CAN WE CHANGE THE OUTCOMES IN PARKINSON'S DISEASE?

Karan Patel
University of Leeds, Medical School

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Introduction

According to the majority of medical literature, Parkinson's disease (PD) is a movement disorder which primarily affects the aged. These textbooks reiterate that PD consists of bradykinesia, rigidity and tremor, and is the result of dopamine deficiency due to degeneration of the substantia nigra (SN) of the brain following accumulation of Lewy bodies and neurites made up of α-synuclein.¹

Whilst the above is true, many of the details are lacking.

Indeed, PD is a condition which has a huge impact on the elderly: 1-2% of those aged 65 and above is thought to suffer from the condition. But although motor symptoms are notoriously present in PD; patients also often suffer from a myriad of non-motor features such as insomnia, lack of energy, pain, bladder dysfunction, constipation, cognitive impairment, moderate to severe depression as well as psychotic disturbances such as hallucinations.² Although medical literature places these symptoms as secondary to those motor, patients seem to differ. A recent survey demonstrated that PD patients found non-motor symptoms a far greater burden than motor problems, with diminished energy and pain deemed the two most debilitating.³

Thus the aim of this essay is to answer whether the outcomes of PD, both motor and non-motor, can be changed.

Changing the outcomes

Four areas must be targeted, when considering tackling the effects of PD. These include:

- early detection;
- prevention of disease progression;
- regeneration and replacement of damaged neurons and
- further improvement of symptom control.

Early detection

Currently, PD is solely a clinical diagnosis which requires the presence of tremor, rigidity and bradykinesia as well as a response to dopamine agonists. However, motor symptoms only present once approximately 80% of dopaminergic neurons connecting the SN and striatum die. A landmark study by Braak et al. devised a staging system for PD by examining the
brains of PD patients who died at different time-points and those who were found to have PD pathology incidentally at autopsies. The study deduced that the disease’s degenerative pathway begins at the brainstem as well as olfactory bulb, half-way it reaches the SN (at which point motor symptoms appear), before finally reaching the neocortex.\textsuperscript{4} It seems illogical that we allow so much of the disease’s outcomes to materialise before we intervene.

As the olfactory bulb is the first to undergo degenerative changes in PD, patients frequently have olfactory dysfunction as their initial symptom. Hence, a simple screening method to detect early-PD could use the following criteria: idiopathic hyposmia, an age of greater than 50 years of age and the presence of two or more early features (e.g. delayed gastric emptying, altered sleep, and depression-like symptoms).\textsuperscript{3} Unfortunately, disturbances in smell occur in other neurodegenerative diseases, and early symptoms are also very non-specific. It is debatable whether a screening tool such as this would prove effective, but a pilot study could provide clues. A population sample could be studied for several years and if there was a strong correlation between those who tested positive for the above criteria and the development of classical PD, then the screening tool could be adapted for the general population.

More complex screening tools are actually being piloted in the US, one of which utilises specific biomarkers, novel brain imaging and anosmia.\textsuperscript{5} Whilst it will be interesting to observe the results from this study, it is difficult to imagine that such an expensive tool would have a place in the NHS anytime soon.

\textit{Prevention}

Medications presently used in PD (dopamine agonists, anticholinergics, levodopa and agents that prevent the breakdown of dopamine) have little effect on disease-progression. Thus if a screening system was installed, newer interventions would need to be established.

The specifics of the pathogenesis of PD are still unknown. However, theories include: microglial-activated neuroinflammation, oxidative stress (OS), glutamate-induced neuronal excitotoxicity and loss of neurotrophic support.\textsuperscript{6} From these theories, numerous methods have been trialled to combat the progression of PD. Firstly, NSAIDs such as aspirin, ibuprofen and meloxicam have been shown to confer neuroprotection in mice with artificially induced PD-like conditions via a mechanism most likely independent of COX-inhibition. Metabotropic glutamate receptor agonists have been demonstrated to prevent neuronal excitotoxicity and hence disease progression. Despite evidence illustrating oxidative stress
to be a possible cause of PD, anti-oxidants have been ineffective in several studies, most notably clinical trials.\(^6\)\(^7\)

