxyphenylserine, MAO = monoamine oxidase, NMDA = N-methyl-D-aspartate, PD = Parkinson's disease.

nocturnal disability and early morning 'off'; however, a five-year randomised multicentre study has failed to demonstrate significant differences between immediate-release and controlled-release carbidopa/L-dopa regarding incidence of motor fluctuations or dyskinesia.[3] This may be partly attributed to the relatively low doses of L-dopa used throughout the five-year study.

An alternative strategy has been to add preparations that increase the availability of synaptic dopamine by blocking enzymatic systems involved in dopamine degradation to conventional L-dopa therapy. Selegiline is a selective inhibitor of monoamine oxidase B that has been used in the past in early onset of disease to increase concentration of existing dopamine and in combination with L-dopa for maintenance. There is some evidence that this agent might also have a neuroprotective effect. In the last five years, however, after the results of a long-term study suggesting an increased risk of death in people who had taken L-dopa combined with selegiline,[4] this agent is more consciously used. Resegiline, another monoamine oxidase B inhibitor, is showing promise in trials.

Table 2: Pharmacological Characteristics of Dopamine Agonists

| Dopamine Agonists | Dopamine Receptors | | | | |
| | D1-like | | | D2-like | |
	D1	D2	D3	D4	D5
Ergot Derivates					
Bromocriptine	-	+	+++	++	+
Cabergoline	+	?	+++	+++	?
Lisuride	+	?	+++	+++	?
Pergolide	+	+	+++	+++	?
Non-ergot Derivates					
Apomorphine	+	+	+++	+++	++
Ropinirole	=	=	++	+++	+
Pramipexole	=	?	++	+++	++

+/+++ = agonistic activity, - = antagonistic activity, = = no activity.

A more effective method of blocking dopamine metabolism involves the inhibition of the enzyme catechol-O-metyltransferase (COMT). Two different medications belong to this group: entacapone[5] and tolcapone. They are both efficacious, and sometimes a reduction of concomitant L-dopa may become necessary to avoid dyskinesias. Tolcapone, however, may cause severe hepatotoxicity and is now unavailable in Europe. Entacapone does not seem to have the same effect on the liver. Symptoms of liver dysfunction must still be carefully looked out for.

Dopamine agonists are analogues of dopamine that directly stimulate the striatal dopaminergic receptors. Characteristics of principal dopamine agonists are shown in *Table 2*.

Most dopamine agonists have comparable clinical benefits and can be used alone, as monotherapy or as adjunctive therapy with L-dopa. The spectrum of side effects is also comparable with those of L-dopa, although they have a greater tendency to produce neuropsychiatric effects such as hallucinations, particularly in older patients.

Some dopamine agonists (i.e. bromocriptine and ropinirole) produce less dyskinesia if given to patients never treated with other anti-parkinsonian medications;[6–8] therefore, many clinicians prefer to use them as monotherapy (particularly with younger patients) – although this remains to be confirmed. The neuroprotective effects of dopamine agonists will be discussed separately.

The mechanism of action of amantadine, an antiviral agent that has shown anti-parkinsonian activity, is still controversial. It is thought to stimulate the release of dopamine, but its predominant pharmacological effect is probably blocking N-methyl-D-aspartate (NMDA) receptors. This might also explain its antidyskinetic effect. Amantadine usually loses its effectiveness after approximately six months and may cause lower extremity oedema and livedo reticularis. Psychiatric complications may also occur.

Anticholinergic drugs were the first drugs used for PD, but dopamine agonists have largely replaced them. They correct the relative central cholinergic excess resulting from dopamine deficiency and are generally used against tremor in the early stages, but they are not effective against bradykinesia and may increase the risk of dementia in later stages.

Better understanding of the basal ganglia pharmacology has highlighted the possibility of manipulating the non–dopaminergic transmitter system to obtain a better control of parkinsonian symptoms. Several agents have been identified as potential therapeutic targets in PD, but they are still in an experimental phase. They include glutamate blockers, adenosine A2A receptor antagonists, 5-hydroxytryptamine (HT) (serotonin) transmission modulators, nicotine, L-threo-3,4-dihydroxyphenylserine (L-DOPS) and GABA blockers such as zolpidem and gabapentin.

