BGS Movement Disorders Award

Innovation and Integration: Changing Outcomes in Parkinson’s Disease

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Introduction

Parkinson’s disease (PD), a neurodegenerative disorder traditionally defined by its cardinal features of rigidity, tremor and bradykinesia, was first described by James Parkinson in 1817. Whilst this traditional diagnostic criterion focuses on the motor manifestations of PD, there has been increasing recognition of the variety of non-motor features including autonomic, sleep, sensory and neuropsychiatric disturbances. Indeed, some of these features can even predate the motor features during the onset of PD. Thus when addressing improving outcomes in PD; one must recognise that the all encompassing nature of the disease provides a broad scope for potential interventions.

Neuroprotection: Delaying progression

Given the chronic progressive nature of PD, there has been much interest in the potential to improve long term outcomes, particularly motor fluctuations and dyskinesia which often complicate levodopa treatment. Whilst the relative short term efficacy of medications currently utilised in PD is reasonably clear, much less is known about long term efficacy and side effects. One of the most promising avenues with current drugs is the possibility of using MAO-B inhibitors to improve long term outcomes, even after levodopa and dopamine agonist therapy are initiated. In a prospective 7 year randomised double-blinded study, subjects with early PD that were randomised to selegiline exhibited slower progression of symptoms and a delayed need for levodopa over placebo subjects in the initial monotherapy phase of the trial. After 78 months, early selegiline was associated with a significant reduction in tremor, bradykinesia and rigidity, lower levodopa dose requirements and better UPDRS scores compared to placebo. Moreover, several similar studies investigating selegiline and rasagiline have exhibited similar results, inferring that earlier initiation and longer exposure to MAO-B inhibitors improves long term outcomes. Similar studies have looked at initial dopamine agonist treatment compared to levodopa in early PD treatment. Overall, whilst a reduction in incidence and onset of dyskinesia was noted, there were no clear differences in overall function and quality of life in the long term. Future studies may seek to predict those who are likely to develop disabling dyskinesia and evaluate early dopamine agonist therapy in this subgroup.

Managing non-motor symptoms of PD

With the increasing recognition of the broader clinical spectrum of PD, recent research evaluated the impact on the quality of life (QoL) from prevalent non-motor features such as depression, autonomic dysfunction and sleep problems. A common finding is that psychosocial well-being has a larger impact on QoL than physical functioning. Despite the high prevalence and disability burden of non-motor symptoms in PD, physician recognition of such clinical features is low. This challenges the widespread predilection for combating the motor features of PD that has existed until recently.

Having made progress in defining the common non-motor manifestations of PD, the next priority is to develop PD-specific tools of assessment to identify and evaluate the severity of such features that are currently underrecognised, hence underreported and undertreated. One example is evaluating psychosis in PD. Since hallucinations and psychotic behaviours occur frequently in PD...
and often go undetected, there is a clear need for tools than can identify such phenomena. Currently, most assessment tools for psychosis are derived from studies in other psychotic disorders like schizophrenia. There is a requirement for a PD-specific tool that recognises and accounts for the variations in psychosis seen between PD and other psychotic conditions, hence becoming a more valid tool of assessment.

On a similar thread, emerging evidence theorizes that not only might behavioural symptoms in PD differ from those observed in the general population with regards to clinical features, but may also vary in the underlying pathophysiology. Thus, simply adopting treatment paradigms based on psychiatric literature derived from non PD populations may be insufficient. Furthermore, there becomes a clear need for randomised controlled trials, evaluating the effectiveness of currently favoured treatments with alternatives to establish best practice.

Non-pharmacological interventions

Given the all encompassing nature of PD and the limitations of current pharmacotherapy and neurosurgical approaches, allied health care provides another set of resources that may complement the former. These resources include those covered by physiotherapy, speech and language therapy (SALT) and occupational therapy. Examples of evidence based physiotherapy interventions include application of cueing strategies to improve gait and cognitive movement strategies to improve transfers. SALT can be useful in addressing hypokinetic dysarthria, swallowing disorders and drooling which often occur in PD.

