

## 7 Management of Parkinson's Disease

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This review is based on previous publications<sup>1</sup> and the National Institute for Health and Clinical Excellence (NICE) guideline on the diagnosis and management of Parkinson's disease.<sup>2</sup>

### ***When to Start Treatment in Parkinson's Disease***

Once Parkinson's disease has been diagnosed, any therapy which can slow or halt progression should be commenced immediately. Such neuroprotective or disease modifying therapy does not exist at present. Many agents have been investigated for neuroprotective properties in vitro and in vivo without success.<sup>2</sup>

Most clinicians delay the introduction of symptomatic treatment until the patient has significant functional disability, i.e. when it is interfering with activities of daily living, on the basis that symptomatic therapy is unlikely to be effective for mild symptoms which are not interfering with life. However, this view may change if it is found that early symptomatic treatment slows progression, as has been suggested.<sup>3</sup>

The results of the rasagiline delayed-start trials (TEMPO and ADAGIO)<sup>4-5</sup> suggest that immediate treatment may be superior. Analogous findings in trials with levodopa (ELLDOPA)<sup>6</sup> and selegiline (DATATOP)<sup>7</sup> imply that any symptomatic therapy may have the same effect, although a recent, as yet unpublished, delayed-start design trial with pramipexole (PROUD) failed to find similar findings with a dopamine agonist.

However, there are many reasons why we should not at present change the current policy of deferring treatment until functional disability develops:

1. In TEMPO, the results with the 1 mg dose were not significant and in ADAGIO, the results with the 2 mg dose were not significant. There is also the possibility of selection bias in all delayed start trials, with a tendency to recruit milder slowly progressive patients who can tolerate no treatment for 18 months, so the results may not be generalisable.
2. The positive results of both TEMPO and ADAGIO were based on differences below 2 total UPDRS units. It has recently been shown that a clinically meaningful difference in total UPDRS in early Parkinson's disease is at least 6 units.<sup>8</sup>
3. This small benefit could be due to symptomatic non-specific effects on the musculoskeletal system rather than a true neuroprotective effect. The European Medicines Evaluation Agency (EMA) requires evidence of an effect on a biomarker of disease progression as well as a clinical effect before it will give a product licence for neuroprotection.
4. There is a suggestion from the PD LIFE audit<sup>9</sup> that quality of life deteriorates quickly in early untreated PD. However, the PD LIFE result may be due to selection bias and such a decline in quality of life has not been found in a similar ongoing Aberdeen study.<sup>10</sup>
5. Treating patients on diagnosis would increase the net cost of treatment. There is no evidence, at present, that this is a cost-effective policy change.
6. Treating patients earlier may result in more of dopaminergic adverse reactions (i.e. nausea, vomiting, hypotension), along with impulse control disorders (e.g. pathological gambling, hypersexuality, punding). Earlier treatment may also expedite motor complications (i.e. dyskinesias and motor fluctuations).

In conclusion, we must consider whether enough evidence has accumulated to change practice. If not, then we may need to perform further trials.

## ***Management of Early Parkinson's Disease***

Once motor symptoms interfere with everyday life, the NICE guidelines recommend commencing an agent from one of three first line drug classes: levodopa, dopamine agonists or monoamine oxidase type B (MAOB) inhibitors (Table 1). Evidence from randomised controlled trials and systematic reviews supports the efficacy of each of these drug classes.<sup>2</sup> What is not clear is which class to choose in any given clinical situation. For instance, many have adopted the policy of using a dopamine agonist in younger patients to delay the onset of motor complications (abnormal involuntary movements, end of dose wearing off and unpredictable 'on'-'off' switching) which are more frequent if treatment is initiated with levodopa.<sup>2</sup> However, levodopa treats motor symptoms better than dopamine agonists and many young patients may still require fine motor skills for work. In an attempt to resolve this uncertainty, the Health Technology Assessment Programme has funded the ongoing UK PD MED trial ([www.pdmed.bham.ac.uk](http://www.pdmed.bham.ac.uk)).

**Table 1 Options for initial symptomatic therapy for Parkinson's disease (from ref 2)**

	First choice option	Degree of symptom control	Risk of side effects	
			Motor complications	Other adverse events
Levodopa	Yes	Good	Increased	Increased
Dopamine agonists	Yes	Moderate	Reduced	Increased
Monoamine-oxidase-B inhibitors	Yes	Limited	Reduced	Increased
Anticholinergics	No	Lack of evidence	Lack of evidence	Lack of evidence
Beta-blockers	No	Lack of evidence	Lack of evidence	Lack of evidence
Amantadine	No	Lack of evidence	Lack of evidence	Lack of evidence

