Is Clinical Trial Design a Barrier to Alzheimer’s Disease Pharmacotherapy Development? An Analysis Based on Drug Class

Tyler Fukunaga, PharmD and MS Candidate; Terry Church DRSc, MA, MS
USC School of Pharmacy, Department of Regulatory and Quality Sciences

Objective

To identify common elements of clinical trial (CT) design among prominent Alzheimer’s Disease (AD) drug classes that have unsuccessful drug development within this disease state and to suggest improvements for clinical development moving forward.

Background

➢ AD is the leading cause of dementia in the United States.¹
➢ AD prevalence is projected to increase from 5.8 to 14 million Americans by 2050.¹
➢ Only five FDA approved drugs are on the market for symptomatic relief for AD patients.²

Methodology

clinicaltrials.gov search criteria:
1. Completed and terminated AD CTs
2. Timeframe: 2015-2020
3. Phase II or III

41 AD Drug Clinical Trials

Four most prominent drug classes:

Amyloid Beta Modulators (n= 14)
BACE Inhibitors (n= 5)
Neurotransmission Enhancers (n= 4)
Anti-Inflammatories (n= 4)

Class by class analysis based on clinical trial design

Findings

<table>
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<tr>
<th>Class (n)</th>
<th>CTs Meeting Endpoints (%)</th>
<th>Significant CT Design Issues and Findings</th>
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| Amyloid Beta Modulators (n= 14)    | 4 (28.6%)                 | ➢ Late initiation of treatment in 50 y/o+ (n=14)  
➢ 4 CTs met safety and target engagement endpoints, whereas 10 CTs did not meet endpoints due to no improvement in cognition |
| BACE Inhibitors (n= 5)             | 1 (20.0%)                 | ➢ Late initiation of treatment in 50 y/o+ (n=5)  
➢ Appropriate biomarker outcomes used (n=5) |
| Neurotransmission Enhancers (n= 4) | 0 (0.00%)                 | ➢ Absence of biomarker outcomes (n=4)  
➢ Failure to improve cognition (n=4) |
| Anti-Inflammatories (n= 4)         | 3 (75.0%)                 | ➢ 3 CTs that met endpoints enrolled <50 patients  
➢ 1 CT that did not meet endpoints enrolled 161 participants |

Conclusions

Amyloid Beta Modulators and BACE Inhibitors
➢ AD irreversible at inclusion criteria ages?
➢ Long-term studies in younger patient populations is questionable.

Neurotransmission Enhancers
➢ Biomarker measurements (e.g. neurofilament or MRI/CT scans), in addition to cognition measurements, should be incorporated to demonstrate target engagement.

Anti-Inflammatories
➢ Smaller population sizes may allow clinicians to more accurately rate cognition than in trials that enroll hundreds to thousands of participants.

Overall, issues in AD drug CTs are not exclusive to one class of AD drug. Inclusion criteria could be expanded to demonstrate the effects of the drugs in diverse populations such as in younger patients where AD can possibly be reversible. Inconsistent endpoint selection such as not using both biomarker and cognitive endpoints does not fully depict the beneficial effects of the drug; therefore, endpoint standardization should be implemented in CTs of AD drugs within the same drug class. Nonetheless, future research is necessary to explore the relationship between these common elements in AD CT design and drug development.

References


Contact
Please contact Tyler Fukunaga at tfukunag@usc.edu for questions or more information.