Disease-modifying therapy trials in PD: what are the issues?

**Summary**

- There is a major unmet need for therapies that slow or stop neuronal cell death in neurodegenerative disorders including PD. Conventional methods of developing new therapies are expensive and have yielded little.
- Innovations in trial design such as the use of re-purposed therapies in studies with multiple arms show much promise.
- Better modeling of PD progression through Natural History studies will contribute to improved trial design.

The search for therapies capable of modifying, slowing or stopping neuronal cell death in neurodegenerative disorders remains elusive. In Parkinson’s disease (PD) a range of agents have been studied as potential disease-modifying therapies (DMTs), including oral agents, and neurotrophic factors and gene-transfection therapies delivered directly to the striatum. Transplants of tissue derived from foetal ventral mesencephalon have also been used with variable outcomes (reviewed in reference 1). It is envisaged that a better understanding of cellular re-programming events will soon herald an exciting new era of cell-based therapies for PD, with disease-modification becoming a realistic proposition.

However, studying DMT effects in PD is far from straightforward. Historically, the promise shown by many agents in phase II trials has not translated into benefits in larger phase III studies. Fundamental flaws in the design of these trials has contributed to this failure rate. In this article I outline the issues which we face in conducting trials of DMTs with particular reference to PD, and explore how innovations in clinical trial conduct and design might aid our evaluation of this exciting new generation of therapies.

**Selection of candidate therapies for DMT trials**

The conventional approach to developing a novel therapy is summarised in Figure 1. There are three main stages: Discovery (target identification, identification of lead compounds through screening, optimisation of lead compound), preclinical evaluation (pharmacological efficacy, evaluation of toxicology and interactions) and clinical development (phase I,II and III trials). Whilst this approach appeals to the scientific rationalist in us, it is time-consuming and costly and has yielded few if any successes in Neurology, and none in the area of DMT.

Alternative strategies must be considered. The re-purposing or re-positioning of drugs already approved in other indications is an increasingly popular approach.¹ The principle is that biological active compounds approved in other indications may have additional ‘off-target’ effects, including neuroprotective effects. By focusing upon agents with existing regulatory approval and safety data we can circumvent some of the cost and time constraints associated with drug development, and in some fields the success rates for re-positioned drugs approaches 30%.

Trials of repositioned drugs are already taking place in Neurology: Dimethyl Fumarate and, more recently, Simvastatin have shown effects in Multiple Sclerosis.¹ In PD, a number of such studies are ongoing (reviewed in reference 6). Exenatide, originally developed as an anti-diabetic drug, has been reported to show DMT properties in a small, open-label ‘learning trial’.² On the strength of such studies collaborative initiatives to advise on and coordinate learning trials of re-purposed agents have been formed.³ Selection of appropriate candidates is the most critical and difficult aspect: criteria such as an ability to penetrate the blood-brain barrier, effects in animal models and a proposed mode of action which accords with current understanding of PD pathogenesis could all reasonably be used. Scientifically this approach is less satisfying: the links with insights from basic science are weakened and, to an extent, it is hypothesis-generating rather than hypothesis-testing. Putative pathogenic mechanisms are invoked after the fact to explain observations, although it is plausible that useful insights into neurodegenerative mechanisms may be uncovered.

**Trial Design**

Given that the natural history of treated PD typically runs for many years, trials of putative neuroprotective agents are likely to involve lengthy follow-up periods in large sample groups. The costs of running such trials is considerable, but could be mitigated, for example, by applying futility designs in pilot studies using smaller sample sizes, screening out therapies which are unlikely to prove effective. Futility designs typically involve the comparison of a single treatment arm with a pre-determined lower limit of success (or an upper limit for worsening) in a one-sample test.⁴ Therapies performing above criterion can then be selected for larger, phase III studies (“seamless” transition). Multiple futility studies can be run in parallel (multi-arm or nested designs), including arms using combinations of therapies (Figure 2). Should one or more arms close, participants can be moved to alternative arms (adaptive design). Efficient trial designs reduce turnaround time and trial costs.
One problem inherent in the application of futility designs to the study of DMTs in neurodegeneration is that such a design assumes that the absence of short-term efficacy precludes long-term efficacy. Theoretically, an agent modifying neuronal cell death signals may show a slow development over such a time-frame would be facilitated. The use of clinimetric rating scales introduces a further issue, namely the extent to which objective responses on such scales translate into day-to-day benefits for patients. As clinicians, instinctively we hone in on p-values, in so-doing prioritising statistically significant differences ahead of clinically important differences. The Minimal Clinical Difference (MCD) is the minimum change on a scale which can be recognised by a control arm, but alternatively control data could be derived from algorithms applied to natural history models.

Related to this is the need to ensure DMT trials are powered appropriately. A priori sample size calculations require an estimate of the anticipated effect size, which may be unknowable. An alternative strategy would be to accept a consensus MCD and base power calculations upon this. It is also necessary to allow for the fact that ‘early looks’ at the data – as would be required in nested or futility designs – reduce statistical power.

The placebo and ‘less-ebo’ effects in PD trials

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The placebo and "less-ebo" effects in PD trials

It has been suggested that the placebo effect is more powerful in PD than in other disorders. There may be an additional confounder that we need to consider in PD: the so-called ‘lessebo’ effect. This term describes a phenomena that emerged from a meta-
analysis of RCTS of dopamine agonists conducted by Mestre et al. The magnitude of the benefit of active drug (UPDRS-III improvement) was reduced in studies that employed a placebo arm. In other words, if participants knew there was a chance of being assigned to placebo, the benefit of the active drug was reduced. Furthermore, the size of this ‘lessee’ effect was proportional to the prior odds of being assigned to placebo. The use of control information derived from natural history models rather than employing a conventional control arm would be one method to reduce the effect of this potential confounder.

**Conclusions**

This review, though by no means comprehensive, has highlighted the important challenges facing clinical trials of DMTs in PD, and by extension other neurodegenerative disorders. Perhaps the neurological community needs to set aside certain scientific prejudices. The selection of agents based on their ability to engage particular targets is inefficient and, I would argue, we must be more pragmatic in our approach. High throughput screening of compounds for DMT effects, including re-purposed therapies, must take advantage of modern trial design innovations. Improved biomarkers of true disease progression should be sought and utilised, and better models of the natural evolution of the disorder with time must inform our selection of meaningful and relevant outcome measures for DMT trials.

This is an exciting era in PD therapeutics: International initiatives such as the cell-transplantation programme TransEuro serve testament to this. Proving the benefits of novel DMTs will require a systematic approach to clinical trial design. This remains a considerable challenge, but one which we are increasingly able to meet.

**REFERENCES**


4. Fox RJ, Miller DH, Phillips JT, Hutchinson M, Havrdova E, Kita M, et al. The benefit of active drug (UPDRS-III improve -control arm would be one method to reduce m odels rather than em ploying a conventional information derived from natural history m ent) was reduced in studies that em ployed a knew there was a chance of being assigned to placebo arm. In other words, if participants the effect of this potential confounder.


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**The 7th PRACTICAL COGNITION COURSE**

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