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Review article

Challenges in detecting disease modification in Parkinson's disease clinical trials

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ABSTRACT

Despite the wealth of encouraging data from numerous compounds that demonstrate "neuroprotection" in pre-clinical studies of Parkinson's disease, and despite numerous clinical trials, to date, no intervention has been demonstrated to able to modify the course of disease progression. While this "failure to translate" is likely due to numerous factors including our incomplete understanding of the pathogenic mechanisms underlying PD together with excessive reliance on data from the toxin-based animal models of PD, here we will discuss the "structural issues" pertaining to inadequate clinical trial design, selection of inappropriate endpoints and poor patient selection which are often not addressed following failed disease modification trials. Future directions to overcome these challenges such as reducing the heterogeneity of patient cohorts, identifying and utilising a pre-diagnostic population, embracing a personalised medicine approach and utilising novel trial designs may be required to ultimately fulfil the goal of conclusively demonstrating evidence of disease modification.

Despite the development of several effective pharmacological and surgical therapies for the treatment of Parkinson's disease (PD), the ultimate goal of slowing of disease progression has not been met. Over time motor symptoms of tremor, rigidity and bradykinesia are invariably complicated by continued degeneration of non-dopaminergic systems leading to mood and behavioural issues, dementia and postural instability leading to worsening functional disability and self-care. Pre-clinical studies have focused on halting or preventing this dopaminergic cell loss and numerous "neuroprotective" compounds have been demonstrated with the hope that these properties will translate to human subjects and slow the progression of symptoms and modify the expected disease course. However, despite the promise of many therapies in pre-clinical trials, no disease modifying trials conducted to date have conclusively demonstrated evidence of disease modification.

This general "failure to translate" is likely related to numerous factors including our incomplete understanding of the pathogenic mechanisms underlying PD together with excessive reliance on data from toxin-based animal models of PD to judge which agents to take to double blind clinical trial evaluation. Detailed discussion of these factors is outside the scope of this article and will not be discussed here (see Ref. [1] for review).

Inherent errors in data collection when conducting clinical trials are mostly unavoidable and often result in diluted effects, the need for larger sample sizes and increased costs. However, "structural errors" pertaining to inadequate trial design, selection of inappropriate endpoints, poor patient selection, or mishandling of missing data, can be minimised and increase the chance of detecting true disease modifying effects [2,3]. This review will consider methodological issues relating to detecting efficacy in disease modification phase III trials and suggest future directions that are being explored that may improve the ability to detect any signal of effect. Earlier stages in drug development and clinical trials present their own specific challenges and these will not be addressed (see Refs. [4,5] for review).

1. Target population for clinical trials

PD patients exhibit remarkable heterogeneity – studies suggest that different pathophysiological mechanisms relate to different clinical subtypes and this disease heterogeneity can influence disease progression [6,7]. Therefore it may seem somewhat counter-intuitive to gather such a heterogeneous group of patients and expect a uniform response to a particular intervention.

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Nevertheless, in all disease modifying trials to date this has been the general approach.

Common methods of refining patient selection are to recruit patients only at a specific stage of disease, although this is by no means a way of predicting subsequent rates of disease progression. Nevertheless, in considering patient recruitment to trials of potential disease modifying interventions, patients can be divided into two categories – early untreated "de-novo" symptomatic patients and those patients on stable dopaminergic treatment that experience disability – both of which have merits and disadvantages for inclusion into disease modifying trials (Table 1).

Another factor when selecting patients is that motor progression in PD is not linear and is thought to occur in phases. Factors such as age of onset, predominant motor phenotype and presence of non-motor symptoms can influence disease severity at presentation, rate of disease progression, and most importantly, response to treatment [8], suggesting the existence of various sub-types of PD. These baseline differences are often not always appreciated when incorporating data into the primary outcome.

2. Future directions – improving patient selection and stratification for clinical trials-

2.1. Reducing heterogeneity of cohorts

Methods to reduce the heterogeneity of patient populations and enable the prediction of rates of disease progression may reduce inherent variability that currently exists between individual participants in a trial and thus increase its statistical power, in turn enabling more efficient and cost-effective collection of data and increase the likelihood of detecting a signal of effect.

Although there are ongoing efforts to identify PD subtypes, well-defined criteria have not yet been widely accepted, but by using clinical, biochemical or genetic markers (or a combination) researchers may be able to improve patient stratification for inclusion of more homogeneous cohorts into future trials (Fig. 1).

