Modification of the 'Randomized Withdrawal' and 'Staggered Start' Clinical Trial Designs: Toward a Practical Demonstration of Disease Modification in Alzheimer's Disease ("Natural History Staggered Start")

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Background

- Demonstration of Disease Modification (DM) in AD is a complicated topic that has been approached in many ways
- Among the strategies proposed are those based on measuring clinical outcomes in a cross-over type study:
  - 'Randomized Withdrawal' design
  - 'Staggered Start' design

  These two designs are complicated by ethical issues and long study durations leading to high dropout rates introducing bias
- A suggested alternative is a parallel groups design assessing DM and symptomatic effects after adjusting for differences due to severity of disease at baseline
  - This analysis may be used to characterize a drug treatment that confers both disease modification and symptomatic benefit

Disease Modifying Effects ("Slope Effects")

- Clinical effects observed result from affecting the underlying disease pathology in a way that does not depend on the continued presence of the drug[1-5]
- Can be referred to as a "slope" effect, proportional to time, since the clinical benefit accumulates as drug continues to be given

Symptomatic Effects ("Shift Effects")

- Clinical effects observed result from affecting disease symptoms and not the underlying disease pathology[1-5]
- Can be referred to as a "shift" effect, non proportional to time, since the clinical outcomes are temporarily shifted while on drug
  - Shift effects are soon evident upon drug initiation and are lost upon drug removal

References: [1]Leber 1997, [2]Velas et al 2007, [3]Mani 2004, [4]Cummings 2007, [5]Whitehouse 1998

Randomized Withdrawal

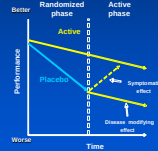
- Take away the treatment and see if any effects are maintained over placebo

Staggered Start

- See whether patients treated for a longer time maintain some benefit over newly treated patients

Withdrawal design

Staggered – Start design

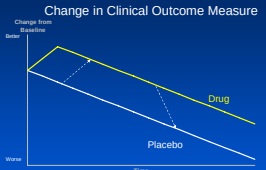


Reference: [1]Leber P. 1997

Equivalent Methods for Demonstrating Disease Modification

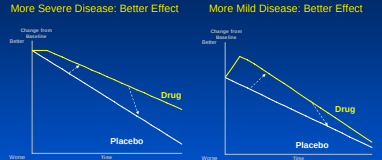
- Randomized Withdrawal and Staggered Start Designs are testing equivalent hypotheses (see poster P-196, Horton et al.)
- Differing results from these two designs can be due to dropout bias affecting the estimates differently
- These designs are not commonly used due to practical and ethical problems
  - They require very long studies with long placebo treatment
  - Randomized withdrawal requires removal of drug which is often not acceptable to patients and families
- These same hypotheses can be tested in a parallel groups study design using the proposed "Natural History Staggered Start" analysis

Symptomatic Effect (Average for large sample) - Same for all Severities



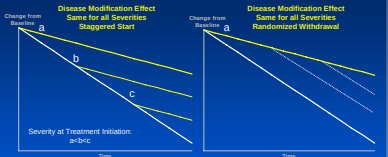
- As patients go onto drug (dashed line) , they 'shift' to the upper path -- As patients go off of drug, they shift back to the lower path
- Linearity of decline illustrated here; same concepts apply for non-linear effects (e.g. floor and ceiling effects)

Symptomatic Effect - Differs by Severity



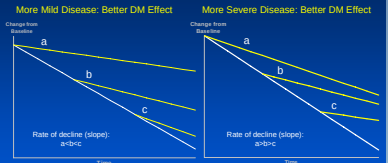
- As patients go onto drug (dashed line), they 'shift' to the upper line. As patients go off of drug, they shift back to the lower line.

Disease Modifying Effects - Same for All Severities



- Patients going on to drug experience a decreased rate of decline
- Response to drug accumulates over the course of treatment as evidenced by diverging declines
- Patients coming off of drug (dashed lines) maintain effect achieved, but return to placebo rate of decline from that point.

