Response type modelling and clinical trial simulation

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Objectives: Drug development in depression is a particular challenge since high apparent variability in response is obscuring a clear dose-response against placebo. New drugs are often interacting at multiple targets, and it seems appropriate to identify patients that share a common response type. We present a statistical model for response type analysis that is applied to clinical trial simulation.

Background: The clinical effects of ketamine in chronic pain [3] and depression [4] are puzzling due to their rapid onset and long duration. The example of ketamine has encouraged the development of novel glutamate N-methyl-d-aspartate (NMDA) receptor antagonists with fewer side effects when used over extended periods.

A simulated clinical study of such an antidepressant (drug X) exemplifies the use of a dose-ranging study to select an optimal dose for future development. Drug X acts as antagonist at the NMDA receptor and activates the ubiquitous mammalian target (mTOR) of rapamycin pathway. That in turn increases the levels of synaptic signalling proteins and new spine synapses. Drug X also potentiates glutamate transmission at α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid (AMPA) receptors. These findings support a model in which drug X acts to both decrease NMDA receptor signalling and to enhance AMPA receptor signalling, with a net effect of enhancement of synaptic plasticity and neurotrophic signalling.

Four patterns of clinical responses were mechanistically plausible. No response could be possible either in the absence of drug X or by inhibition at NMDA without activation of mTOR and no action at AMPA sites. A short response was attributed to a stimulation at AMPA; a long response to an inhibition of NMDA and stimulation of AMPA. The continued sustained response was attributed to a permanent enhancement of synaptic plasticity via the mTOR pathway.

Methods:

- A between subject model mixture (BSMM Word 2007 Document) was implemented in Monolix 4.1 [1] that estimated the probabilities of four different response types. The types were: no response, short, long, and continued response.
- Considering dose as a categorical covariate, the probability distribution of the response type was estimated as a composite of the probability distribution in each treatment arm.
- The population parameters of the model were estimated using the SAEM algorithm for BSMM.
- The prediction distribution of the response in each treatment arm was estimated by simulation using the population parameters.

	t_1	t_2	t_3	t_4
f_1 non response	BLN	BLN	BLN	BLN
f_2 short response	BLN	BLN-EFF	BLN-FAC	BLN-FAC
f_3 long response	BLN	BLN-EFF	BLN-EFF-FAC	BLN-FAC
f_4 sustained response	BLN	BLN-EFF	BLN-EFF-FAC	BLN-EFF-FAC

BLN: baseline score
EFF: reduction from BLN at t_2
FAC: additional reduction

For $j=1, 2, 3, 4,$ the response function f_j is the continuous linear interpolation between the values defined at times t_1 , t_2 , t_3 , t_4 (= 0, 3, 6, and 8 weeks for simulation).

Results:

A clinical anti-depression trial was simulated using the first prototype of the clinical trial simulator (CTS) developed by Inria for DDMoRe [2] with 200 patients being randomly allocated to four equal treatment arms (placebo, 50, 100, and 150 mg), each treatment having a distinct response pattern (Figure 3). The treatments were administered for 3 weeks and response was simulated up to 8 weeks. Without a response type analysis all three active treatments seemed to be equally effective in comparison to placebo (Figures 1 and 2). A response type analysis allocated, however, each patient to one of four responses (Figure 4). The distinct probability distributions for the four response type under each treatment demonstrated a clear dose-response (Figure 5). The simulation of the prediction distribution of the response in each treatment arm (Figure 6) demonstrated the clinical superiority (continued response) of the 100 mg dose over the two others.

