

# **Title:** Joint Factor and Regression Analyses of Multivariate Ordinal Outcome Data - Application to Psychiatric assessments

**Authors:** Diao, G<sup>1</sup>, Gottipati, S<sup>2</sup>, Zhang, P<sup>2</sup>

**Affiliations:** <sup>1</sup>Department of Statistics, Volgenau School of Engineering, George Mason University, Fairfax, VA, USA;  
<sup>2</sup>Otsuka Pharmaceutical Development & Commercialization, Inc., Princeton, NJ, USA

## **Abstract:**

### **The Methodological Question Being Addressed:**

Can we improve upon outcome and disease states measures in psychiatric patients enrolled in CNS clinical trials by accounting for subjectivity?

### **Introduction (Aims):**

Efficacy assessments in CNS trials are multivariate ordinal outcomes data where each variable is an item in the assessment and is assigned a score. The most common practice to compare endpoints in two or more treatment arms or measure improvement in efficacy over time is done by comparison of summary scores (typically the sum) between assessments. This approach typically assumes that distances between two consecutive levels across items as perceived by patients or raters are the same across all variables and each item has the same weight in the summary score.

### **Methods:**

We propose a joint model for the confirmatory factor analysis and regression analysis of multivariate ordinal outcomes. The proposed method accommodates the ordinal nature of the data and assesses the covariate effects on the latent factors. We develop estimation and inference procedures by using the composite likelihood function. We apply the proposed method on baseline PANSS scores measured in acutely relapsed schizophrenia inpatients enrolled in a placebo-controlled clinical trial to study efficacy of aripiprazole - NCT00080327.

### **Results:**

Extensive simulation studies demonstrated that the proposed methodology performs well in practical situations. The proposed maximum composite likelihood estimators have little biases, the standard error estimates accurately, and the 95% confidence intervals have correct coverage probability. In the real data analysis, we consider the 5-factor model of the PANSS score with the following five factors: 1) Negative symptoms; 2) Positive symptoms; (3) Disorganized thought; (4) Uncontrolled hostility/excitement; and (5) Anxiety/Depression. We include age, gender, and race in the regression model and evaluate their effects on the five latent factors. The ranges of the factor loadings for the five factors are: (1) 0.543 – 0.770; (2) 0.218 – 0.786; (3) 0.400 – 0.701; (4) 0.531 – 1.004; and (5) 0.335 – 0.908. Males appear to have

lower values in factor “Anxiety/Depression” with a parameter estimate of -0.448 (p-value=0.008). Compared to other race groups, “White” patients have higher values in latent factors “Positive symptoms”, “Uncontrolled hostility/excitement”, and “Anxiety/Depression” with parameter estimates of 0.484 (p-value<0.001), 0.343 (p-value=0.004), and 0.462 (p-value=0.001). Older patients have lower values in latent factors “Positive symptoms” and “Uncontrolled hostility/excitement” with p-values of 0.032 and 0.012, respectively.

### **Conclusions:**

Our method models potential sources of subjectivity to better measure outcomes and disease states in psychiatric patients to further CNS drug development. In terms of the power for testing covariate effects on the latent factors, the proposed method tends to outperform the existing methods in which each item is equally weighted in defining the factor scores when the factor loadings are different across different items. While our model addresses certain sources of subjectivity, there are other factors like rater to rater variability, rater bias stemming from the order in which he/she rates patients, etc., that are unaccounted in this work and will be addressed in future work. This model will be further developed to compare treatment effects between arms by modeling longitudinal data.

### **Disclosure:**

Study was funded by Otsuka Pharmaceutical Development & Commercialization, Inc. and Srikanth Gottipati and Peter Zhang are employees of the company.