

The Randomized Start Design for Assessing Disease-Modifying Effects in Parkinson Disease: Issues and Controversies

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With acknowledgements to my colleague

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Disclosures/Disclaimers

- I was heavily involved in and am a co-author of publications from the “TEMPO” study of rasagiline in PD (conducted by the Parkinson Study Group and sponsored by TEVA Pharmaceuticals) which will be referenced here.
- I did not receive any personal compensation for this work.
- I am not involved with the subsequent “ADAGIO” study of rasagiline, which has been reported recently.
- Any opinions expressed in this talk are mine alone.

Why “Disease-Modifying”?

- Symptoms of Parkinson’s disease (PD) are caused by the degeneration of certain neurons in the brain which produce an essential neurotransmitter, dopamine.
- Many drugs are available that can, in the short term, replace the missing dopamine or enhance the effect of the reduced amount being produced.

Why “Disease-Modifying”?

- These medications (e.g. levodopa, or dopamine agonists) usually provide some immediate relief of symptoms.
- However they tend to lose effectiveness over time, requiring increasing dosages, and/or use of different medications in combination, increasing the likelihood of unacceptable side-effects.
- We do not have an unambiguous way to measure the progression of the underlying disease process (*whatever that is*).

Single-Period Design

- In the usual placebo-controlled study patients are randomized to one or more dosages of active medication or to placebo, and changes in certain functional scales from baseline to last visit are compared between the groups.
- Most common outcome measure in PD trials is the “UPDRS” – Unified Parkinson’s Disease Rating Scale – and its Mental, ADL and Motor components.

Single-Period Design

- In the course of a typical 6 or 12 month trial in patients with early, previously untreated PD, many patients will reach a level of disability that requires additional “symptomatic” therapy prior to their completing the study.
- This may confound assessment of the primary outcome.
- Usual to analyze data only up to this “endpoint” determination, together with an imputation scheme (e.g. LOCF).

Two-Period Designs

- For these reasons, and the lack of any validated marker of disease progression in PD, it can be hard to distinguish effects of study medication due to relief of symptoms from true effect on disease progression.
- This has led to consideration of alternative study designs in which some or all patients switch treatment during the course of the study – so-called “Two-Period Designs”.

