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

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Background

- Demonstration of Disease Modification in AD is a complicated methodological and regulatory issue that has been approached in several ways
- Among the strategies proposed are those based on measuring clinical outcomes in cross-over type studies:
  - "Randomized Withdrawal" design
  - "Staggered Start" design

  These two designs are complicated by ethical issues and long study durations leading to unbalanced dropout rates introducing bias
- A suggested alternative is a parallel-groups design assessing disease modification 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

Definitions

Disease-Modifying Effects ("Slope Effects")

- Clinical effects observed result from affecting the underlying disease process (pathology) in a way that does not depend on the continued presence of the drug
- 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")

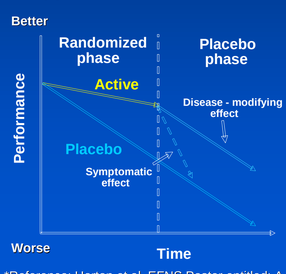
- Clinical effects observed result from affecting disease symptoms and not the underlying disease process (pathology)
- Can be referred to as a "shift" effect since the clinical outcomes are temporarily shifted while on drug

Refs: Leber 1997, Velas et al 2007, Mani 2004, Cummings 2007, Whitehouse et al 1998

Traditional Leber Designs (Equivalent*)

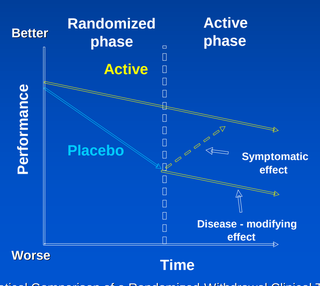
Randomized Withdrawal

- Are any treatment effects maintained over placebo when active treatment is stopped?



Staggered Start

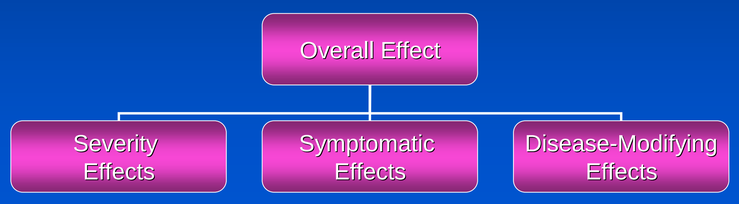
- Do patients treated for a longer time maintain some benefit over newly treated patients?



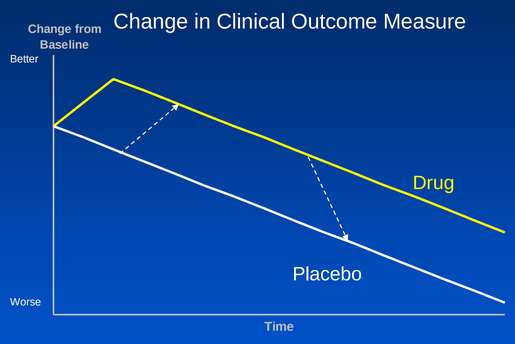
*Reference: Horton et al. EFNS Poster entitled: A Mathematical Comparison of a Randomized-Withdrawal Clinical Trial Design and a Parallel Groups Design to demonstrate disease modification in Alzheimer's disease (AD)

"Natural History Staggered Start"

- A suggested alternative is a parallel-group design that adjusts for differences due to severity – using baseline disease status – allowing separation of disease modification and symptomatic effects

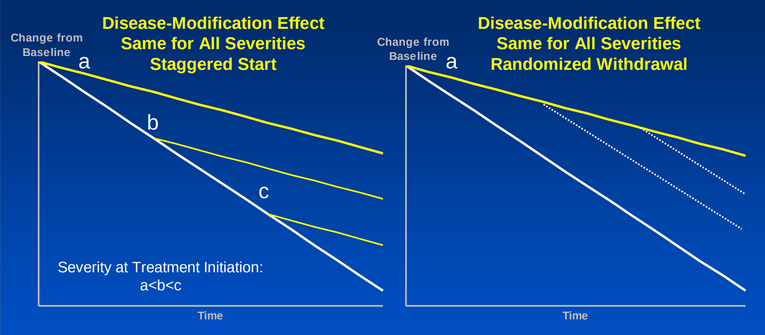


Symptomatic Effect (Average for large sample) - Same for All Severities



- 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)

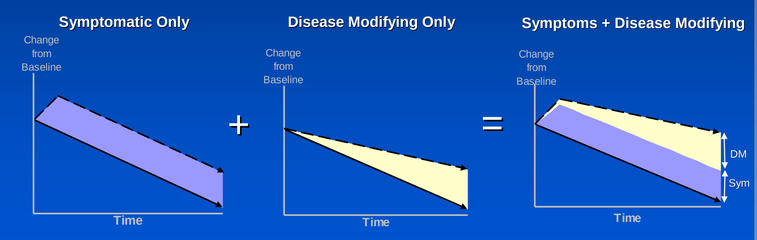
Disease-Modifying Effects – Same for All Severities



