

A Bounded Integer Approach to Evaluate AIMS Score for Deutetrabenazine in Patients with Tardive Dyskinesia

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Background

- Tardive dyskinesia (TD) is a serious hyperkinetic movement disorder that appears as a complication of the prolonged use of dopamine receptor antagonists (e.g., antipsychotic agents).
- Deutetrabenazine, a deuterated form of tetrabenazine, effectively reduces TD symptoms [1,2].
- In TD patients, the total motor Abnormal Involuntary Movement Scale (AIMS, items 1 to 7) measures the severity of abnormal movements on a composite scale ranging from 0 to 28 – higher scores indicative of more severe TD.
- For large categorical scales, an ordered categorical modeling approach is not conceivable. Treating the total score as a continuous variable on a logit scale ignores its categorical nature and only predicts extreme values asymptotically.

Objectives

- To evaluate the novel bounded integer (BI) modeling [3,4] as an alternative approach to predict changes in AIMS scores in response to twice daily administration of deutetrabenazine.

Methods

The bounded integer approach

- From a standard normal distribution, k cut-off values (Z scores) are defined via the *probit* function so that each score has the same probability density and that the probability of all scores combined sums to 1 (**Figure 1, Left**).
- The cut-off values are then fixed and used to section the distribution of a latent variable which is assumed to be normally distributed. The resulting areas within the cut-off values define the probability of each score (**Figure 1, Right**).
- The mean and variance of the normal distribution for the latent variable are described by the model including typical values, inter-individual variability (IIV) and covariate effects.

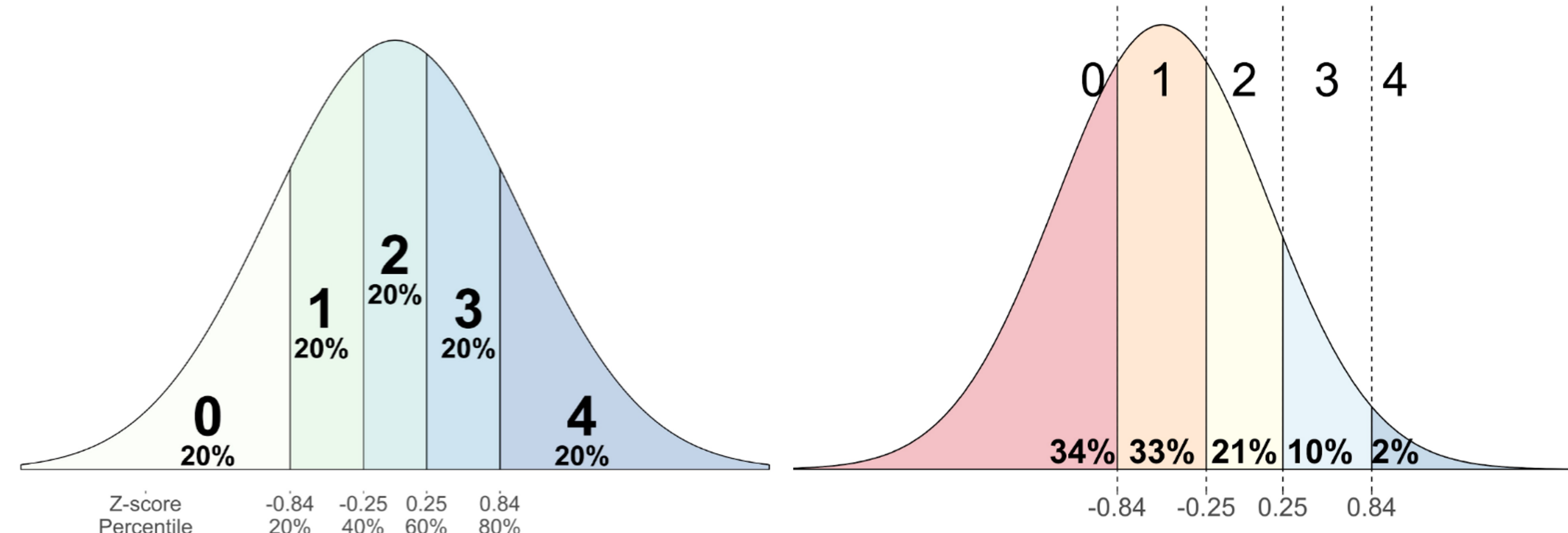


Figure 1. (Left) Illustration of the BI cut-off values (Z scores) for a 5-point scale defined through the probit function for the standard normal distribution. (Right) Example illustrating how changes in mean (-0.545) and variance (0.7) impact the probabilities for the different scores. Reprinted from [5] with permission.

Data and Drug Exposure

- A pooled dataset from 2 Phase 2/3 studies [1,2] comparing twice daily administration of deutetrabenazine to placebo over a 12-week period was used for the exposure response modeling. The data contained 1,964 total motor AIMS scores from 410 TD patients.
- Pharmacokinetic (PK) exposure parameters (i.e., average concentration (C_{avg}), maximal concentration (C_{max})) were predicted the total ($\alpha+\beta$)-HTBZ concentration (i.e., sum of the active α -HTBZ and β -HTBZ deutetrabenazine metabolites) for each patient using previously developed and qualified population PK models.