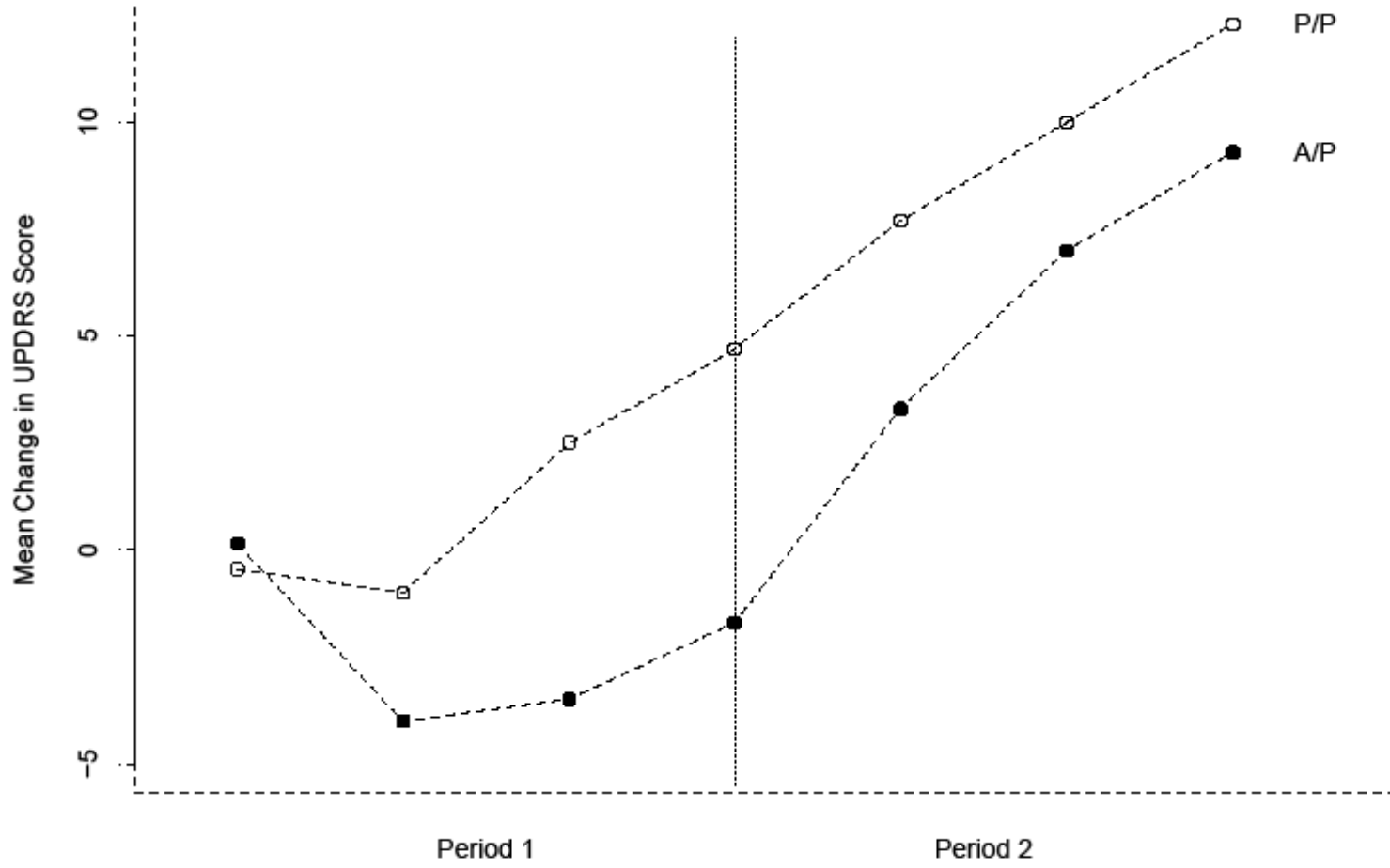
Two-Period Designs

- Problems with single-period designs
 - Difficult to determine whether treatment effect is symptomatic, disease-modifying, or both
 - Absence of valid markers of underlying disease progression
 - Reliance on clinical measures of outcome

Withdrawal Design

- Leber (1996)
- Subjects randomized to active treatment followed by placebo (A/P) vs. placebo followed by placebo (P/P)
- Period 1: Estimation of total treatment effect ($\alpha_T = \alpha_D + \alpha_S$)
- Period 2: Estimation of symptomatic (α_S) and disease-modifying (α_D) components