It has been known for many years that the ergot-derived dopamine agonists (i.e. bromocriptine, lisuride, pergolide and cabergoline) can produce the rare side effect of pleural, pericardial or peritoneal effusions and fibrosis. It is thought that the non-ergot agonists (i.e. pramipexole, ropinirole and rotigotine) are less likely to produce such problems, but clinical experience has been much shorter. The UK Committee on Safety of Medicines produced a report which highlighted the yellow card reporting of such cases with pergolide and cabergoline. This was followed by several case series reporting the new problem of cardiac valvulopathy with pergolide and cabergoline. As a result, the UK Medicines and Healthcare products Regulatory Agency (MHRA) changed the pergolide Summary of Product Characteristics in January 2005 such that: "Pergolide should be used second-line after a non-ergot dopamine agonist." More recently, similar limitations have been applied to cabergoline. This has led to a move away from the ergot agonists in favour of the non-ergot dopamine agonists.

## ***Management of Later Parkinson's Disease***

The majority of patients will eventually require levodopa, so motor complications are inevitable. At this stage, the NICE guidelines recommend adjuvant therapy to levodopa with either a dopamine agonist, a MAOB inhibitor or a catechol-O-methyl transferase (COMT) inhibitor (Table 2).<sup>2</sup> There is good evidence from randomised controlled trials and systematic reviews to show that these drugs reduce 'off' time and levodopa dose, but at the expense of significant side effects.<sup>2</sup> However, it is not clear whether one class of adjuvant agent is superior to any other. This is the subject of the second part of the PD MED trial.

*Table 2 Options for adjuvant therapy in later Parkinson's disease (from ref 2)*

	First choice option	Degree of symptom control	Risk of side effects	
			Motor complications	Other adverse events
Dopamine agonists	Yes	Moderate	Reduced	Increased
Catechol- <i>O</i> -methyltransferase inhibitors	Yes	Moderate	Reduced	Increased
Monoamine-oxidase type B inhibitors	Yes	Moderate	Reduced	Increased
Amantadine	No	Not significant	Reduced	Increased
Apomorphine	No	Limited	Reduced	Increased

### ***Management of Advanced Parkinson's Disease***

Three randomised controlled trials were included in a Cochrane review of amantadine used to treat dyskinesias in later Parkinson's disease.<sup>11</sup> Whilst the number of patients included was small (n=53) and the trials short, the NICE guidelines recommended that amantadine be used as an anti-dyskinesia agent.<sup>2</sup>

The dopamine agonist apomorphine is not effective orally due to extensive first-pass metabolism in the liver. It was developed as intermittent bolus injections to rescue patients from severe 'off' periods or as a subcutaneous infusion for patients with many 'off' periods. Both uses require continuous treatment with the antiemetic domperidone to prevent nausea and vomiting. Three small trials (n=56) documented the efficacy and safety of intermittent injections of apomorphine, but only observational studies are available for the continuous infusion.<sup>2</sup> Nevertheless, the NICE guidelines approved both for use in treating motor complications which are intractable to changes in oral therapy.

The NICE guidelines were prepared before the continuous infusion of a levodopa gel directly into the jejunum (Duodopa®) was licensed for the management of severe motor complications. Small trials showed that these infusions reduce 'off' time and improve motor function, activities of daily living, and quality of life.<sup>12-13</sup> However, its use will be restricted by cost (£30,000 pa) and the need for a gastrostomy in potentially ill patients.

### ***Surgery (see Chapter 9)***

Improved understanding of the neural mechanism of Parkinson's disease showed that the subthalamic nucleus (STN) is overactive.<sup>14</sup> This led to the development of bilateral subthalamic (STN) stimulation surgery to switch off this nucleus. There have been many uncontrolled case series of STN stimulation, and only recently four randomised controlled trials (RCT)<sup>15-17</sup> including the UK PD SURG trial. These showed that STN stimulation reduces 'off' time and 'off' time disability, so medication can be reduced, thereby reducing dyskinesia. Meta-analysis of the results of these RCTs shows a consistent improvement compared with deferred surgery at 6, 12 and 18 months of around 5 points on the patient-rated quality of life scale Parkinson's Disease Questionnaire Summary Index (PDQ 39 SI), a difference which has previously been shown to be clinically significant.<sup>8</sup>

The NICE guidelines recommended STN stimulation for patients with motor complications refractory to best medical treatment, who are biologically fit with no clinically significant active co-morbidity, who are levodopa responsive and have no clinically significant active mental health problems (depression or dementia).<sup>2</sup> Questions still remain about the long-term safety of STN stimulation, as depression and suicide may be more common, and more information on cost-effectiveness of this expensive procedure is required. This should come from follow up of the PD SURG cohort.