AIMS score model

Placebo model

- The BI model was used to describe the longitudinal placebo data. Constant (i.e., time independent), linear, and exponential placebo effect models were evaluated on the mean of normal distribution.
- Covariates effects (i.e., body weight, age, sex, race, and CYP2D6 genotype) were evaluated on the mean of the normal distribution.
- The introduction of a Markovian component (PM) was evaluated as an inflation of the probability from the previously observed score.

$$P_{i,j}(k | Y_{i,j-1} = k) = \frac{P_{k,i,j} + PM}{1 + PM} \quad P_{i,j}(k | Y_{i,j-1} \neq k) = \frac{P_{k,i,j}}{1 + PM}$$

Drug effect model

- Data from the deutetrabenazine treatment arm was introduced, and the effect of the different PK exposure parameters was sequentially evaluated using linear and Michaelis-Menten kinetics on the mean of the latent variable distribution.

Conclusions

- The novel BI modeling approach was successfully applied to the prediction of the longitudinal exposure-response relationship of ($\alpha+\beta$)-HTBZ in TD patients following deutetrabenazine administration.
- The developed exposure-response model was applied to the prediction of the change in the AIMS score under different exposure.

Results

AIMS score model

- The developed BI model featured a linear placebo effect (i.e., time), and a linear effect of ($\alpha+\beta$)-HTBZ C_{max} on the the mean of the normal distribution – nonlinear models were not identifiable (**Table 1**).
- No covariate effect was retained in the selected model.
- The Markovian component was not supported by the data.

Table 1. Parameter estimates of the selected model

Parameter	Typical value (RSE%)	IIV ^a (RSE%)
Normal distribution mean	-0.526 (3.53)	0.337 (4.28)
Normal distribution standard deviation	0.177 (2.98)	0.278 (6.11)
Placebo effect slope on the normal distribution mean	-0.00159 (13)	0.00179 (12.3)
Drug effect slope on the normal distribution mean	0.002 (19.6)	0.863 (16.3)

^a IIV reported as standard deviation. RSE: relative standard error.

- The selected model appropriately predicted the total motor AIMS score, the change from total motor AIMS baseline score, as well as the proportion of each score over time (**Figure 2**).