Withdrawal Design



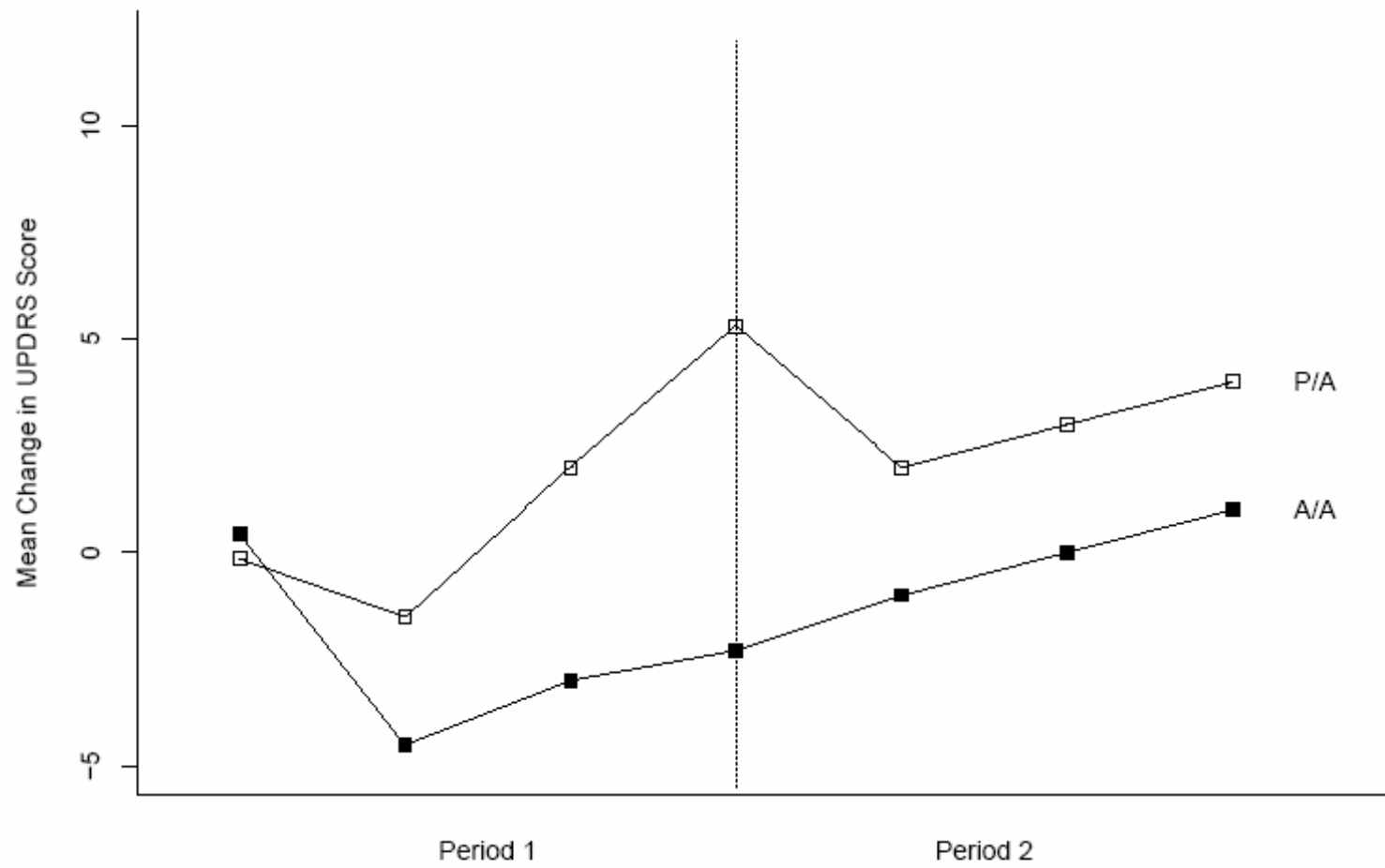
Withdrawal Design

- Potential problems
 - Lack of blinding in Period 2
 - Differential bias in evaluation of those declining more rapidly?
 - Difficulties in subject recruitment and retention

