Future treatments for Parkinson’s disease

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Background

The classic clinical descriptions of Parkinson’s disease (PD) emphasise the motor aspects of the disorder, specifically resting tremor, bradykinesia, rigidity and loss of postural reflexes. In the early years following presentation and diagnosis, these motor features tend to dominate the clinician’s (and often also the patients’) focus, and these usually respond gratifyingly to pharmacological replacement using dopaminergic medications. The most effective medication for the relief of the motor symptoms of PD is inarguably L-dopa; however, prescribing practice has been greatly influenced by concerns regarding the development of long-term adverse effects of L-dopa use, namely ‘peak-dose dyskinesias’ and unpredictable fluctuations or ‘on/off phenomena’.

There is evidence that these adverse effects are either delayed or are less severe using medication regimens promoting continuous rather than pulsatile stimulation of postsynaptic dopamine receptors. Poly-pharmacy, using combinations of a long-acting dopamine agonist drug (eg ropinirole, pramipexole or rotigotine), supplemented with the introduction of lower doses of L-dopa as and when required, is now widespread practice. The ergot-derived dopamine agonists (bromocriptine, pergolide and cabergoline) have been shown to cause cardiac and pulmonary fibrosis, and should be avoided. Modest beneficial symptomatic effects are associated with the use of monoamine oxidase B inhibitors (MAO-Bi), such as selegiline and, more recently, rasagiline; and, in the later stages of PD, it is without doubt that the MAO-Bi drugs, as well as inhibitors of the catechol-O-methyltransferase (COMT) enzyme (entacapone and tolcapone) can prolong the action of L-dopa and improve symptom control among patients with On/Off phenomena. Large randomised controlled trials have hinted at possible beneficial disease-modifying effects of the MAO-Bi drugs; however, there is still controversy surrounding the appropriateness of the routine use of these drugs in early PD.

Acceptable control of the motor symptoms of PD is usually achievable for several years after diagnosis, using individually tailored combinations of these drugs. However, with further advancing disease, additional more invasive therapies, namely subcutaneous apomorphine, deep brain stimulation (DBS) surgery, or administration of intra-jejunal L-dopa gel (Duodopa®), might be needed, particularly among patients with early onset of disease, and thus requiring several decades of effective symptom control. Apomorphine can be given via intermittent ‘rescue’ injections to relieve unpredictable or sudden ‘Off’ periods, or administered via a pump delivering a continuous background infusion over the waking day.1 DBS, although requiring invasive neurosurgery, now has a strong evidence basis for its safety and efficacy and, in well-selected patients, can lead to long-term improvements in quality of life.2 Stimulation of the subthalamic nucleus (STN) can improve the ‘Off’ symptoms of PD to a similar extent to L-dopa, but in a more continuous fashion, whereas globus pallidus interna (GPI) stimulation can reduce the severity of dyskinesias, enabling effective doses of medication to be better tolerated. Severe tremor, even when refractory to L-dopa, can respond well to stimulation of the motor thalamus.3 Patients who are not eligible for apomorphine or DBS, and who have erratic responses to oral L-dopa, can experience marked improvements in their PD control using continuous infusions of intra-jejunal L-dopa through a percutaneous jejunostomy (PEJ) tube rather than the unpredictable plasma levels accompanying repetitive oral dosing.

Despite some of these successes in PD treatment, increasing recognition is now made of non-motor features of the illness, which are clearly evident in many patients even during the first years after diagnosis. Features, including cognitive dysfunction and dementia, sleep disturbance, loss of olfactory ability, and an array of autonomic symptoms, are common.4 Although motor symptoms are clearly linked to degeneration of the dopaminergic cells of the nigrostriatal pathway, non-motor features are likely to be related to similar degenerative processes impacting other brainstem nuclei and the olfactory bulbs, processes that are seemingly underway even before significant loss of the nigrostriatal dopaminergic cells.5

Although simple symptomatic treatments are also available for some of the non-motor symptoms of PD, such as postural hypotension, depression and rapid eye movement (REM) sleep behaviour disorder (Table 1), the treatment of early and severe cognitive dysfunction (which implies more widespread cortical degeneration and usually heralds a poor prognosis) is particularly unsatisfactory.