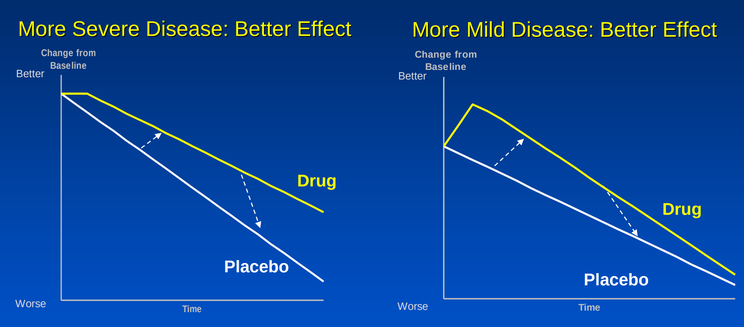
- Patients going on to drug experience a decreased rate of decline
- Response to drug accumulates over the course of treatment
- Patients coming off of drug (dashed lines) maintain effect achieved, but return to placebo rate of decline from that point

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



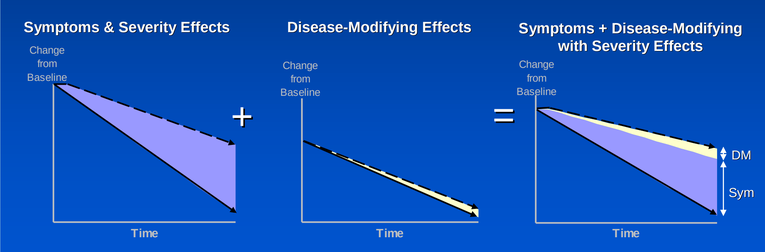
Symptomatic Effects - Differ by Severity



- 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

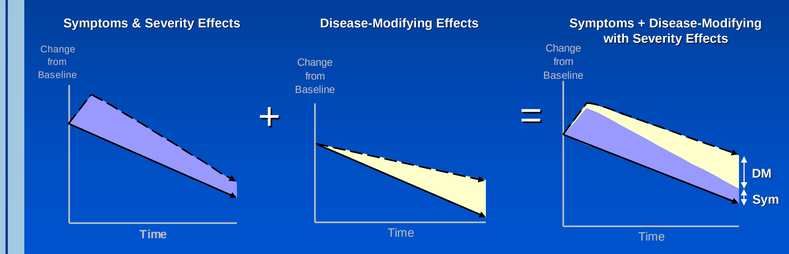
Symptomatic Effects That Look Like Disease-Modifying Effects

- 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

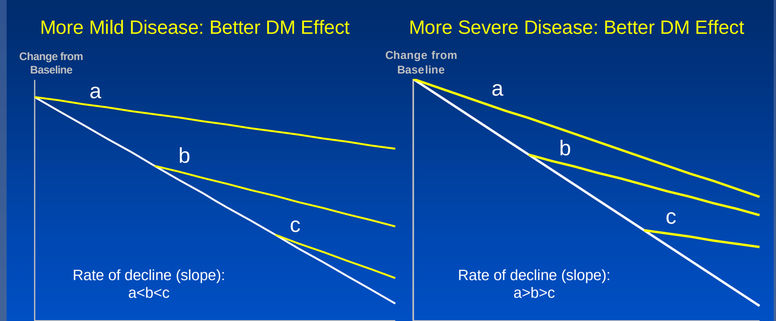


Symptomatic Effects That Mask Disease-Modifying Effects

- 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



Disease-Modifying Effects – Differ by Severity



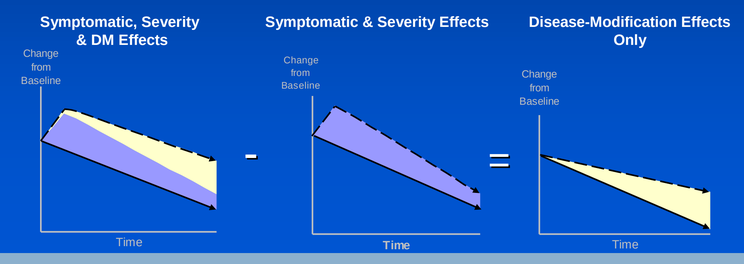
- Patients going on to drug experience a decreased rate of decline, but receive less benefit if they delay treatment
- Patients going on to drug experience a decreased rate of decline, but receive a better initial benefit to the decline rate if they delay treatment

A Parallel-Group Assessment of Disease Modification

- Adjusting for severity effects allows separation of symptomatic and disease-modification effects
- Patients' different disease severities at baseline reflect a staggered initiation of drug and allow estimation of the severity effect
- This new analysis method is referred to as a "Natural History Staggered Start" analysis

"Natural History Staggered Start"

- Fit a General Linear Model or a Mixed Model with terms for:
  - Treatment
  - Treatment*Baseline
  - Treatment*Time (Linear combination required for treatment estimate)
  - Treatment*Time*Baseline (Linear combination for treatment estimate)
  - Treatment*Time^2
- After adjustment for severity differences, slope (or curvature) changes represent disease-modification effects and shifts will measure symptomatic effects



"Natural History Staggered Start" 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
- The Leber Staggered Start design assumes that patients who achieve a more severe disease status after some amount of time on placebo are similar to newly treated patients who are more severe at baseline
- 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 inherent bias and ethical concerns
- A novel and practical parallel-group analysis – the "Natural History Staggered Start" – tests the same hypotheses without the complications of the cross-over designs
- Correcting for severity effects by using baseline disease severity allows estimation of the true slope – disease modification – effect
- This method is not limited to AD but is generally applicable to 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 Neurol*. (1):56-62.
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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