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 task 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 designs are complicated by ethical issues and long study durations leading to high dropout rates introducing bias.
- An augmented alternative is a parallel groups design assessing DMD 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 combines 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.
- Can be referred to as a "slopeslope" effect, proportional to time, since the effect is linear.
- 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.

Disease Modifying Effects - Same for All Severities

- A symptom 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.

Disease Modifying Effects - Differs by Severity

- More Severe Disease: Better Effect
- More Mild Disease: Better Effect

Symptomatic Effects That Look Like Disease Modifying Effects

- A symptom 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

- Correctly, a symptom 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 slope, stop and severity effects in a parallel group design requires assessment of the same treatments and then comparison of the outcomes. This can be achieved by controlling for patient severity differences.

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 some 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 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


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