# CONTROVERSIES IN PARKINSON'S DISEASE

*The treatment of Parkinson's disease has always been controversial.*

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Parkinson's disease (PD), one of the commonest neurodegenerative disorders to affect mankind, has always been vexed by a number of controversies regarding treatment. To a certain extent, research in recent years has shed some light on these matters.

## IS DOPAMINE BAD?

There is a long history of concern that dopamine itself may be neurotoxic, but this has been largely put to rest, and in fact one interpretation of the recent ELLDOPA study is that dopamine may be neuroprotective.[1] In this study patients with early-onset PD were placed on either placebo or various strengths of dopamine, ranging from 150 mg to 600 mg daily. To everybody's surprise, at the end of the study when the drugs were withdrawn, the group of 600 mg daily did not deteriorate to baseline and the group of placebo remained significantly worse. The most parsimonious interpretation of this is simply that the wash-out period was not long enough and that dopamine has effects which last much longer than 2 weeks. However, if dopamine were to be newly released on the market, it might well be hailed as the newest and the best form of neuroprotection available: there is certainly no evidence that dopamine adversely affects disease progression.[2]

## WHAT IS THE TREATMENT OF CHOICE FOR NEWLY DIAGNOSED PD?

### Overview

Frequently, algorithms and practice guidelines suggest that the drugs of first choice in the treatment of PD should be dopamine agonists. The reasoning underlying this recommendation is the concern that early use of dopamine is associated with the development of fluctuations and dyskinesias. Dopamine agonists available in South Africa include the following: bromocriptine (Parlodel), pergolide (Permax) and newer agonists such as ropinerole (Requip) and pramipexole (Pexola).

To some extent the background history of the recommendations reflects the ease of developing an animal model induced by the chemical MPTP and the rapid (within weeks) development of dyskinesias and fluctuations in these models. Another piece of the jigsaw puzzle is the theory which, although likely to be correct, remains unproven, namely that either constant levels of dopamine or other dopamine receptor-stimulating agents are more likely to be of benefit to patients than intermittent dopaminergic stimulation.

The fundamental underpinning of problems such as fluctuations and dyskinesias in PD reflects the progression of illness and relentless loss of dopaminergic neurones and, in particular, loss of functional storage capacity of these neurones. In the extreme case, in the virtual absence of any dopaminergic neurones, normal basal ganglia function becomes entirely dependent on dopamine from an external source. By contrast, early on in the disease, with a relatively large number of surviving neurones and relatively good storage capacity, patients will often have virtually normal motor function throughout the day. With progression of disease and progressive loss of storage capacity, there is increasing evidence of the short half-life of dopamine, and patients will start to experience the phenomenon of 'wearing off', where their dose clearly lasts a shorter time than it had before. Subsequently many of these patients will go on to develop clear motor fluctuations. Fluctuations largely consist of changes in the motor state, and hence are often referred to as on and off phenomena, reflecting good and impaired motor function respectively.

### What are dyskinesias and are they important?

Dyskinesias are involuntary movements, often of a choreiform nature. They are frequently complex, particularly in their relationship with the level of dopamine in the basal ganglia. Common patterns include dyskinesias restricted only to the off-state, dyskinesias restricted only to the on-

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state (peak-dose dyskinesias) and dyskinesias which occur as the clinical state moves from off to on and again from on to off. Treatment of dyskinesias can be difficult and taxing for both patient and neurologist.

In the ideal situation, constant stimulation of dopaminergic receptors may result in less fluctuation and fewer dyskinesias. Indeed, a number of trials have clearly shown that using dopamine agonists delays the development of dyskinesias.[4-6] Delay in development of dyskinesias is the major reason that dopamine agonists are often held to be the agent of first choice in the patient with newly diagnosed PD.

An important question is, 'how common are dyskinesias?' A review of the current literature indicated that slightly less than 40% of patients will develop dyskinesias after 4 - 6 years of dopamine treatment.[7] A community study based at the Mayo Clinic has shown that dyskinesias are relatively uncommon in the elderly, with an incidence of 16%. Compared with this group, patients who had PD that started between the ages of 40 and 59 years had an incidence of dyskinesias of 50%.[8] The authors of this study concluded 'these data suggest that troublesome dyskinesias are not a high risk among PD patients in the community, and many may be completely spared'.[8] It is important to note that although figures vary, the usual age of onset for PD is in the early sixties, and thus the majority of PD patients have substantially less risk for developing dyskinesias than do young-onset PD patients.

An additional question is related to the severity of dyskinesias. Many studies have reported a high incidence of dyskinesias, but these are frequently relatively trivial for the patient, and can be improved by minor adjustments of medication. Reviewing the quality of life in early PD, motor complications (fluctuation and dyskinesias) were not important in the first 4 years of treating PD.[9]

## How much dopamine agonist do you need to prevent dyskinesias developing?

It is important to realise that the dose of dopamine agonist is not trivial: daily doses of 16.5 mg of ropinerole were given in the study of Rascol *et al.*,[5] 12 mg daily in the REAL-PET study,[6] and 2.8 mg daily of pramipexole in the CALM-PD study.[4]