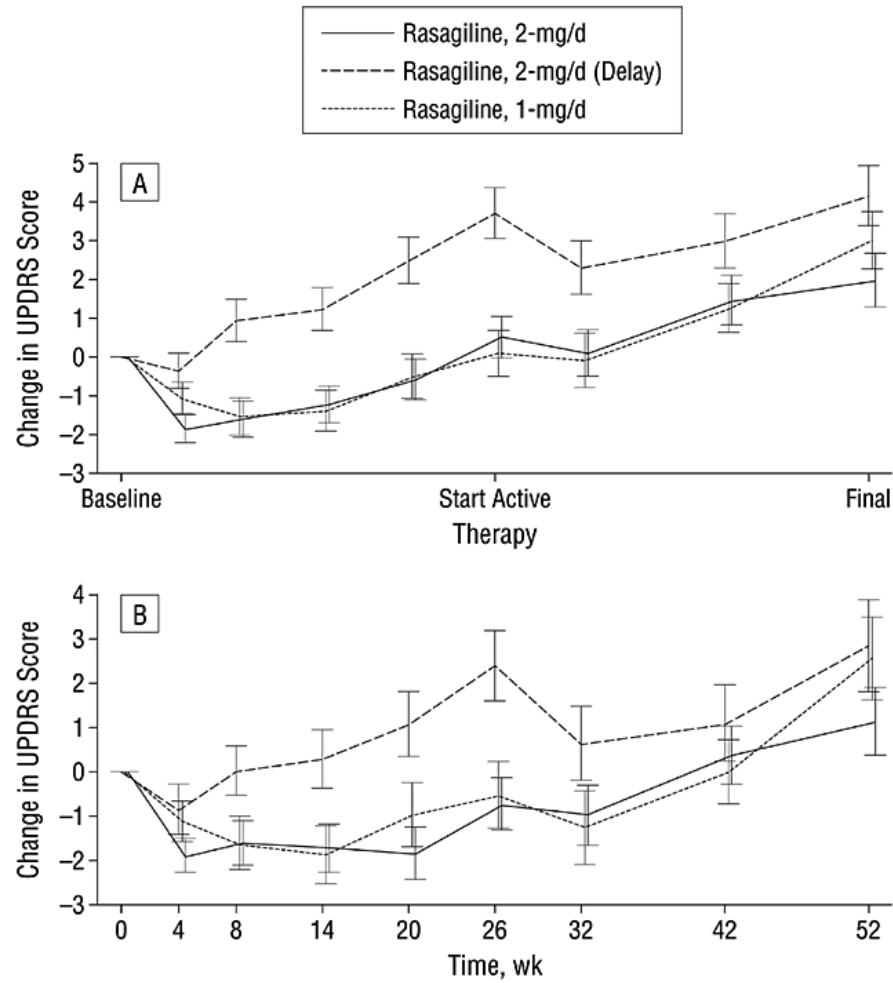
Delayed Start Design

- Leber (1996); Bodick et al. (1997)
- Subjects randomized to active treatment followed by active treatment (A/A) vs. placebo followed by active treatment (P/A)
- Period 1: Estimation of total treatment effect ($\alpha_T = \alpha_D + \alpha_S$)
- Period 2: Estimation of symptomatic (α_S) and disease-modifying (α_D) components

Delayed Start Design



Delayed Start Design in the TEMPO Trial



Parkinson Study Group. Arch Neurol 2004; 61:561-566.

Further Analytic Issues

- It is generally accepted that one should proceed to test the “disease-modifying effect” (effect at the end of Period II) only if there is an effect at the end of Period I.
- Logically, this is not necessary, because the two effects (symptomatic and disease-modifying) could be in opposite directions.
- For true “disease modification”, the curves should remain separated following the end of follow-up.
- This data is not observable, but we can test whether the two curves are converging and, if they are, estimate the point where they would meet.

Model Assumptions

- Disease-modifying effect acquired during Period 1 remains with the subject through the end of Period 2.
- Symptomatic effect acquired during Period 1 disappears by the end of Period 2.
 - Can be difficult to verify.

Model Assumptions

- Incremental effect acquired during Period 2 is the same for the P/A and A/A groups
 - Magnitude of the incremental effect is independent of whether or not the subject received active treatment during Period 1
 - Strong assumption that may compromise the ability of a delayed start design to provide a conclusive distinction between symptomatic and disease-modifying effects
 - Can be tested in a more complex design (complete two-period design, McDermott et al. 2002).

Issues in Implementation

- Lengths of follow-up periods
 - Period 1 needs to be long enough for the disease-modifying effects of treatment to become apparent
 - Period 2 needs to be long enough to allow the symptomatic effects of treatment to completely disappear (withdrawal) and/or become fully apparent (delayed start)
 - Long duration or slow-onset of symptomatic effect

Issues in Implementation

- Lengths of follow-up periods
 - Above assumptions are very difficult to test
 - Concerns about retention and the need for dopaminergic therapy are greater as the required length of follow-up increases

Issues in Implementation

- Three main steps in the analysis
 - Estimation of the total treatment effect at the end of Period 1
 - Is the pattern of the treatment effect over time in this period informative regarding potential disease-modification?
 - Estimation of disease-modifying and symptomatic effects at the end of Period 2
 - Comparison of end-of-trial means

Issues in Implementation

- Three main steps in the analysis
 - Comparison of slopes near the end of Period 2
 - Noninferiority comparison
 - How should the noninferiority margin be chosen?
 - Large sample size requirement
 - Necessary/practical?
 - Could be re-framed as a problem of establishing constant (or non-decreasing) separation between the group means over time (particularly helpful if the change over time is non-linear)

Issues in Implementation

- Three main steps in the analysis
 - Gatekeeping strategy
 - Natural hierarchy of analyses
 - Preservation of Type I error probability
- Subject withdrawal
 - Need for treatment of emerging symptoms
 - Other reasons for withdrawal
 - Validity of MAR assumption?

