Application of Item Response Theory in Early Phase Clinical Trials: Utilization of a Reference Model to Analyse the Montgomery-Åsberg Depression Rating Scale

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Introduction

- Antidepressant effect of ketamine is often measured through total score of Montgomery-Åsberg Depression Rating Scale (MADRS) questionnaire.
- Limitation: Assumption that all items (=questions) provide similar information.
- Solution: Item response theory (IRT) uses all item responses and transforms them into a value for depression severity; the latent variable ($\psi$) [1,2]. Instead of the total MADRS score, $\psi$ can also be used to demonstrate treatment effect.
- Problem: Datasets of early phase clinical trials are too small for IRT model development [3]

Aim

Evaluate assumptions and applicability of a reference IRT model for the analysis of a small clinical dataset investigating the treatment effect of ketamine on the MADRS.

Methods

Major depressive disorder (MDD) patients treated with 40 min infusion of (R,S)-ketamine or placebo in cross-over design (N=17) *

MADRS

<table>
<thead>
<tr>
<th>Item 1</th>
<th>Item 2</th>
<th>Item 3</th>
<th>Item 4</th>
<th>Item 5</th>
<th>Item 6</th>
<th>Item 7</th>
<th>Item 10</th>
</tr>
</thead>
</table>

Total score

IRT model #1

- Treatment resistant MDD (Fig 1.)

IRT model #2

- Non-treatment resistant MDD

Figure 1. Subset of item characteristic curves of IRT model #1

3 approaches for $\psi$ distribution were tested

A. No specified distribution
B. Estimated normal distribution per treatment per time
C. Reference population: standard normal distribution

Treatment effect

Linear mixed model analysis

Results

1. Approaches resulted in similar $\psi$ profiles over time (Fig 2.)
2. IRT model #2 resulted in significant overall increase in $\psi$
3. Significance of treatment effect
   a) improved by using $\psi$ versus total score
   b) minimal change between IRT model #1 and #2

Table 1. Example responses on MADRS questions resulting in identical total scores with differing disease severities

<table>
<thead>
<tr>
<th>Item</th>
<th>ID1</th>
<th>ID2</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Reported sadness</td>
<td>4</td>
<td>3</td>
</tr>
<tr>
<td>2. Reduced sleep</td>
<td>5</td>
<td>2</td>
</tr>
<tr>
<td>3. Suicidal thoughts</td>
<td>2</td>
<td>6</td>
</tr>
<tr>
<td>...</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total score</td>
<td>35</td>
<td>35</td>
</tr>
</tbody>
</table>

Figure 2. Estimated individual $\psi$ values over time using different approaches and IRT models of representative individuals.

Conclusion

Reference IRT models can be used for analysis of treatment effect in early phase clinical trials when only small datasets are available.


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