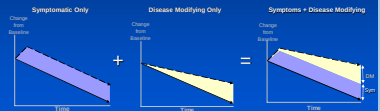
Disease Modifying Effects - Differs by Severity



- Patients going on to drug experience a decreased rate of decline, but receive less benefit if they delay treatment
- Patients going on to drug experience a decreased rate of decline, but receive a better initial benefit to the decline rate if they delay treatment

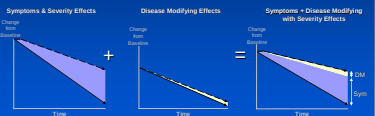
Symptomatic and Disease Modifying Effects

- If symptomatic and disease modifying effects do not depend on severity of disease, it is straightforward to separate them statistically by analyzing the shift and the slope separately



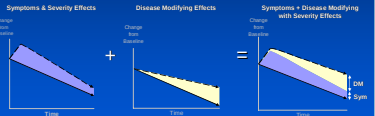
Symptomatic Effects That Look Like Disease Modifying Effects

- A symptomatic effect that is larger for patients with more disease severity may look like a disease modifying effect since placebo and drug-treated groups may show slope differences.



Symptomatic Effects That Mask Disease Modifying Effects

- Conversely, a symptomatic effect that is larger for milder patients may mask a slope effect since it can reduce the divergence of the groups over time.

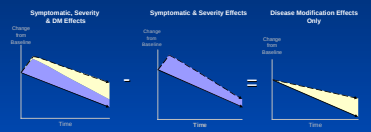


A Parallel Groups Assessment of Disease Modification

- Separating shift, slope and severity effects in a parallel group study requires assessment of the treatment effect differences related to disease severity
  - If there are no differences in drug effect depending on disease severity, then slope changes represent disease modification and shift effects represent symptomatic effects
  - If there are differences related to disease severity, then the model must be adjusted for this effect before slope and shift effects can be identified
- This new analysis method is referred to as a "Natural History Staggered Start" analysis because patients' different disease severities at baseline reflect a staggered initiation of drug and allow estimation of the severity effect

Natural History Staggered Start

- Step 1: Estimate shift and slope differences associated with severity of disease (using a general linear or mixed model analysis)
- Step 2: Calculate the portion of the treatment effect that is due to severity over the duration of the study
- Step 3: Subtract this severity effect from the overall effect, and then run a mixed model analysis to separate slope and shift effects.
- After adjustment for severity differences, slope changes will represent disease modification effects and shifts will measure symptomatic effects



Assumptions

- Requirements:
  - The range of disease severity of the patient population at entry into the study must include the expected mean severity of the placebo group at the end of the study
  - Only data collected after shift effects are fully evident should be used to calculate slopes
  - The study duration must be long enough and sample size large enough to provide appropriate slope estimates
- There is an implicit assumption that the patients who are more severe at baseline are similar to placebo treated patients who achieve that same severity after some time on placebo
- Although examples have been linear over time and over severity, these same principles and methods apply to non-linear patterns over time

Conclusions

- The Staggered Start and Randomized Withdrawal designs are impractical to demonstrate disease modification and have ethical concerns
- A novel and practical parallel groups analysis – the 'Natural History Staggered Start' -- allows the same hypotheses to be tested without the complications of the cross-over designs
- Correcting for severity effects allows estimation of the true slope (disease modification) effect
- This new method reduces practical and ethical concerns while still allowing estimation of disease modifying effects
- This analysis method is not limited to AD but is generally applicable to measuring disease modification in any chronic degenerative disease

References:
1. Leber P. 1997. Alzheimer Dis Assoc Disord. 11:Suppl 5:S10-21.
2. Velas B et al. 2007. Lancet Neurology (1),:55-62.
3. Mani R. 2004. Stat Med. 23(2):305-14.
4. Cummings JL. 2006. Alzheimer's & Dementia 2(4):263-271.
5. Whitehouse PJ et al. 1998. Alzheimer Dis Assoc Disord. 12(4):281-94.

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