Effect of Differential Withdrawal

- A strong symptomatic effect of active medication may permit some subjects to complete Period I and enter Period II, while a matched comparison subject in the placebo group would withdraw prior to entering Period II.
- So the treatment subgroups entering Period II may be unbalanced between not only in numbers but also in baseline characteristics.
- Subjects entering Period II from an active treatment group will tend to have been more impaired at baseline on average than those entering Period II from the placebo group.
- Effect of this imbalance on the estimated treatment effect will depend on the method of analysis and the mechanism leading to withdrawal.
- Requires further study.

Baseline Characteristics in TEMPO

Mean total UPDRS at baseline and number of subjects (n) by treatment group, Standard deviations in each cell range from 8.2 to 11.8 units.

	Placebo	1mg	2mg
All subjects	24.5 (138)	24.7 (134)	25.9 (132)
Completers (Period I)	22.9 (113)	24.1 (112)	24.5 (106)
Completers (Period II)	21.0 (86)	23.1 (86)	23.1 (77)

Issues in Implementation

- Sample size
 - Noninferiority comparison at the end of Period 2 (slopes)
 - Sample size depends on:
 - Between-subject variation in individual slopes
 - Within-subject variability about the fitted line
 - Number and timing of within-subject observations
 - Noninferiority margin
 - Need to account for subject withdrawal.

Alternative Approaches

- Time-to-event (milestone)
 - DATATOP trial
 - Can be affected by symptomatic treatment
 - Event that is not impacted by symptomatic treatment (e.g., postural stability)?

Alternative Approaches

- Use of biomarker/surrogate marker
 - Ideal solution to the problem?
 - Absence of valid biomarkers
 - PET/SPECT imaging
 - Would require validation
 - Difficulties in establishing the validity of surrogate outcomes
 - Validity of the marker may be treatment-dependent

Alternative Approaches

- Allow concomitant dopaminergic therapy
 - Perform key evaluations in the “practically-defined ‘off’ state”
 - Very difficult to successfully implement in practice
 - ELLDOPA trial
 - Nature of the effects of dopaminergic medications is not clear
 - Disease-modifying components?

Alternative Approaches

- Disease and pharmacodynamic modeling
 - Holford et al. (2006)
 - Description of disease-modifying and symptomatic effects
 - Can accommodate multiple concomitant treatments, including dopaminergic treatments

Alternative Approaches

- Disease and pharmacodynamic modeling
 - Model assumptions/validity
 - Learning vs. confirmation
 - Inferential methods
 - Computationally intensive
 - Methods for causal inference useful here?

Alternative Approaches

- Natural history staggered start design
 - Hendrix et al. (2007); Horton et al. (2007)
 - Symptomatic effects are modeled as “shift effects” and disease-modifying effects are modeled as “slope effects”
 - Design attempts to account for the possibility that the magnitude of the symptomatic effect depends on the severity of the disease
 - “Staggered start” comes from subjects starting drug at different levels of baseline severity

Alternative Approaches

- Natural history staggered start design
 - Design attempts to distinguish between symptomatic and disease-modifying components of the treatment effect in a single-period design
 - Estimation of “slope effects” must use only data collected after the “shift effects” have become fully apparent

Other Design Considerations

- Entry criteria
 - Very early stage?
 - Difficulties in accurate diagnosis
 - Slow vs. rapid progressors
 - Need to minimize co-morbid conditions
 - Long-term follow-up; retention
 - Allowance of concomitant medications
 - Homogeneity vs. heterogeneity
 - Recruitment of large sample

Other Design Considerations

- Frequency of follow-up
 - Minimizing subject burden, cost
 - Retention is of paramount importance
 - Interim phone contacts
 - Need detailed information on subjects who withdraw
 - Imputation of missing data
 - Comparison of slopes near the end of Period 2

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