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

M.E. Otto, K. Bergmann, G. Jacobs, M.J. van Esdonk
Centre for Human Drug Research, Leiden, the Netherlands
✉ **motto@chdr.nl**
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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 (ψ) [1,2]. Instead of the total MADRS score, ψ can also be used to demonstrate treatment effect.
- **Problem:** Datasets of early phase clinical trials are too small for IRT model development [3]

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

Item	ID1	ID2
1. Reported sadness	4	3
2. Reduced sleep	5	2
3. Suicidal thoughts	2	6
…	…	…
Total score	35	35

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

Item 1 | Item 2 | Item 3 | Item 4 | Item 5 | Item 6 | Item 7 | … | Item 10 → **Total score**

IRT model #1
Treatment resistant MDD (Fig 1.)

IRT model #2
Non-treatment resistant MDD

Carmody et al. (2015) [4]

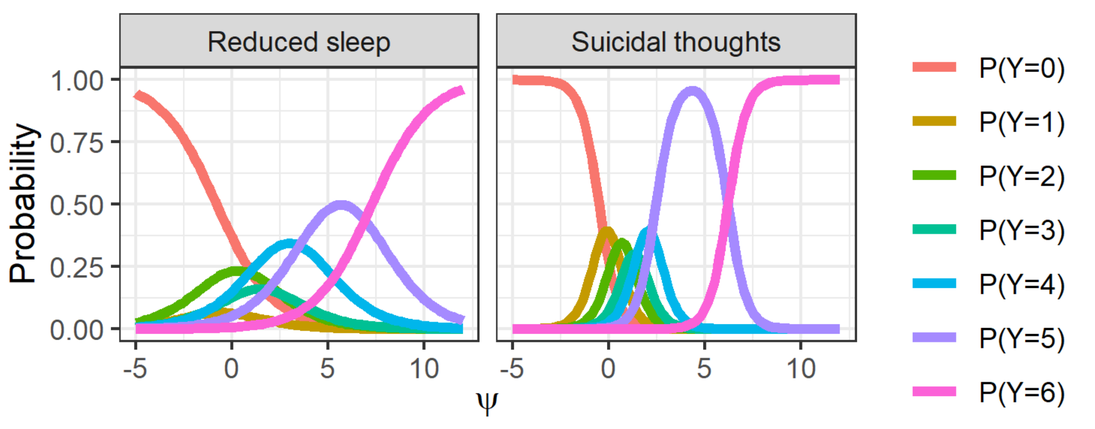

Figure 1. Subset of item characteristic curves of IRT model #1

3 approaches for ψ distribution were tested

A. No specified distribution

B. Estimated normal distribution per treatment per time

C. Reference population: standard normal distribution

ψ

Treatment effect
Linear mixed model analysis

Results

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

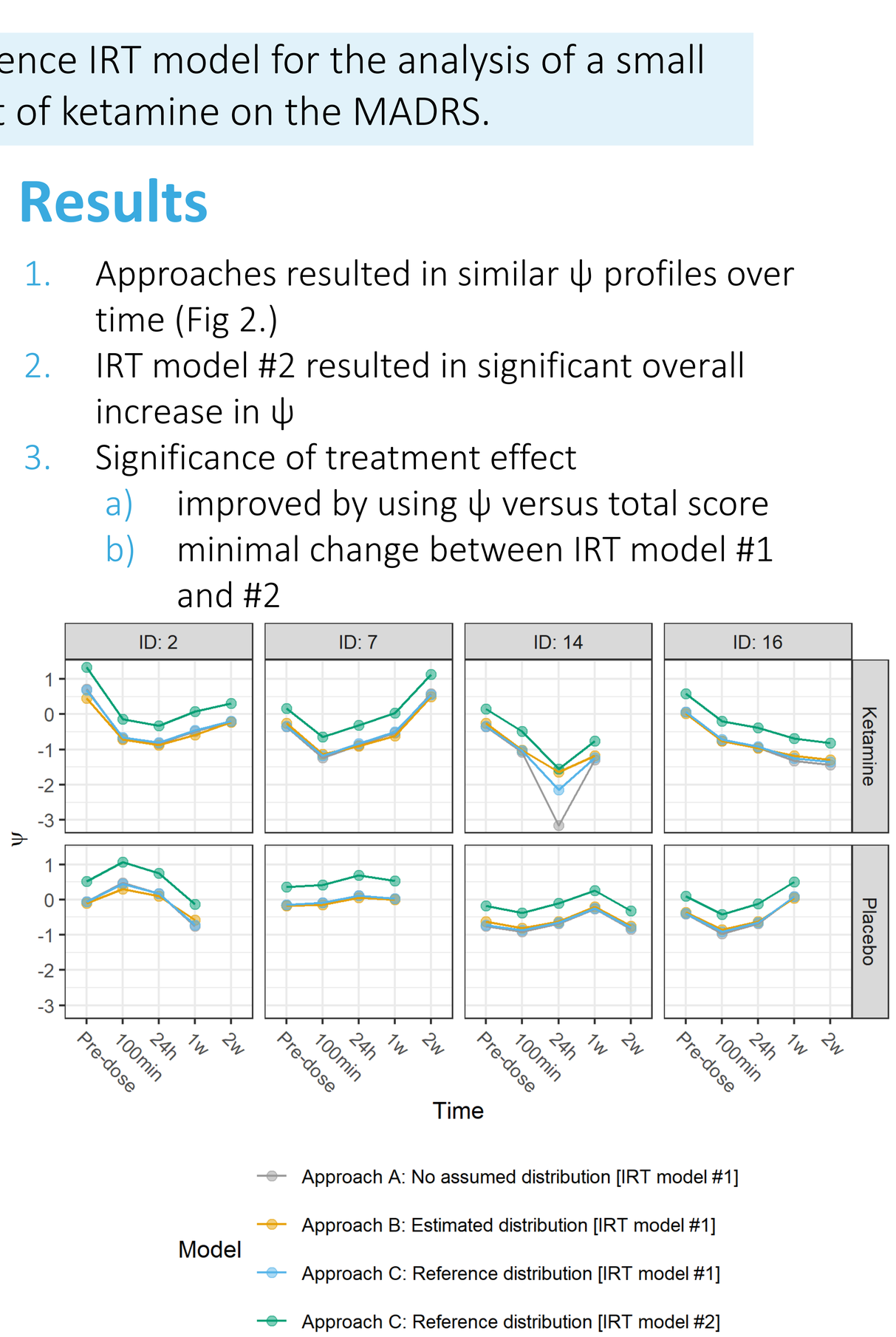

Figure 2. Estimated individual ψ values over time using different approaches and IRT models of representative individuals.

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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Centre for Human Drug Research | Zernikedreef 8 | 2333 CL Leiden | The Netherlands | Tel +31 71 52 46 400 | info@chdr.nl | www.chdr.nl