Basic clinical markers (i.e. motor phenotype) can be potentially useful to predict disease progression. Analysis of data from the Parkinson's Progression Markers Initiative (PPMI) database suggests that older age of onset is associated with a more severe motor and non-motor phenotype, greater dopaminergic dysfunction on DaTSCAN, and reduction of CSF alpha synuclein and total tau [9]. Similarly tremor-dominant PD is associated with slower disease progression and less-severe cognitive impairment than akinetic-rigid PD [10], while a recent study demonstrated that the presence of mild cognitive impairment, orthostatic hypotension and REM Sleep behaviour disorder at baseline is associated with a more malignant disease course [11]. Building on this, a recent model has been validated that allows individual patient prognostication. Based on 3 predictor variables, namely higher patient age, higher Unified Parkinson's Disease Rating Scale motor examination axial score, and a lower verbal fluency score for animals at baseline, patients can be reliably predicted to be more likely to develop non-levodopa responsive symptoms of dementia and postural instability at 5 years from diagnosis [12]. These simple variables could be used to create a more homogenous cohort with a predictable disease course.

Clinical markers may however be unstable in early disease and may also be substantially influenced by symptomatic therapy [13]. Recent studies suggest that biochemical markers may be able to more precisely identify molecular subtypes that have differential responses to treatment. A recent study suggested that patients with low levels of Aβ1-42 or highest t-tau/Aβ1-42 had more severe non motor dysfunction, whereas lower alpha-synuclein levels were associated with worse cognitive performance [14] and therefore may potentially be useful to predict patient subgroups likely to have accelerated disease progression. Similarly, the presence of high levels of pro-inflammatory immune markers in patient serum is associated with more rapid motor progression and lower MMSE scores [15].

Table 1
Patient suitability for disease modifying clinical trials.

De novo untreated patients	Symptomatic stable treated patients
Advantages	**Advantages**
• Considered "early" disease – more salvageable neuronal population (30–50% of neurons lost) [1,2]	• Easy to identify and recruit into trials
• No cofounding effects of symptomatic medication	• Clinical changes in disability more likely to be detected rating scales
• Minimal clinical fluctuation	• Less likely to include recruiting patients without idiopathic PD
Disadvantages	**Disadvantages**
• Fewer in number, recruitment is slow, incurring greater expense	• Symptoms influenced by effects of medication
• Patients with greater disability at baseline will have shorter "untreated" tolerable window – narrowing chance to detect disease modifying effects	• Clinical fluctuation and variable response to medication make longitudinal assessments difficult
• Maintaining patients with mounting disability on placebo may be unethical	• "Ceiling" effects of clinical rating scales such as UPDRS make changes in advanced disability difficult
• Increasing disability in some patients may induce high dropout rate – leading to over representation of patients with slower disease course	• In trials with placebo arm, may exhibit increased magnitude of placebo effect
• Drop out may lead to difficulties with data analysis	• Advanced neurodegeneration may mean that any neuroprotective therapies may be "too little, too late"
• Risk of including patients with atypical forms of parkinsonism (and alternative pathologies) – 10% of patients clinically diagnosed with early PD have SWEDD who majority do not go to develop PD [3,4]	• Greater number of co-morbidities in advanced population may preclude lengthy longitudinal assessments [5]
• Clinical rating scales at early stage disease may not be sensitive to detect changes in disability and create floor effects	• Heterogeneous clinical progression
• Heterogeneous clinical progression	

2.2. Embracing precision/personalised medicine

Additionally, identification of genes involved in familial PD has suggested that distinct pathophysiology could also underlie different forms of PD [16] and also affect clinical phenotype and motor progression [17]. This may allow trials to offer "personalised" interventions that specifically target an aspect of PD disease pathophysiology known to be abnormal in individual patients and recruit patients accordingly, increasing the chance of influencing disease progression. A recent study using neural cells generated from induced pluripotent stem cells derived from PD patients and pre-symptomatic individuals carrying mutations in the PINK1 (PTEN-induced putative kinase 1) and LRRK2 (leucine-rich repeat kinase 2) genes [18] analysed the subsequent cellular responses when treated with potential neuroprotective agents coenzyme Q10, rapamycin and LRRK2 inhibitors. The study indicated that treatments had varying levels of effectiveness, depending on the genetic mutation involved; for example rapamycin reduced oxidative stress and mitochondrial stress in LRRK2 mutant neural cells but not in PINK1 patient neural cells. This technology could be used to predict drug efficacy, and identify potential drug-responsive cohorts for selection in clinical trials.

A precision or personalised medicine approach in combination with genetic and epigenetic testing is commonplace in patient selection for cancer clinical trials and has yielded numerous successes. Patients with breast cancer that overexpress human

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