Figure 1

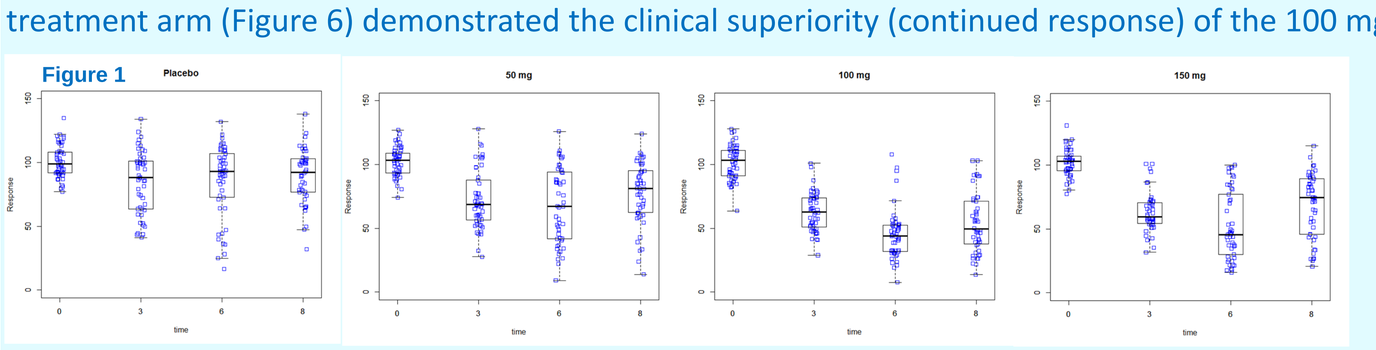


Figure 2

	Mean response at times (h):			
Dose (mg)	0	3	6	8
0	100.9	84.4	85.8	89.9
50	102.1	72.5*	68.0*	78.0*
100	101.9	63.0*	45.7*	54.3*
150	101.7	63.0*	52.3*	68.9*
* Significant at p<0.05 compared to Dose = 0 mg				