## Which is better – dopamine or dopamine agonists?

In general, dopamine agonists are likely to be less effective, have a worse side-effect profile and are expensive.[4,5] What is critical about guidelines suggesting that dopamine agonists be the first line of treatment for PD is that all studies have shown that the beneficial effect on motor function of dopamine agonists is significantly worse than that of dopamine itself: therefore in the REAL-PET study, the mean UPDRS (a rating scale for PD function) score change from baseline showed a significantly greater improvement with levodopa compared with the agonist: improvement of 5.6 versus a decline of 0.7 (CI 3.5 - 9.1).[6] Similarly, in the CALM-PD study motor UPDRS scores had a difference of 5 ($p < 0.001$).[4]

One reason for patients to have developed less dyskinesia in these studies is simply that they were treated with less potent medicine. Finally, as with many conditions where there are valid arguments to be made on both sides, the final result may not be all that different, and it is worth noting that in the initial study on the effect of dopamine agonists on dyskinesia incidence, by the end of 5 years two-thirds of the patients on dopamine agonists required the addition of supplementary levodopa.[5]

On theoretical grounds, dopamine agonists with longer half-lives may be better than those with shorter half-lives, and the clinician should be aware of the existence of 2 dopamine agonists that may prove useful, both with long half-lives, namely the drug rotigotine, which has been quite widely tested in South Africa in phase 3 trials in the form of a topically applied patch, and the dopamine agonist, cabergoline, which is available in South Africa for the reduction of lactation.

## Who must get dopamine agonists as first-line treatment?

Young-onset PD patients are particularly prone to dyskinesias, and it seems sensible that they should start with a dopamine agonist if possible. However, many younger patients will inevitably require surgery for severe dyskinesias, and patients should not be denied the greater efficacy of dopamine if they are not responding well to dopamine agonists, particularly if their livelihood is affected.

The definition of young onset is naturally an arbitrary one: for the purpose of deciding whether to give dopamine agonists or not, the usual age given is 50 years. Neurologists may well decide that patients aged 50 - 60 may also fall into a higher risk category for developing dyskinesias, although their risk is lower than for younger patients.

## What other drugs are available as first-line treatment?

Other agents available as first-line treatment include:

- Anticholinergics, which are probably

particularly useful in the control of tremor.
There are significant concerns about long-term use of anticholinergics and their use in the elderly needs to be viewed with caution, particularly since they potentially cause dementia.

- Amantadine, which has benefit, but typically for a short duration only.
- Selegiline and rasagiline.

## NEUROPROTECTION IN PD

The Holy Grail in PD is unquestionably the development of neuroprotection to prevent damage to cells from accumulating injury. Currently the treatment of PD is purely symptomatic and there are no proven forms of neuroprotection.

Drugs which have been closely associated with neuroprotective strategies include monoamine oxidase inhibitors, antioxidants, such as selegiline and, more recently, rasagiline. The idea behind these agents is once again derived from animal models of PD, in which selegiline was successfully able to counter the effects of the mitochondrial toxin, MPTP. It is reasonable to ask whether this animal model is a good one (opinions differ) and how important mitochondrial dysfunction is in PD (opinions differ).

Selegiline was tested in the DATATOP study and appeared to delay the progression of PD.[10] The fly in the ointment was that drugs which block monoamine oxidase are likely to lead to direct symptomatic benefits and elucidating whether there is an additional neuroprotective aspect over and above the direct symptomatic benefit derived from MAOI treatment is difficult. A similar effect is seen with rasagiline.[11]

Although a neuroprotective study has been carried out, and may show benefit, the study design is novel, and interpretation of the potential benefit of rasagiline as a neuroprotective agent is difficult.[12]

Virtually all drugs associated with the treatment of PD are also thought to potentially have neuroprotective function: this would include dopamine agonists and COMT inhibitors. Although studies using dopamine agonists (REAL-PET and CALM-PD) have had imaging findings suggestive of neuroprotection, this did not reflect an improvement in motor benefit, and the imaging findings were possibly related to different effects on imaging parameters, rather than actual neuroprotection.[4,6]

## WHAT IS THE ROLE OF STEM-CELL THERAPY FOR PD?

Principally, stem-cell therapy can be viewed as tackling 2 arms of PD – firstly, the neuroprotective arm and, secondly, the symptomatic arm. It is critical to realise that PD is a progressive illness in which a number of monoaminergic systems as well as other, predominantly brainstem, systems are disrupted. Prominent symptoms of PD sufferers include conditions such as altered speech, cognitive impairment, autonomic dysfunction and disorders of gait and balance, the majority of which will often respond poorly to dopamine replacement and are therefore likely to represent dysfunction of non-dopaminergic systems. Therefore, stem-cell strategy that is directed only at dopaminergic neurones is unlikely to be successful. Where stem cells may be more promising is in the field of neurotrophic factors and neuroprotection. Trials which have been at least technically successful have already been performed using agents such as a glial-derived neurotrophic factor. In addition, current trials are aimed at elevating inhibitory neurotransmitters in the subthalamic nucleus, based on the concept that excessive excitation of cells may result in cell death.

## SURGERY IN PD

Given that PD is a progressive disorder, it is reasonable to enquire whether surgical procedures are useful, given that they are largely palliative. Unfortunately the situation is clouded by the fact that there are a number of different procedures with variable anatomical sites and variable methods of achieving the desired result. However, there is good evidence that pallidotomy and subthalamic nucleus (STN) deep brain stimulation are efficacious as adjunctive therapy, and are likely to be efficacious in the treatment of motor complications.[13]

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