Evaluation of Beta Transformation to Estimate Treatment Effect in Depression and Schizophrenia Trials with Nonlinear Mixed Effects Analyses

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Objective

Compare treatment effects with longitudinal bounded clinical scores with beta transformation versus untransformed (raw) data.

Methods

Data:

- **PANSS** Scores from a randomized placebo-controlled, 6-week, parallel-arm clinical trial with an antipsychotic treatment at two doses (Arms 1 & 2) and olanzapine (Arm 3) as a positive control in patients with schizophrenia(1). The longitudinal model was:

$$PANSS(t) = Baseline \cdot e^{(-k \cdot time)} + Slope \cdot time$$

k - exponential rate of decrease in PANSS,
Slope - linear rate of PANSS relapse.
PANSS score is bounded between 30 and 210

- **HAMD-17** scores from a randomized placebo-controlled, 8-week, parallel-arm clinical trial with an antidepressant treatment at two doses in patients with major depressive disorder(2). The longitudinal model was:

$$HAMD(t) = Baseline \cdot e^{\left(-\frac{time}{td}\right)^b} + Hrec \cdot time$$

td - time to 63.2% of maximal change from baseline,
b - sigmoidicity factor,
Hrec - remission rate
HAMD-17 is bounded is between 0 and 54.

- Data from each clinical study were fitted with NONMEM with untransformed (raw) and beta transformation approach. The mixed-effects beta regression models were implemented using Nemes' approximation to the gamma function(3).

Treatment Effect

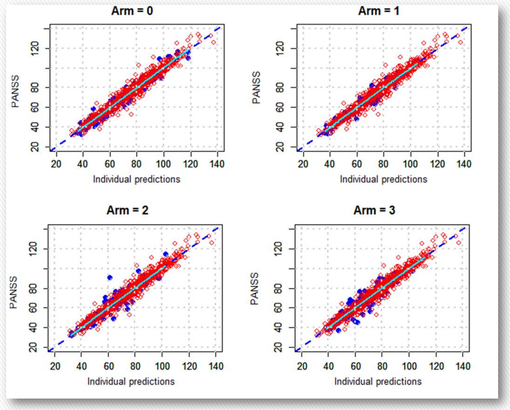
- The Treatment Effect (TE) is defined as the change from baseline in the clinical score at the end of the study. The TE were calculated for the observed data (reference TE) across treatment arms.
- Longitudinal models fitted to the data (raw and beta transformed) simulated to two hundred (N=200) trial replicates with the original study design. The TE were calculated for each of these trial replicates across different treatment arms.
- The TE (α_{ij}) estimated in each simulated trial (i) and for each treatment arm (j) was compared with the reference TE from the observed data (β). The bias in the TE for each simulated trial was then computed as:

$$BIAS = |\alpha_{ij} - \beta_j|$$

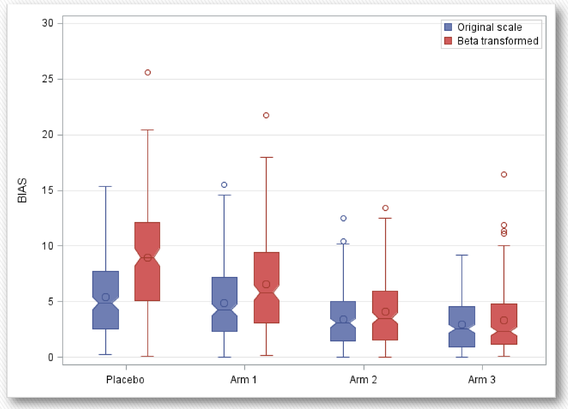
Results

PANSS Scores: Schizophrenia trial

- A total of 217 subjects were randomized in the trial: 52 to placebo (Arm0), 54 each to test drug with 20mg (Arm1) and 40mg (Arm2) and 57 to olanzapine (Arm3). Data were equally well fitted with untransformed & beta transformed methods.



Goodness-of-fit plots. The red points represent model fits from beta transformation and the blue dots from the untransformed data



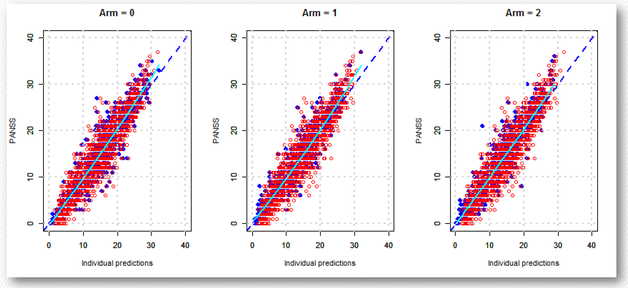
BIAS in the treatment effect (TE) by treatment arm using the untransformed and the beta transformed analysis

Median Bias		
Arm	Untransformed	Beta Transformation
0	4.84	8.99
1	4.24	5.78
2	3.05	3.51
3	2.54	2.30
Average	3.67	5.15

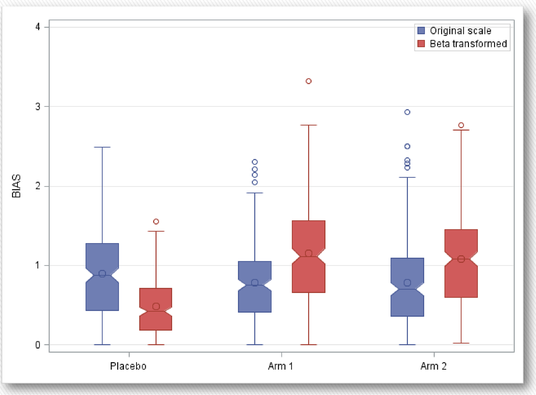
Summary of the BIAS in TE using the untransformed and the beta transformation approach

HAMD-17 Scores: Depression trial

- A total of 447 subjects were randomized in the trial: 153 to paroxetine 12.5 mg (Arm1), 148 to paroxetine 25 mg (Arm2) and 146 to placebo (Arm3). Data were equally well fitted with the untransformed and beta transformed methods.



Goodness-of-fit plots. The red points represent model fits from beta transformation and the blue dots from the untransformed data



BIAS in the treatment effect (TE) by treatment arm using the untransformed and the beta transformed analysis

Median Bias		
Arm	Untransformed	Beta Transformation
1	0.87	0.42
2	0.75	1.11
3	0.70	1.08
Average	0.77	0.87

Summary of the BIAS in TE using the untransformed and the beta transformation approach

Conclusions

- The analysis indicate that beta transformation appears to introduce a bias in the estimation of TE versus the using untransformed data.
- The extent of bias appears to be influenced by the distribution of the data and according to the values of the boundaries.
- These results need to be confirmed using other datasets.
- However, the findings suggest caution should be employed when evaluating TE using beta transformation as it may provide false positive outcomes.

References

(1) *Eur Neuropsychopharmacol. 2013; 23(11):1570-1576.*
(2) *Clin Pharmacol Ther. 2008 Sep;84(3):378-84*
(3) *J Pharmacokinet Pharmacodyn (2013) 40:537–544*