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.
- A suggested alternative is a parallel-group design assessing disease modification and symptomatic effects after adjusting for differences due to severity of disease at baseline.
- The analysis may be bias if a staggered drug introduction accelerates both disease modification and symptomatic benefits.

Definitions

- Disease-Modifying Effects (“Slope Effects”)
  - Clinical effects observed resulting 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 occurs as drug continues to be given.

- Symptomatic Effects (“Shift Effects”)
  - Clinical effects observed resulting 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.

Traditional Leber Designs (Equivalent*)

- Randomized Withdrawal
  - 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?

“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

<table>
<thead>
<tr>
<th>Change in Clinical Outcome Measure</th>
<th>Drug</th>
<th>Placebo</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patient A</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td>Patient B</td>
<td>2</td>
<td>1</td>
</tr>
<tr>
<td>Patient C</td>
<td>3</td>
<td>2</td>
</tr>
<tr>
<td>Patient D</td>
<td>4</td>
<td>3</td>
</tr>
</tbody>
</table>

Disease-Modifying Effects – Same for All Severities

- Patients going off drug experience a decreased rate of decline.
- Response to drug accumulates over the course of 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 - Differ by Severity

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

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.

Conclusions

- The “Staggered Start” and “Randomized Withdrawal” designs are inappropriate to demonstrate disease modification and have inherent bias and ethical concerns.
- A novel and practical parallel-group analysis is the “Natural History Staggered Start” - tests the same hypotheses without the complications of the cross-over designs.
- Correcting for severity effects by using baseline 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.