Title: *Quantitative disease-drug-trial models for evidence of effectiveness – a case study of negative adolescent schizophrenia trials*

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Methodological Question Being Addressed: How can prior information be leveraged into a quantitative framework to provide evidence of effectiveness and aide in identifying potential reasons for failed/negative trials?

Objective:
Psychiatric drug development faces several impediments including substantially large placebo effects, underexplored exposure-response relationships, and high dropout rates. Approximately 35% of all short-term adult schizophrenia registration trials that were submitted to the U.S. Food and Drug Administration (FDA) were concluded to be "failed" or "negative" trials. Similarly, 2 out of 6 (33%) of all adolescent registration trials demonstrated a lack of separation of the investigated drug from placebo. However, the same two drugs that were not shown to be effective in adolescents are currently labelled for use in adults. Translational methodologies have consistently been shown to "de-risk" and guide pediatric drug development by leveraging prior quantitative knowledge. This analysis will demonstrate how quantitative disease-drug-trial models can serve as a platform to design informative pediatric trials, inform dose-selection, and ultimately provide supportive evidence of effectiveness.

Methods:
Patient level clinical trial data from two drug programs (referred as Drug A and B) with an approved adult indication and a failed/negative adolescent study was collected using sponsor submitted applications to FDA. Steady state exposure metrics such as area under the curve and average concentration were derived using drug-specific population pharmacokinetic models. A non-linear mixed effect and parametric time to event modeling approach was utilized to develop a disease-drug-trial model that considers the underlying placebo response, exposure-response relationship, and dropout patterns to predict longitudinal changes in the total Positive and Negative Symptom Scale (PANSS) scores. Clinical trial simulations using the developed DDT model were used to identify potential reasons for negative findings in the two adolescent studies.

Results:
Drug A and B concentration ranges were found to be similar in adults and adolescents. A non-linear model (E_{max} model) adequately described the relationship between average concentrations of Drug A and B and the proportional change in total PANSS scores relative to baseline. Parameter estimates for maximal treatment effect and average concentration needed to achieve 50% maximal effect were found to be similar between adults and adolescents across both drug programs. A statistically significant exposure-response relationship was identified for Drug A, therefore suggesting that the medication was effective in lowering total PANSS scores even though conventional mixed models repeated measures (MMRM) analysis demonstrated no effect. Clinical trial simulations further confirmed that the adolescent study conducted for Drug A was underpowered and an increased sample size was needed to demonstrate a significant drug effect. Simulations for Drug B suggested that a significant drug effect could have been apparent if a fixed dose study design was implemented. Optimal dose ranges between adults and adolescents were confirmed to be similar for both programs.

Conclusions:

The use of quantitative disease-drug-trial models demonstrated similarities in exposure-response relationships between adults and adolescents for Drugs A and B. Furthermore, the established exposure-response supported evidence of effectiveness in adolescents. Clinical trial simulations indicated that changes in study design could have led to positive findings. Leveraging prior information using a quantitative framework can aide in designing informative clinical trials and ultimately lead to useful labeling information.

Disclosure:

Nothing to disclose