Figure 3

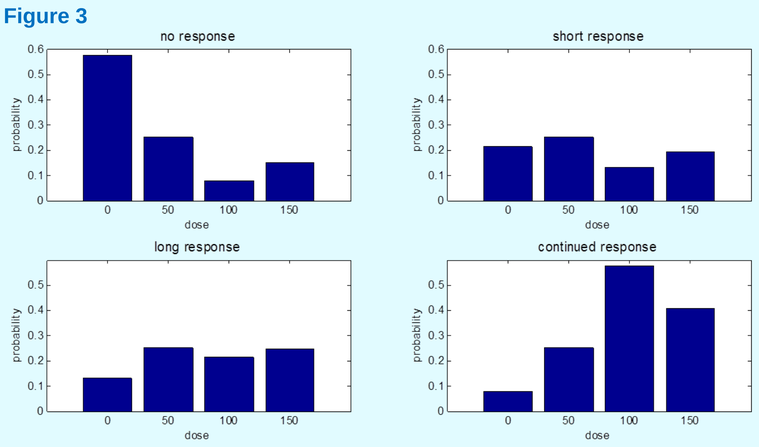


Figure 4

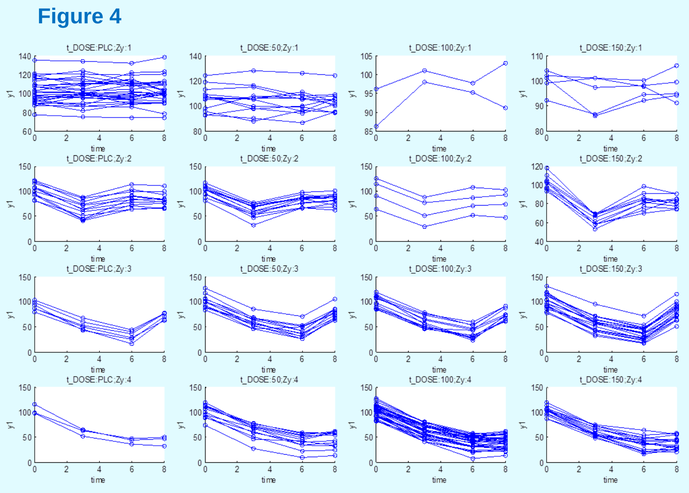


Figure 5

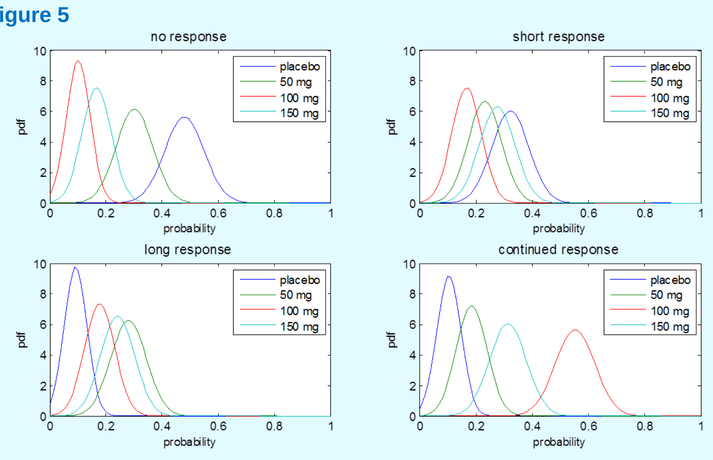
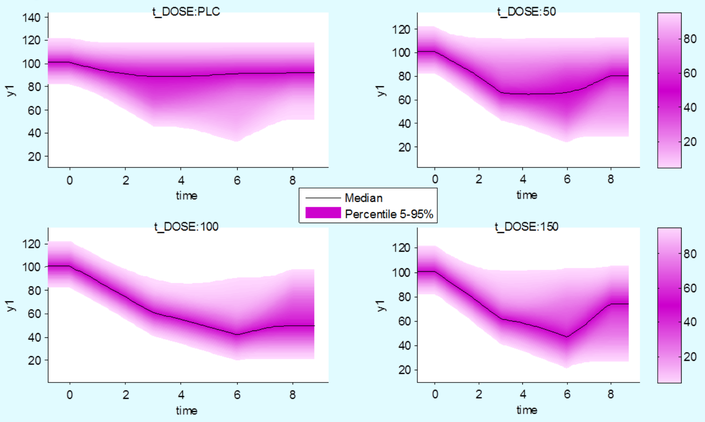


Figure 6

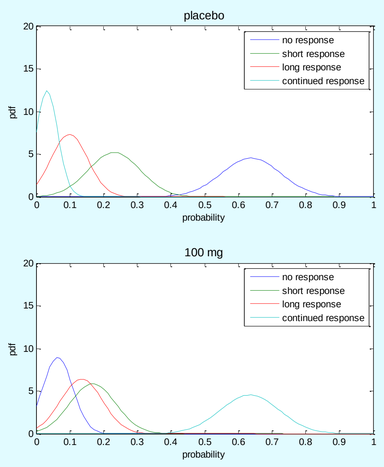


Design of a future study:

The current model was applied to determine the required sample size of a study comparing 100 mg against placebo in a similar patient population. The probability distributions of the response types are shown in Figure 7. About 30 patients per arm should be sufficient.

Figure 7

Number of patients	P-value for detecting significant difference between response types 1 and 4
100	1.23E-07
50	3.34E-05
40	8.49E-08
30	2.28E-05
25	5.51E-02
20	1.15E-01



Discusion:

- The objective to analyse the time course of response rather than the difference in response at a certain time point was clinically motivated, and the FDA asked as well: What is the probability of a sustained response to this anti-depressive treatment?
- Response type analyses within the framework of mixed models is technically feasible. The acceptance by the regulators is currently evolving.
- The probability distributions of the response types (Figure 5) can help to evaluate complex dose-response relationships.
- The probabilistic dose-response model aids the optimal design of a confirmatory trial.

References:

[1] Monolix 4.1 User Guide, http://www.lixoft.com/wp-content/uploads/2011/10/UserGuide.pdf.
[2] DDMoRe, http://www.ddmore.eu.
[3] Dahan A, et al. (2011). Population pharmacokinetic-pharmacodynamic modeling of ketamine-induced pain relief of chronic pain. Eur. J. Pain 15(3), 258-67.
[4] Manji H, et al. (2003). Enhancing neuronal plasticity and cellular resilience to develop novel, improved therapeutics for difficult-to-treat depression. Biol. Psych. 53(4), 707-742.

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