However there are obstacles currently limiting the application of allied health care in PD. Firstly, allied health interventions are currently often utilised in isolation, with a lack of understanding amongst healthcare professionals and hence integration of the various interventions alongside current standard care. In addition, there is a current paucity of quality randomized controlled trials to define the efficacy of many potential interventions that fall under the umbrella of allied healthcare. Furthermore, the heterogeneity of individuals with PD may dictate that the effectiveness of certain interventions will vary between PD subgroups. Currently a large national trial, PD REHAB, is underway and aims to address these issues with regards to physiotherapy and occupational therapy. The results of this trial should assist in the ability to ‘tailor’ these treatment approaches to PD patients, resulting in better patient outcomes and limiting unnecessary interventions.

Novel strategies

Whilst current therapeutic strategies aim to improve the motor manifestations of PD, there are three current limitations that remain unresolved:

- Managing the “dopa-resistant” motor and non-motor symptoms.
- Managing the drug-related dopaminergic side effects.
- Halting, slowing or reversing the progression of PD.

Although advances are being made with the first two of these challenges, the ultimate goal is to stop, slow or reverse the progression of PD and thereby render the first two challenges almost obsolete.

Pathological and neuroimaging studies have elicited the presence of a ‘subclinical’ period (Fig.1 a-d) where characteristic dopaminergic neuronal degeneration occurs in the absence
of motor symptoms. This subclinical period has been speculated to begin 10 to 20 years before the onset of motor symptoms. Should the ability to detect pre-motor PD be acquired, it would be fascinating to evaluate the potential of existing or novel therapies to delay or halt progression.

One promising novel therapeutic approach that would significantly benefit from early PD diagnoses is targeting mitochondrial dysfunction. This approach stems from a volume of evidence from animal models, post-mortem and genetic analysis implicating mitochondrial dysfunction as a significant pathological mechanism in PD. Within this field, creatine supplementation is currently the most advanced option and has been shown to possess neuroprotective activity in vitro and in vivo studies. Phase II trials have elicited an improvement in mood and delayed progression of UPDRS scores in creatine supplemented groups and a phase III trial is now underway. Delving further into this field, mitochondrial targeted antioxidants and peptides also have promise by combating reactive oxygen species at the site of origin in the mitochondria itself.

Another approach that aims to restore neurological function in PD is cell-replacement therapy. Clinical trials with human foetal graft transplantation in the late 1980s demonstrated a proof of concept that dopaminergic cell replacement can achieve clinical benefit in PD. Unfortunately, two more recent trials failed to show significant benefit, with focus shifting to other potential cell sources. Embryonic stem cells (ESC) are one such source. Interestingly, by pre-differentiating ESCs into dopaminergic neurons prior to transplantation, their tumorigenic potential appears to be significantly reduced. However, in addition to tumorigenic risk, other limiting factors to this approach include graft-induced dyskinesias and that grafts appear to be susceptible to PD pathology propagation.

An alternative strategy is to utilise and manipulate endogenous neurogenesis. By understanding the processes which dictate endogenous stem cell activation, differentiation, migration and integration; it

![Figure 1. Schematic of the current concepts on the natural history of early PD. (a) Neuronal dysfunction begins but the brain can compensate, preventing the expression of symptoms. (b) Initial non-motor symptoms occur (smell loss, rapid eye movement (REM) sleep disturbances and so on) (c) Cardinal motor symptoms occur but not yet noticed by the patient. (d) Motor symptoms now noticeable by patient prompting presentation and diagnosis. Figure reprinted from Schapira et al. With permission.]
may become possible to moderate these pathways and hence avoid more invasive interventions such as grafting.\textsuperscript{10} Despite the undoubted obstacles, cell-replacement therapy represents an exciting and developing potential strategy for ‘neurorestoration’ in PD.

**Conclusion**

Since it was first described in 1817, the progress in the understanding of PD and the available management strategies has been steady but profound. However, the challenges facing the research community today have remained steadfast and PD sufferers face much the same outcomes as they did 10 years ago. Despite this, advances in understanding of the aetiology, pathophysiology, preclinical diagnosis, management and novel therapeutic strategies are creating a sense of momentum. Through bringing together and integrating such advances from all the fields discussed, the prospect of redefining the outcomes of PD remains an exciting possibility.

**Words: 1,476**

**References**


10. Luo Y, Kuang SY, Hoffer B. How useful are stem cells in PD therapy?