Symptomatic Surgical Therapy

The attempt to correct the relative central overactivity of some basal ganglia nuclei is also the main goal of several surgical treatments available for PD. Ablation procedures (pallidotomy, thalamotomy and subthalamotomy) have now been largely replaced with deep brain stimulation (DBS), which permits benefits to be obtained without the need to make destructive brain lesions. Stereotaxic thalatomy or DBS of ventralis intermedius (VIM) nucleus should be considered in patients with predominant tremor who are resistant to conventional drug therapy. Akinesia remains unaltered by these treatments. Medial pallidotomy and GPi stimulation are effective in ameliorating tremor and L-dopa-induced dyskinesias, and effects on bradykinesia are inconsistent. Subthalamic nucleus stimulation has shown the most improvement in bradykinesia and may ultimately prove to be the site of choice for stereotaxic lesioning.[9]

Neuroprotective Treatments

Neuroprotective treatments is currently the most challenging field in PD research. It aims at the protection of neurons from cell death induced by the various biochemical abnormalities associated with aetiology and pathogenesis and would result in a slower progression of the natural course of the disease.

Several agents have been, and are being, tested as putative neuroprotective drugs. They include anti-apoptotic drugs (i.e. CEP 1347 and CTCT 346), antioxidants, lazaroids, bioenergetic agents (such as coenzyme Q10), antiglutamatergic agents (e.g. riluzole) and dopamine agonists.[10]

Currently, dopamine agonists appear to be the most promising. Extensive *in vitro* and animal studies suggest that dopamine agonists may exert a neuroprotective effect via both dopamine receptor mediated and non-dopamine-receptor-mediated mechanisms.[11,12] In addition, the first trials comparing the rate of progression in patients treated *de novo* with either dopamine agonists or L-dopa have now been reported. Whone et al.[13] have recently reported that the administration of ropinirole, compared with L-dopa, in *de novo* PD patients was associated with a relative 30% slowing of the progression of disease as evidenced by serial putamen [18]-fluorodopa uptake

clinical results in most, but not all, studies.[18] Synaptic dopamine release from embryonic nigral transplants in the striatum of a patient with PD who had received a transplant in the right putamen 10 years earlier has recently been evaluated. [11C]-raclopride PET was used to measure dopamine D2 receptor occupancy by the endogenous transmitter released after acute stimulation with methamphetamine. It was demonstrated that grafts had restored both basal and drug-induced dopamine release to normal levels. This was associated with sustained, marked clinical benefit and normalised levels of dopamine storage in the grafted putamen.[19]

The first prospective randomised double-blind sham-placebo controlled trial of dopaminergic transplants has failed to show an improvement of the primary end-point, quality of life—although significant clinical benefits were seen in patients younger than 60 years of age. In addition, 15% of transplanted patients

Extensive **in vitro** *and animal studies suggest that dopamine agonists may exert a neuroprotective effect via both dopamine receptor mediated and non-dopamine-receptor-mediated mechanisms.*

measurements with positron emission tomography (PET) performed two years apart.

Similarly, the Parkinson Study group,[14] which has used [123]-I-ß-CIT single photon emission computed tomography (SPECT) to compare the relative rates of loss of terminal dopamine transporter (DAP), has reported that patients initially treated with pramipexole display a 40% reduction in the rate of loss of striatal [123]-I-ß-CIT uptake compared with those treated initially with L-dopa over a four-year period. In conclusion, both studies support the notion that treatment with dopamine agonists slows the rate of loss of striatal dopamine terminal function relatively by 30–40% in the early stages of PD compared with L-dopa therapy.

Restorative Treatments

Neural Transplantation

In animal models, implanted foetal nigral neurons survive, re-innervate the striatum, produce dopa-mine and improve motor features in rodent and non-human primate models of PD.[15–17] Based on this evidence, small open clinical trials of dopaminergic transplants were initiated in PD with generally good

developed inexplicable severe dyskinesias, even in the absence of L-dopa.[20] The mechanism of these dyskinesias is still being debated.[21] These findings suggest that the procedure, although promising, still needs refinements and ameliorations before it can become a viable therapy for PD. In the meantime, research continues for alternative sources of dopaminergic tissue such as xenografts and stem cells.

Trophic Factors

Trophic factors appear to have clinical potential in the treatment of PD and other neurodegenerative diseases. Among these, the glial-derived neurotrophic factor (GDNF) seems to have the greatest capacity to protect or rescue dopaminergic neurons in both tissue culture and *in vivo* models of PD. In a recent study, GDNF was delivered directly into the putamen of five PD patients. After one year, a 39% improvement in the off-medication motor sub-score of the Unified Parkinson's Disease Rating Scale (UPDRS) was observed. Medication-induced dyskinesias were reduced by 64% and were not observed off medication during chronic GDNF delivery. Serial [18]-fluorodopa PET scans showed a significant 28% increase in putamen dopamine storage after 18 months, suggesting a direct effect of GDNF on dopamine function.[22] ■

References

1. Koller W C, Lang A E, "Age of onset of Parkinson's disease", Can J Neurol Sci (1987);14(2): pp. 179–180.

2. Albin R L, Young A B, Penney J B, "The functional anatomy of basal ganglia disorders", Trends Neurosci (1989);12(10): pp. 366–375.