Thus, existing contemporary therapies can usually lead to effective relief of many of the motor problems of PD and can ameliorate some of the non-motor symptoms; however, despite the many successes of PD therapies, there remain major unmet needs, including:

- Balance problems: freezing and falls can be refractory to all of the above treatments.
- Treatments for the non-motor symptoms, especially cognitive decline are inadequate.
Future treatments for Parkinson’s disease

Expected to have only small incremental advantages over existing dopaminergic treatments. Furthermore, demonstration of efficacy in small trials rarely equates to an undisputed advantage over and above that of existing treatments, and few commercial companies are prepared to take the risk of head-to-head comparisons against their competitors.

Among the newer medications for the treatment of non-motor symptoms, encouraging developments include: the potential use of histamine 3 inverse agonists, such as pitolisant, to reduce the excessive daytime somnolence seen in PD; the development of a noradrenaline precursor (droxidopa) as an effective additional option for the treatment of postural hypotension; and an observation that the anti-epileptic drug zonisamide might reduce impulsive compulsive behaviours in patients with PD.

Neurosurgical attempts to further improve PD symptom control are also ongoing (Table 2). In the wake of the successes of DBS, and growing knowledge regarding how brain networks are disrupted by the neurodegenerative process, there is ongoing research evaluating new targets in the brain for relief of PD symptoms (refractory to optimal conventional medication) using high- or low-frequency stimulation via implanted electrodes. For a few patients, beneficial effects on dopa refractory gait freezing can follow stimulation of the pedunculopontine nucleus area, whereas in a single case report, deficits in memory and apraxia showed marked improvement following stimulation of the cholinergic nucleus basalis of Meynert.

Functional neurosurgery is also being exploited for the delivery of gene therapy treatments directly into the brains of patients with PD. There are four major PD gene therapy programmes currently being evaluated, three of which aim to improve on the symptomatic control of the disease. Two commercial programmes involve the delivery of enzyme replacement to improve the synthesis of dopamine by non-dopaminergic

### Table 1. The major non-motor symptoms of Parkinson’s disease (PD) and existing available treatments.

<table>
<thead>
<tr>
<th>Non-motor symptoms</th>
<th>Available treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sleep disturbances</td>
<td></td>
</tr>
<tr>
<td>Rapid eye movement (REM) sleep behaviour disorder</td>
<td>Clonazepam</td>
</tr>
<tr>
<td>Excessive daytime somnolence</td>
<td>Reduce dopamine agonists, amantadine and modafinil</td>
</tr>
<tr>
<td>Neuropsychiatric issues</td>
<td></td>
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<tr>
<td>Depression and/or anxiety</td>
<td>Serotonin-norepinephrine reuptake inhibitors; eg venlafaxine, mirtazapine and anxiolytics; and counselling</td>
</tr>
<tr>
<td>Psychosis and/or hallucinations</td>
<td>Reduce PD drugs, especially anti-cholinergics, amantadine and dopamine agonists</td>
</tr>
<tr>
<td>Impulsive and/or compulsive behaviours</td>
<td>Consider atypical antipsychotics (eg quetiapine, olanzapine or clozapine)</td>
</tr>
<tr>
<td>Dementia and/or hallucinations</td>
<td>Slow reduction and/or withdrawal of dopamine agonist drugs</td>
</tr>
<tr>
<td>Autonomic symptoms</td>
<td></td>
</tr>
<tr>
<td>Orthostatic hypotension</td>
<td>Adjust PD drugs, and/or add fludrocortisone, midodrine or ephedrine</td>
</tr>
<tr>
<td>Bladder urgency and/or frequency</td>
<td>Oxybutynin, tolterodine or desmospray</td>
</tr>
<tr>
<td>Salivary drooling</td>
<td>Oral administration of atropine eye drops, hyoscine transdermal patches, intra-salivary Botulinum toxin injections</td>
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</table>

