

## How Drugs May Slow Disease Progression

Nick Holford

*University of Auckland, Auckland, New Zealand*

**Objectives:** To introduce the concept of disease progression and the challenges for clinical trials of disease modifying drugs

**Disease Progression:** Symptomatic drug treatments produce effects that are simply additive offsets to the natural history of disease status. These effects may occur rapidly or develop slowly. Disease modifying treatments change the rate of progression of a disease and this will typically take some time to manifest. The distinction between symptomatic (offset) effects and disease modifying effects is important for extrapolating the benefits of continued treatment beyond those observable in typical clinical trials (1). With a limited time horizon for observing the effects of drug treatment it may be impractical to distinguish symptomatic effects from disease modifying effects because both may develop slowly and not reach a steady state before the end of a trial. Under specific assumptions about the time course of drug effects it may be possible to distinguish these two kinds of effects.

**Clinical Trials:** Attempts to identify disease modifying effects of drug treatments in Parkinson's disease have been fraught with difficulties of interpretation (2-4). Three trial designs have been discussed to try to identify disease modifying effects – parallel group, washout and delayed start. Model based descriptions of the response to levodopa (5) and washout (6) successfully predicted the magnitude of response (7) in a washout trial design (3). However, evaluation of the properties of trial designs requires prospective simulation of treatments with known properties. The complexities of the time course and relative contributions of symptomatic and disease modifying effects point to the need for a parametric mixed effect modelling approach to the analysis of this kind of clinical trial.

### References:

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