3. Block G, Liss C, Reines S, Irr J, Nibbelink D, "Comparison of immediate-release and controlled release carbidopa/levodopa in Parkinson's disease. A multicenter 5-year study. The CR First Study Group", Eur Neurol (1997);37(1): pp. 23–27.

4. Churchyard A, Mathias C J, Boonkongchuen P, Lees A J, "Autonomic effects of selegiline: possible cardiovascular toxicity in Parkinson's disease", J Neurol Neurosurg Psychiatry, (1997);63(2): pp. 228–234.

5. Piccini P, Brooks D J, Korpela K et al., "The catechol-O-methyltransferase (COMT) inhibitor entacapone enhances the pharmacokinetic and clinical response to Sinemet CR in Parkinson's disease", J Neurol Neurosurg Psychiatry (2000);68(5): pp. 589–594.

6. Rascol A, Guiraud B, Montastruc J L, David J, Clanet M, "Long-term treatment of Parkinson's disease with bromocriptine", J Neurol Neurosurg Psychiatry (1979);42(2): pp. 143–150.

7. Lees A J, Stern G M, "Sustained bromocriptine therapy in previously untreated patients with Parkinson's disease", J Neurol Neurosurg Psychiatry (1981);44(11): pp. 1,020–1,023.

8. Rascol O, Brooks D J, Korczyn A D 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 StudyGroup", N Engl J Med (2000);342(20): pp. 1,484–1,491.

9. Hammerstad J, Hogarth P, "Parkinson's disease: surgical options", Curr Neurol Neurosci Rep (2001);1(4): pp. 313–319.

10. Djaldetti R, Melamed E, "New drugs in the future treatment of Parkinson's disease", J Neurol (2002);249(suppl. 2:II): pp. 30–35.

11. Olanow C W, Jenner P, Brooks D, "Dopamine agonists and neuroprotection in Parkinson's disease", Ann Neurol (1998);44(3 suppl. 1): pp. S167–S174.

12. Schapira A H, "Dopamine agonists and neuroprotection in Parkinson's disease", Eur J Neurol (2002);9 (suppl. 3): pp. 7–14.

13. Whone A L, Watts R L, Stoessl A J et al., REAL-PET Study Group, "Slower progression of Parkinson's disease with ropinirole versus levodopa: The REAL-PET study", Ann Neurol (2003);54(1): pp. 93–101.

14. Parkinson Study Group, "Dopamine transporter brain imaging to assess the effects of pramipexole vs levodopa on Parkinson disease progression", JAMA (2002);287(13): pp. 1,653–1,661.

15. Bjorklund A, Stenevi U, "Reconstruction of the nigrostriatal dopamine pathway by intracerebral nigral transplants", Brain Res (1979);30;177(3): pp. 555–560.

16. Dunnett S B, Isacson O, Sirinathsinghji D J, Clarke D J, Bjorklund A, "Striatal grafts in rats with unilateral neostriatal lesions—III. Recovery from dopamine-dependent motor asymmetry and deficits in skilled pawreaching", Neurosc (1988);24(3): pp. 813–820.

17. Bankiewicz K S, Plunkett R J, Jacobowitz D M et al., "The effect of fetal mesencephalon implants on primate MPTP-induced parkinsonism. Histochemical and behavioral studies", J Neurosurg (1990);72(2): pp. 231–244.

18. Polgar S, Morris M E, Reilly S, Bilney B, Sanberg P R, "Reconstructive neurosurgery for Parkinson's disease: a systematic review and preliminary meta-analysis", Brain Res Bull (2003);15;60(1-2): pp. 1–24.

19. Piccini P, Brooks D J, Bjorklund A et al., "Dopamine release from nigral transplants visualized in vivo in a Parkinson's patient", Nat Neurosci (1999);2(12): pp. 1,137–1,140.

20. Freed C R, Greene P E, Breeze R E et al., "Transplantation of embryonic dopamine neurons for severe Parkinson's disease", N Engl J Med (2001);8;344(10): pp. 710–719.

21. Piccini P, "Dyskinesias after transplantation in Parkinson's disease", Lancet Neurol (December 2002);1(8): p. 472.

22. Gill S S, Patel N K, Hotton G R et al., "Direct brain infusion of glial cell line-derived neurotrophic factor in Parkinson disease", Nat Med (2003);9(5): pp. 589–595.