## New symptomatic treatments for PD

Most new symptomatic medications being developed aim to reduce the risk of the motor complications resulting from chronic L-dopa exposure (ie disabling fluctuations and dyskinesias) and, thus, avoid the need for invasive treatments such as DBS. A more detailed understanding of basal ganglia circuitry and the role of other neurotransmitter systems with relation to dopaminergic function have led to modestly encouraging developments. Antagonists for the adenosine A2a receptor, such as istradefylline and preladenant, can reduce ‘Off’ time by approximately 1 h per day, whereas an antagonist for the metabotropic glutamate receptor mGlur5 (AFQ056) has been shown in small trials to reduce the severity of dyskinesias. There are also multiple programmes continuing to develop new agents that have actions on dopaminergic pathways, but realistically these can be expected to have only small incremental advantages over existing dopaminergic treatments. Furthermore, demonstration of efficacy in small trials rarely equates to an undisputed advantage over and above that of existing treatments, and few commercial companies are prepared to take the risk of head-to-head comparisons against their competitors.

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effects. Current understanding of the pathophysiological processes that underlie PD is undoubtedly improving thanks largely to worldwide cooperation between PD geneticists, as is understanding of the relationships between genetic risks, age and environmental exposures. Converging evidence points to the importance of toxicity owing to accumulation of alpha synuclein protofibrils, cellular energy processes and, specifically, mitochondrial function, in the pathogenesis of the neurodegeneration of PD. Therefore, the most promising agents are those that are known to provide neurotrophic support to stressed neurons, or have a direct effect on mitochondrial turnover or the normal processes of mitochondrial bioenergetics.

Trials of agents that have been convincingly shown to reverse pathology in animal models of PD are ongoing. One such agent is creatine, a guanidine derivative present in dietary meat and also produced endogenously. Administration of creatine has beneficial effects on mitochondrial function and ATP homeostasis.

Disease modification

Improving the effective relief of symptoms of PD, although undeniably of major importance, is of lower priority than the identification of agents that have significant and clinically important disease-modifying ‘neuro-protective’ or even ‘neuro-restorative’ effects. Current understanding of the pathophysiological processes that underlie PD is undoubtedly improving thanks largely to worldwide cooperation between PD geneticists, as is understanding of the relationships between genetic risks, age and environmental exposures. Converging evidence points to the importance of toxicity owing to accumulation of alpha synuclein protofibrils, cellular energy processes and, specifically, mitochondrial function, in the pathogenesis of the neurodegeneration of PD. Therefore, the most promising agents are those that are known to provide neurotrophic support to stressed neurons, or have a direct effect on mitochondrial turnover or the normal processes of mitochondrial bioenergetics.

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through an action on the mitochondrial permeability transition pore and is also involved in the packaging of glutamate into synaptic vesicles. It has protective effects in vitro and in vivo models of Parkinsonism, is well tolerated in humans and is the subject of a large ongoing National Institutes of Health (NIH) trial looking to identify disease-modifying effects, which is due to report in May 2015.

Further agents have emerged as potential disease-modifying candidates from epidemiological studies. Exposure to dihydropyridine calcium antagonists has been associated with a lower risk of developing PD (although the association is not consistent across all studies), and one such agent (isradipine) has shown beneficial effects in animal PD models and has been proposed to have an ‘energy-saving’ effect by blocking calcium channel-dependent pacemaker activity of dopaminergic nigrostriatal neurons. A further drug (inosine; a precursor of uric acid) is also being trialled as a potential neuroprotective agent for patients with PD. Uric acid is known to have strong antioxidant properties and, among large cohorts of patients with PD, individuals with higher levels of uric acid deteriorated less quickly than did patients with lower levels. Protective effects from exogenous administration of uric acid have also been seen in animal models of Parkinsonism.

Exendin-4 is a novel peptide identified in 1992 in the saliva of the Gila monster lizard. It acts on the glucagon-like peptide 1 (GLP-1) receptor, and has been shown to stimulate insulin release in a glucose level-dependent manner. Multiple phase 3 trials have confirmed a synthetic equivalent ‘exenatide’ to be an effective and safe treatment for patients with type 2 diabetes mellitus (T2DM) and it is now licensed for this indication. This agent has also been shown by multiple groups to have dramatic positive effects in animal models of PD. Possible mechanisms include: reduction of inflammatory mediators such as tumour necrosis factor (TNF)-α, stimulation of neurogenesis in the subventricular zone, or stimulation of mitochondrial biogenesis.10,11 In response to these observations, exenatide is the subject of a randomised controlled trial in patients with PD at the UCL Institute of Neurology, and in patients with Alzheimer’s disease at NIH in the USA.