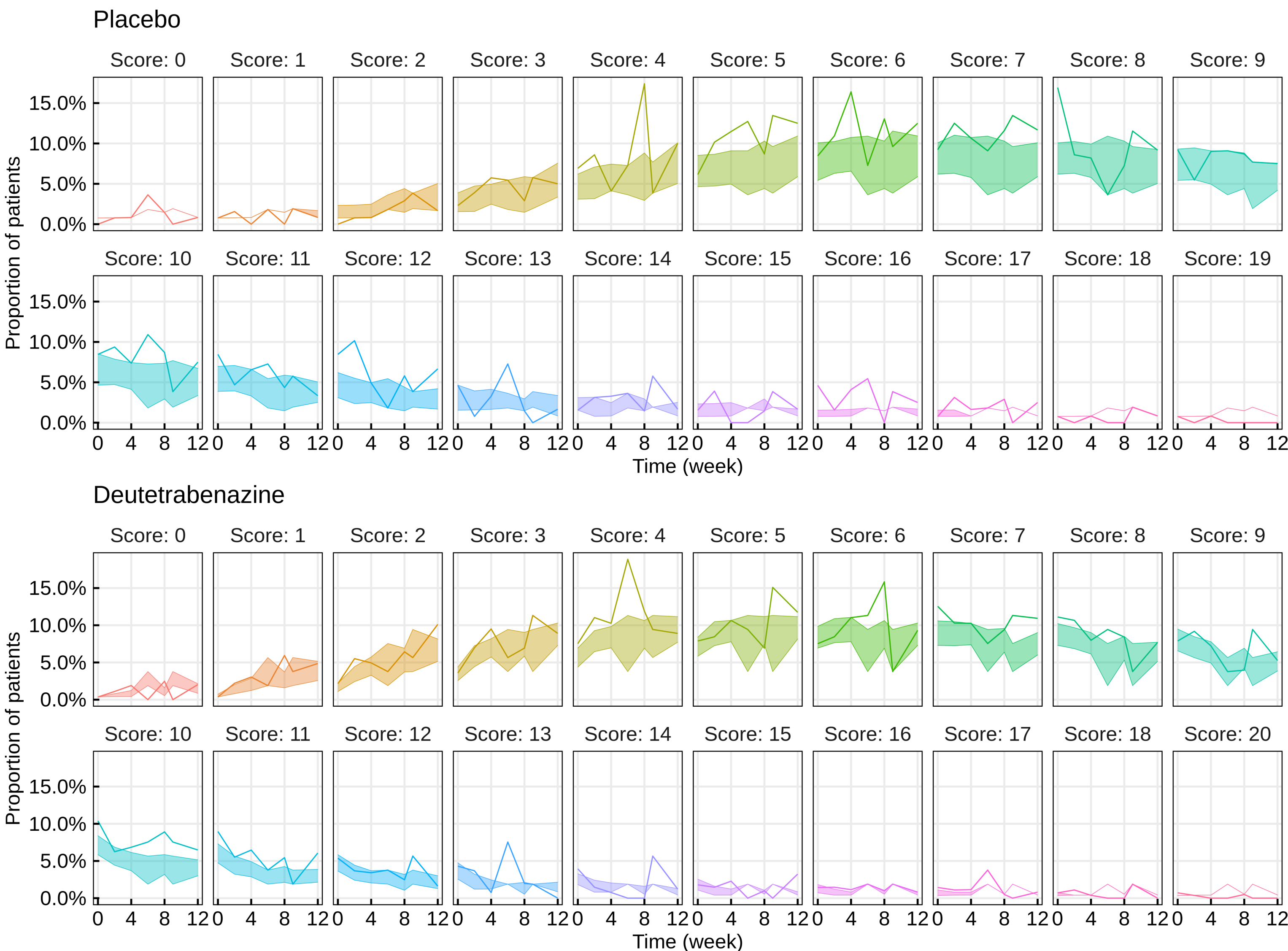


Figure 2. Visual predictive check of the selected model showing the proportion of patients by score for the placebo (Top), and deutetrabenazine (Bottom) groups. Scores without any observations are not shown.

- The predicted median and 95% confidence interval of the change from baseline score for total AIMS are presented in **Figure 3** over time and by quartile of C_{max} exposure.

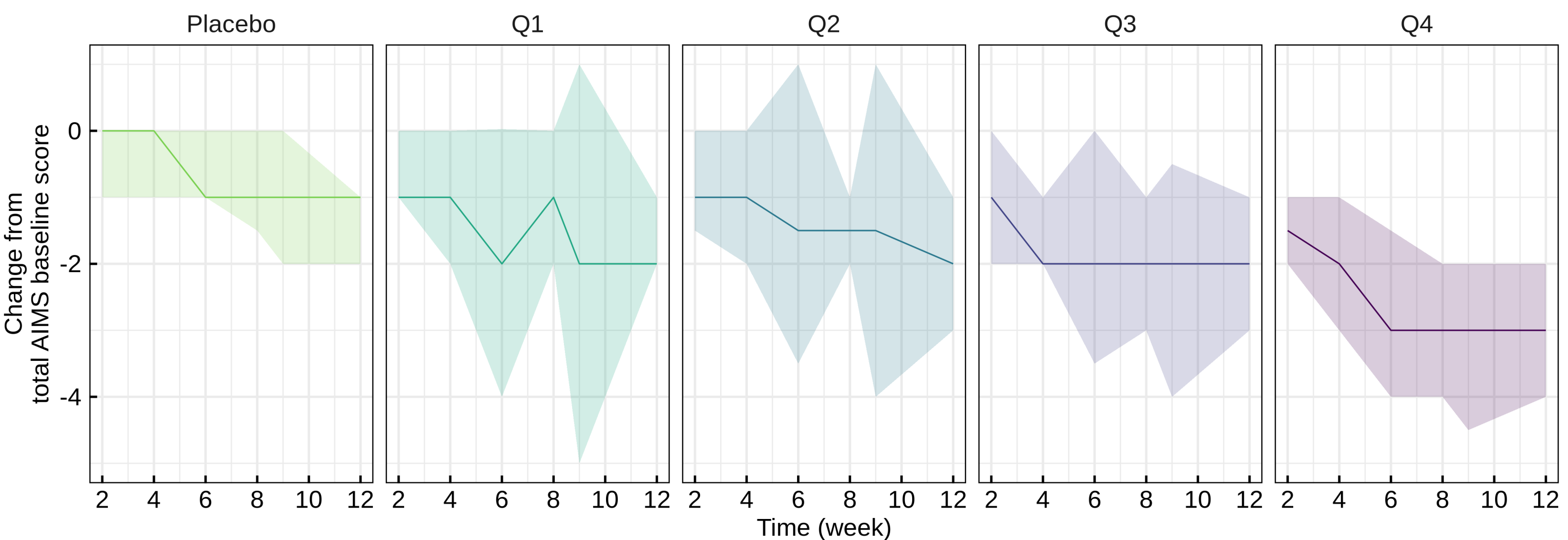


Figure 3. Q1, Q2, Q3, Q4 refer to the first, second, third, and fourth quartiles of C_{max} exposure at Week 12. Showing the median (lines) and their 95% confidence interval (shaded areas) based on model simulations (N=1,000).

References : [1] Anderson *et al. Lancet Psychiatry* (2017) ; [2] Fernandez *et al. Neurology* (2017) ; [3] Wellhagen *et al. The AAPS Journal* (2019) ; [4] Ueckert *et al. JPKPD* (2020) ; [5] Wellhagen *Uppsala University DiVA* (2020).

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