Of the above medication, ibuprofen is the only drug that has been successful in humans (pooled risk ratio: 0.76%, CI = 0.65-0.89)\(^7\). This is probably because the above in vitro animal models are poor simulations of PD. Rasagiline, a MAO-inhibitor already used in PD, has delayed the deterioration in PD in a number of trials when given earlier, suggesting that the drug may have neuroprotective effects. However, in the only double-blinded RCT which compared early and delayed administration of rasagiline, 1 mg but not 2 mg rasagiline slowed PD progression – thus further clinical research needs to be performed before any firm conclusions are made.\(^6\)

**Regeneration and replacement**

Along with disease prevention, cell regeneration and replacement have also been considered to alter the outcomes of PD. As mentioned above, one of the hypotheses of PD pathogenesis is hippocampal neurotrophic growth factor loss. The loss glial cell-derived neurotrophic factor (GDNF) is believed to disturb neuronal homeostasis and thus upset their defence systems. One open-label study using intraputamenal GDNF gene therapy showed clear positive results using humans; however a similar but double-blind, placebo-controlled trial illustrated no such effect. Possible reasons for this include that the double-blind trial used patients with too mild PD to demonstrate benefits and a too brief follow-up period (six months).\(^8\) Trials with GDNF therapy were halted, but are soon to be resumed since relicensing of the molecule.\(^9\)

Cell replacement, on the hand, may remain forgotten. Replacement of degenerated nigral neurons with healthy foetal ones once looked to be promising for the future of PD, but recent follow-up studies described that the grafts develop same pathology as host nigral cells after a decade.\(^6\)

**Improving symptomatic control**

Whilst it is beneficial to investigate dramatic ways to alter the outcomes in PD, it is also vital to consider more short-term methods.

Neuropsychiatric symptoms in PD are now surfacing, but little progress has been made in their treatment. PD-induced depression is now recognised as mostly the product of
dopamine insufficiency in the SN and locus caerulus. Although dopamine agonists have been shown to be beneficial, no data looking at PD-induced depression as a primary-outcome has been published. Treatment of psychoses in PD is limited by the fact that symptoms are often the consequence of dopaminergic medication and the majority of antipsychotics block dopamine action; thus exacerbating PD’s motor features. Admittedly since the more widespread of usage of atypical anti-psychotics, this has been less problematic. Cognitive decline, on the other hand, is a huge problem in PD, particularly as anticholinergics accelerate the process. Pain and insomnia are also poorly managed and greater attention to these features may improve patient quality-of-life. Probably one of the most significant aspects of symptom control that needs to be addressed is the “on-off effect”. This phenomenon consists of alternating bouts of dyskinesia and immobility, and is associated with desensitisation to long-term levodopa. An exogenous dopamine source at all times seems to be the most effective method to tackle the effect. This may be in the form of apomorphine (subcutaneous non-selective dopamine agonist) COMT-inhibitors (prevent neuronal breakdown of dopamine), and duodenal (infusion using PEG) transdermal and controlled-release levodopa. In addition, early use of dopamine agonists and MAO-inhibitors has been shown to delay the initiation of levodopa and lower its dose.

Conclusion

So can we change the outcomes of PD? Ultimately, there is no straightforward answer. At present, utilising treatments we already have more appropriately appears to be the most effective method at our disposal. This includes prescribing dopamine agonists and MAO-inhibitors earlier and ensuring sustained-dopamine administration to abbreviate “on-off” periods. Identifying non-motor features such altered sleep, pain and depression and treating them also has a huge effect on patient quality-of-life.

Unfortunately, apart from rasagiline, none of the drugs of mainstay PD treatment have been shown to combat the long-term outcomes of PD. However, although approaches such as cell replacement and anti-oxidants have failed in studies, research has proposed initiatives that could employed in both the near and more-distant future. This essay believes that a simple screening scheme is the necessary first step in ensuring clinicians intervene in PD earlier; but producing screening criteria is difficult. Another way of improving long-term outcomes of PD is preventing progression. Certain NSAIDs such as ibuprofen have some evidence for
such activity, and their low-costs would be welcomed if they became part of the core
treatment for PD. GDNF gene therapy has had mixed results, but hopefully further research
will give a greater insight into whether it may resume normal functioning in PD patients in the
relatively distant future.

In conclusion, we can currently change PD outcomes to an extent but it may be some time
before we can prevent or cure the disease.
References:


