

A new, second-order indirect model of depression time course

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Introduction

The limited understanding of placebo effect and drug action in psychiatric diseases has led to a widespread use of ad-hoc empirical models^{1,2} and simple indirect response models^{3,4} to describe the time course of clinical scores such as HAM-D. However, the ability to describe complex response profiles and the handling of adaptive dosing schedules (e.g. dose escalations) are still open issues.

This motivates the present work, where a new approach inspired by indirect response and extended indirect response modelling³ is investigated. A new, second-order indirect model is proposed in order to capture the structural properties of the treatment response, e.g. improvement, relapse, response to dose escalations. In particular, we incorporate a feedback mechanism⁵ so as to model the possible onset of tolerance effects.

Second-order indirect model with feedback

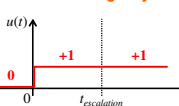
Model equations

$$\begin{cases} \frac{dx_1(t)}{dt} = -kx_1(t) + k_{in} \left(\frac{\bar{x}}{x_2(t)} \right)^{\gamma} \left(1 - \frac{u(t)^{\lambda}}{IC_{50}^{\lambda} + u(t)^{\lambda}} \right) \\ \frac{dx_2(t)}{dt} = kx_1(t) - kx_2(t) \end{cases}$$

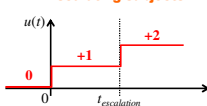
$$y(t) = x_1(t) + \varepsilon \quad x_1(0) = x_2(0) = \bar{x} \quad k_{in} = k\bar{x}$$

Input signal $u(t)$

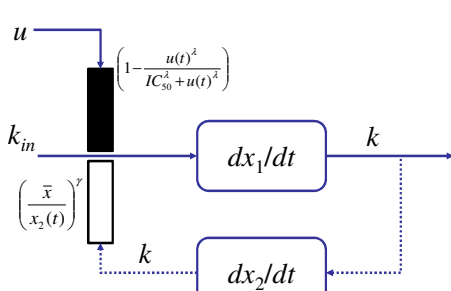
Non-escalating subjects



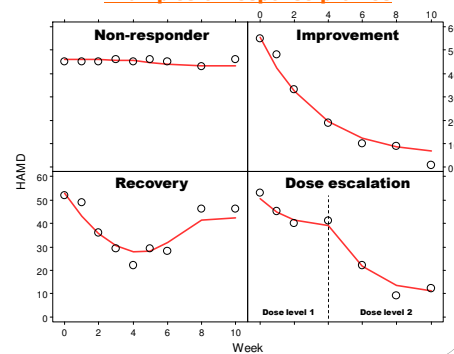
Escalating subjects



Model scheme



Examples of response profiles



Materials

- Two Phase II randomized, double-blind, placebo-controlled trials relative to a GSK investigational antidepressant compound.
- Flexible dosing scheme: non-responding patients without safety/tolerability issues were escalated to a higher dose level at week 4 in both arms.
- Parameter identification: NONMEM 6.2⁶ (FOCE with interaction), log-normal inter-individual variability (IIV), additive residual error.

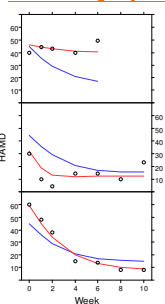
Results

- The new model successfully captured different patterns of response profiles, e.g. steady improvement, non-responders, or relapsing patients (Figures 1 and 2).
- Additionally, the model was able to describe changes in the response time course due to dose escalations.
- Precise parameter estimates in general (Tables 1 and 2). Relatively high standard errors in few cases where data were not sufficiently informative (e.g. IIV of γ or IC_{50}).
- VPCs (Figures 3 and 4): proper characterization of the population distribution, but dropout should be accounted for (see Study 1, drug arm, non-escalating subjects).

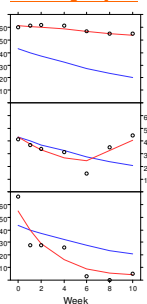
Study 1

Placebo arm

Non-escalating subjects

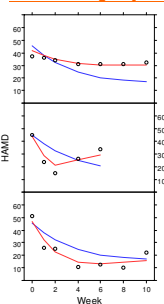


Escalating subjects



Drug arm

Non-escalating subjects



Escalating subjects

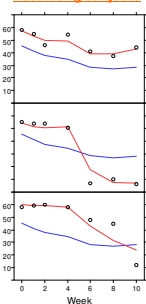


Figure 1: Individual fittings (orange) and typical curve (blue) for a subset of subjects from Study 1.

Parameter	Estimate	CV%	Parameter	Estimate	CV%	Parameter	Estimate	CV%	Parameter	Estimate	CV%
TV $\bar{x}$	44.5	4	TV $\bar{x}$	43.2	3	TV $\bar{x}$	45.3	1	TV $\bar{x}$	45.7	3
TV k	0.29	13	TV k	0.109	54	TV k	0.262	6	TV k	0.267	84
TV γ	0.644	72	TV γ	0.411	>100	TV γ	1.94	>100	TV γ	1.94	>100
TV IC_{50}	0.261	46	TV IC_{50}	0.39	>100	TV IC_{50}	0.41	10	TV IC_{50}	1.18	69
TV λ	—	—	TV λ	0.964	74	TV λ	1.47	25	TV λ	1.47	25
IIV $\bar{x}$	0.0477	38	IIV $\bar{x}$	0.0316	24	IIV $\bar{x}$	0.0173	24	IIV $\bar{x}$	0.0336	24
IIV k	0.22	68	IIV k	0.304	90	IIV k	0.291	53	IIV k	0.162	61
IIV γ	0 FIX	—	IIV γ	4.92	69	IIV γ	3.54	44	IIV γ	0.772	>100
IIV IC_{50}	2.56	46	IIV IC_{50}	4.06	>100	IIV IC_{50}	4.35	35	IIV IC_{50}	0.08	>100
IIV λ	—	—	IIV λ	0 FIX	—	IIV λ	—	—	IIV λ	1.27	>100
σ^2	31.4	18	σ^2	29.6	12	σ^2	38.2	18	σ^2	30.3	15

Table 1: Parameter estimates from Study 1. CV%: percentage coefficient of variation. TV: typical value. IIV: inter-individual variability. σ^2 : error variance.

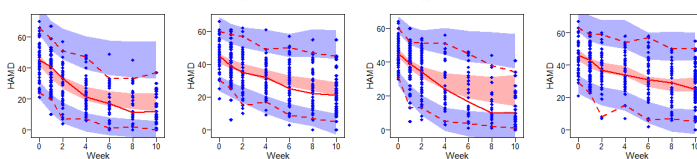
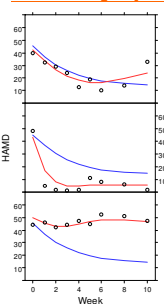


Figure 3: VPCs obtained from Study 1. Observed median and 95% percentiles (red) are shown, along with their 95% prediction intervals.

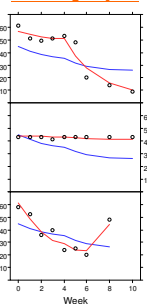
Study 2

Placebo arm

Non-escalating subjects

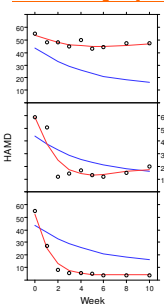


Escalating subjects



Drug arm

Non-escalating subjects



Escalating subjects

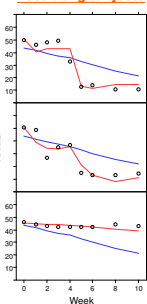


Figure 2: Individual fittings (orange) and typical curve (blue) for a subset of subjects from Study 2.

Parameter	Estimate	CV%	Parameter	Estimate	CV%	Parameter	Estimate	CV%	Parameter	Estimate	CV%
TV $\bar{x}$	45.1	2	TV $\bar{x}$	44.9	3	TV $\bar{x}$	43.5	3	TV $\bar{x}$	43.7	2
TV k	0.265	16	TV k	0.288	10	TV k	0.197	22	TV k	0.0853	17
TV γ	0.541	60	TV γ	0.85	14	TV γ	0.302	68	TV γ	1.76	31
TV IC_{50}	0.259	42	TV IC_{50}	1.56	15	TV IC_{50}	0.326	53	TV IC_{50}	0.903	6
TV λ	—	—	TV λ	1.41	15	TV λ	—	—	TV λ	5.61	12
IIV $\bar{x}$	0.0235	23	IIV $\bar{x}$	0.0396	18	IIV $\bar{x}$	0.0467	19	IIV $\bar{x}$	0.0224	24
IIV k	0.182	97	IIV k	0.045	68	IIV k	0.46	33	IIV k	1.51	20
IIV γ	3.06	53	IIV γ	1.16	26	IIV γ	4.44	83	IIV γ	0.0715	>100
IIV IC_{50}	2.23	39	IIV IC_{50}	0.779	30	IIV IC_{50}	3.07	35	IIV IC_{50}	0.0508	>100
IIV λ	—	—	IIV λ	0.888	40	IIV λ	—	—	IIV λ	0 FIX	—
σ^2	35.8	16	σ^2	19.8	5	σ^2	25.9	6	σ^2	28.4	10

Table 2: Parameter estimates from Study 2. CV%: percentage coefficient of variation. TV: typical value. IIV: inter-individual variability. σ^2 : error variance.

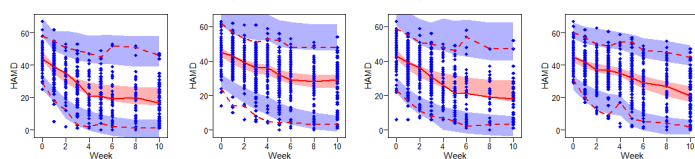


Figure 4: VPCs obtained from Study 2. Observed median and 95% percentiles (red) are shown, along with their 95% prediction intervals.

Conclusions

- We extended the well-known methodology of indirect response models to account for the complex patterns of response usually observed in psychiatric trials.
- Placebo response is accounted for. Next step: inclusion of plasma exposure (drug arm).
- Further extensions: joint fitting of all subpopulations, integration of dropout, application to different diseases.

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