## ***Non-motor Features of Parkinson's Disease (see Chapters 4 and 8)***

The motor features of Parkinson's disease can be controlled reasonably well in most patients with the measures outlined above. It is the non-motor features of the disorder which now present the greatest management challenge, including dementia, psychosis, imbalance and falls, autonomic dysfunction, sleep disorders, and pain. The NICE guidelines found a paucity of treatment trials for non-motor features.<sup>2</sup> What evidence there was related to mental health conditions, particularly dementia. The trial evidence to support the efficacy and safety of cholinesterase inhibitors for Parkinson's disease dementia was inadequate and further trials are required.<sup>2</sup>

## ***Nursing and Allied Health Professional Interventions***

Three randomised controlled trials assessed the efficacy of Parkinson's Disease Nurse Specialists versus standard care.<sup>2</sup> The benefits of nurses related to the overall patient care experience and delivery of services rather than in outcome measures such as quality of life or health economics. Therefore, the NICE guidelines recommended Nurse Specialists for clinical monitoring and medication adjustment, a continuing point of contact for support, and a reliable source of information about clinical and social matters for patients and carers.<sup>2</sup>

The evidence for the use of physiotherapy, occupational therapy and speech and language therapy in Parkinson's disease is based on a small number of trials with few participants, but clinical experience suggests that they are valuable.<sup>2, 18</sup> The NICE guidelines concluded that all three interventions should be available to patients throughout the disease (Table 3). However, the NICE guidelines recommended that further large scale trials should be performed with these therapies, such as the ongoing UK PD REHAB trial ([www.pdrehab.bham.ac.uk](http://www.pdrehab.bham.ac.uk)).

***Table 3 Roles of allied health professional interventions in Parkinson's disease<sup>2</sup>***

<b>Physiotherapy</b>	Gait re-education, improvement of balance and flexibility
	Enhancement of aerobic capacity
	Improvement of movement initiation
	Improvement of functional independence, including mobility and activities of daily living
	Provision of advice regarding safety in the home environment
<b>Occupational therapy</b>	Maintenance of work and family roles, home care and leisure activities
	Improvement and maintenance of transfers and mobility
	Improvement of personal self-care activities such as eating, drinking, washing and dressing
	Environmental issues to improve safety and motor function
	Cognitive assessment and appropriate intervention
<b>Speech and language therapy</b>	Improvement of vocal loudness and pitch range, including speech therapy programmes such as Lee Silverman Voice Treatment
	Teaching strategies to optimise speech intelligibility
	Ensuring an effective means of communication is maintained throughout the course of the disease, including use of assistive technologies
	Review and management to support the safety and efficiency of swallowing to minimise the risk of aspiration.

## ***Future Treatments***

It is crucial that neuroprotective agents are found to slow or halt the progression of Parkinson's disease. However, there are fundamental questions about neuroprotection trial design, particularly delayed-start design trials<sup>19</sup> and futility studies.<sup>20</sup>

Continuous dopaminergic stimulation throughout 24 hours may reduce motor complications by avoiding pulsatile stimulation of dopamine receptors. The new dopamine agonist rotigotine has been formulated in a transdermal delivery system which provides 24 hour stimulation.<sup>21</sup> Once daily prolonged-release versions of the non-ergot dopamine agonists ropinirole and pramipexole are also available now.<sup>22</sup>

Much effort has gone into developing non-dopaminergic agents for parkinsonian symptoms and/or dyskinesias (e.g. the adenosine A2A receptor antagonist preladenant). However, many have proved disappointing in clinical trials, perhaps because animal models do not truly reflect Parkinson's disease.<sup>23</sup>

The prospect of neurorestoration with stem cell grafts continues to generate considerable attention. However, two trials of foetal midbrain grafts found that, whilst beneficial effects occur, severe 'off' period involuntary movements developed which necessitated pallidotomy in some cases.<sup>24-25</sup> There have also been recent post mortem results from these early grafting trials showing the development of Lewy bodies in the grafts.<sup>26</sup>

It will be many years before stem cell implants are shown in large clinical trials to be free from tumour formation and capable of controlled dopamine release. In the meantime, various nerve growth factors may be shown to stimulate the development of remaining dopaminergic neurones.<sup>27</sup>

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### ***Further Reading***

NICE guidelines (<http://www.nice.org/>)

Cochrane reviews (via National Library for Health or <http://www.update-software.com/publications/cochrane/>)

Clarke CE. Parkinson's disease in Practice. Royal Society of Medicine Press: London. Second Edition. 2006.

### ***Information Resources***

Parkinson's Disease Society (<http://www.parkinsons.org.uk/>)

European Parkinson's Disease Association (<http://www.epda.eu.com/>)

American Parkinson's disease Association (<http://www.apdaparkinson.org/user/index.asp>)

National Parkinson Foundation

(<http://www.parkinson.org/netcommunity/Page.aspx?&pid=201&srcid=-2>)

National Institute of Neurological Disorders and Stroke

([http://www.ninds.nih.gov/disorders/parkinsons\\_disease/parkinsons\\_disease.htm](http://www.ninds.nih.gov/disorders/parkinsons_disease/parkinsons_disease.htm))

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