Title: Optimizing trial designs for distinguishing short (symptomatic) and long-term (protective) treatment effects from natural disease progression.

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Objective: We have explored the advantages and disadvantages of parallel group designs with or without washout and delayed start designs to help understand the difficulties in defining a long term (disease modifying) effect of drug treatment in slowly progressive diseases.

Introduction: Parkinson’s and Alzheimer Disease are neurological diseases which progress relatively slowly (years). Ideally, treatment should slow down or even reverse the progression of the disease. The onset of the treatment effect might either be short and reversible after cessation of treatment or long and persisting after stopping treatment. Reversible short term effects are referred to as ‘symptomatic’ while long-term effects are referred to as ‘protective’ or ‘disease modifying’ [1]. In order to estimate the actual treatment effect it is essential to distinguish the time course of treatment effects from those due to natural disease progression. Therefore, changes in clinical status over time in untreated patients should be taken into consideration in the analysis of clinical trials in slowly progressing diseases [1]. In addition, the trial design should allow for distinguishing short-term and long-term treatment effects from natural disease progression. Examples of trial designs which try to distinguish symptomatic from protective effects include the delayed start and the parallel group designs with or without follow-up after treatment withdrawal. In the delayed start design, one of the groups receives placebo treatment first for a period of say 6 months followed by active treatment for the same period, whereas another group receives active treatment immediately and continues for 12 months. A different clinical response at the end of the trial for the immediate start group compared to the delayed start group is considered to be due to disease modifying effects. The change in the unified Parkinson’s disease rating scale (UPDRS) over time for a drug with an effect on the slope and offset of the natural disease progress in the 3 different designs is illustrated in figure 1.

The effects of levodopa were studied in the ELLDOPA trial with a washout design [2] and rasagiline effects were studied in a delayed start trial [3]. Both trials can be interpreted as showing long-term ‘protective’ effects. However, conclusions require assumptions on the time-course of untreated disease progression and drug action. A disease modifying effect of levodopa, which supported earlier exploratory analyses [4], is dependent on assuming a relatively rapid wash out of the symptomatic effect [5]. The analysis of the rasagiline trial assumed maximum placebo effect was achieved within 6 months without considering the possibility of a slow onset symptomatic effect.

Methods: Effect sizes of rasagiline [3] and deprenyl [6] were estimated by analyzing naïvely pooled data on the time-course of UPDRS in placebo and active treatment groups. Disease progression modeling included effects on the offset, slope or both offset and slope under the assumption of linear disease progression in untreated patients. The between subject variability in the treatment effects was set to the previously estimated values of deprenyl [4]. The washout and delayed start designs were implemented in WinPOPT, which is designed to optimize the determinant of the Fisher information matrix [7]. The Fisher information matrix criterion obtained with a mixed effect non-linear regression model was used for comparison of the designs.

Results: No rasagiline effect on the slope of the disease progression could be estimated when the naïvely pooled rasagiline data from the delayed start trial showed was analyzed with a disease progression model. These data were best described with a model with just an offset effect of rasagiline of approximately -5 points in the UPDRS score. On the other hand, a combined slope and offset effect could be identified for deprenyl with values of approximately -5 UPDRS unit/year and -1 unit respectively.

The effect sizes obtained from the deprenyl analysis were used to investigate design efficiency. A washout-out period of 3 months after 9 months of treatment in a placebo controlled parallel group design resulted in an
approximately 50% more efficient design compared to a 12 month treatment period without washout. The washout-design is approximately 44% more efficient than a delayed start trial in which subjects are switched to 6 months of active treatment after 6 months placebo treatment.

**Conclusions:** Under the assumption of the same treatment effect size, trial duration, number of subjects, treatment groups and status measurements a washout design is more efficient to distinguish the time course of treatment effects from those due to natural disease progression compared to a delayed onset design or a parallel group design without washout.

**References:**