Interestingly, another drug used for the treatment of T2DM has also been shown to have neuroprotective properties in animal models. Pioglitazone acts on peroxisome proliferator-activated receptor (PPAR)-γ and might have additional effects on expression of proteins in the mitochondrial membrane. Again, without certainty regarding possible mechanism(s) of action, the known safety profile of pioglitazone has prompted a randomised trial of the drug in patients with PD.

There has been detailed study of glial cell-derived neurotrophic factor (GDNF) as a putative PD neuroprotective agent. Direct administration of GDNF into the striatum showed benefits in open-label trials, but adaptation of the technique in a double-blinded trial did not replicate the earlier successes.12 Improvement in an intraputaminal delivery system for GDNF administration in a further blinded trial is now being pursued by a team in Bristol, UK. Alternative methods of administering GDNF are also being studied. An oral agent, Cogane™, which crosses the blood–brain barrier, and has been shown to stimulate endogenous GDNF release, is being trialled in patients with early-stage PD. An analogue of GDNF, neurturin, is the subject of the fourth major gene therapy programme, and patient recruitment has been completed to a randomised controlled trial involving the delivery of this vector to both the striatum and the substantia nigra of patients with PD.

There is also renewed interest in cell therapy as a repair strategy in PD. A decade ago, two sham surgery controlled trials failed to demonstrate an overall clinical advantage of the use of fetal cell grafts placed in the putamen, and some of the recruited patients developed graft-induced dyskinetic disorders that persisted despite withdrawal of medication. Furthermore, in a few post-mortem individuals, Lewy body pathology was identified in the grafted cells, suggesting that cell to cell transmission of the PD process occurred. Nevertheless, selected individuals have continued to receive sustained benefits following fetal cell grafts, managing to withdraw from PD medication, with accompanying evidence of dopamine production on positron-emission tomography (PET) scans. The issues that need to be overcome to establish cell repair mechanisms as a treatment strategy for PD are being re-evaluated in a European multi-centre trial of fetal dopaminergic cell transplantation for PD called ‘Transcero’.

Conclusions

The development of disease-modifying treatment for PD remains hindered by several long-standing issues. The major obstacle in identifying agents with true disease-modifying effects is that the animal models of PD used to judge which compounds to take to the clinic remain inadequate representations of the progressive neurodegenerative nature of the human disease. Furthermore, neuroprotective agents are most likely to have beneficial effects when taken early in the course of the disease, a time when clinical diagnostic uncertainty is greatest and recruited patients might include patients with other movement disorders, such as dystonic tremor, or whose symptoms subsequently evolve into one of the Parkinson plus disorders. An additional issue relates to the use of pharmacological therapies and/or invasive procedures with unpleasant adverse effects, or accompanied by small but definite risks of significant morbidity, as this can hinder recruitment (or lead to poor compliance and/or early dropout) among a population in the early stages of a chronic disease, with only mild symptoms and who, on an individual basis, have an unpredictable rate of progression. These issues need to be considered during the design and planning of trials of possible neuroprotective strategies.

Additionally, given the complexity of the cellular pathways involved, it is no surprise that there is considerable heterogeneity of patients that all meet currently accepted clinical diagnostic criteria for PD. It should be expected that subgroups of patients with PD might have different responses to novel therapies.

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Classification of PD subgroups purely based on gene testing might enable treatments (e.g., LRRK2 inhibitors) to be tailored to patients developing PD secondary to specific genetic defects. The development of safe and effective medical therapy is however a hugely expensive and lengthy process and commercial pharmaceutical companies inevitably will consider carefully the size of the possible market (small subgroups of PD patients) for these products in the decision to develop them. Similar problems exist for cell repair technologies; demonstration of long-term beneficial effects from fetal dopamine cell grafts poses major questions regarding both ethics and the ‘good manufacturing practice’ needed to supply equivalent standardised sources of cells for larger numbers of patients.

Poly-pharmacy is already the norm for patients with PD. It is likely that ongoing research will discover multiple agents that each has small but important benefits on either long-term symptom relief or slowing of the neurodegenerative process. Combination therapy using both medical and surgical delivery methods is likely to remain commonplace for years to come.

References


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