Replication of a Statistical Method to Reduce Pseudospecificity and Enhance Understanding of Score Changes Among PANSS Factors

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Background

The Methodological Question Being Addressed

- Factor analyses of the Positive and Negative Syndrome Scale (PANSS) conducted so far have revealed varying degrees of intercorrelation. Consequently, improvement in a clinical domain of interest (e.g., negative symptoms) could be associated with and hence may be attributable to another correlated domain (e.g., positive symptoms) and is often considered "pseudospecific." This study addresses the methodological question about whether other statistical approaches can be utilized to reduce this pseudospecificity.

Introduction (Aims)

- PANSS is the gold standard measure of the symptoms of schizophrenia, particularly in clinical trials of acutely exacerbated symptoms. The PANSS consists of 30 items with three subscales (positive, negative, and general psychopathology). Factor analyses of the PANSS have consistently identified a five factor structure (Marder factors)[1] that has been considered to be more representative of the symptom domains measured by the PANSS. Analysis of changes in Marder factors is commonly used for secondary analysis in clinical studies. It has been shown, however, that there are substantial correlations between Marder factors. Because of these correlations, it is not possible to delineate whether these improvements represent a treatment effect in a given domain or are due to other non-specific effects between correlated symptoms.
- At the February 2017 meeting of ISCTM, Loebel et al presented a method to transform PANSS scores to reduce these correlations that exist among the Marder factors.[2] The goal of these transformations is to provide a more accurate profile of antipsychotic treatment effects. The transformation done by Loebel et al was based on multiple acute efficacy trials with an atypical antipsychotic, lurasidone. The transformed scores minimally correlated with all other factor scores, and each new factor corresponded well with its respective Marder score.
- We present in this poster a replication of the transformation of PANSS scores from the results of a recently completed Phase 2 study of the phosphodiesterase 10A inhibitor TAK-063 in subjects with an acute exacerbation of psychotic symptoms.

Methods

- The study used for this analysis was a six-week study of 20-mg TAK-063 versus placebo in subjects with acute exacerbation of psychotic symptoms (study TAK-063_2002). Approximately 80 subjects were enrolled in each treatment group. The results of this study have been reported previously.[3]
- A post hoc application of the method utilized by Loebel et al was performed on data from study TAK-063_2002.
- The SCORE matrix was estimated using PROC FACTOR procedure of SAS 9.4, with maximum likelihood method rotated using varimax algorithm and compensated for communality greater than 1 using Heywood criteria without a limit on the number of factors produced. The change from baseline PANSS data for all subjects and all observations was a matrix of dimensions (number of observations [N] x 30 items). To increase precision, the score matrix coefficients were determined using all change-from-baseline observations at weeks 1-6. The SCORE matrix (30 items x f factors) was used to transform individual PANSS item change scores (without standardization) to reduce the dimensionality into f factor values for each PANSS assessment.
- The following method was used to transform PANSS data into transformed PANSS factor scores:

  $[\text{PANSS Data}]_{(Nx30)} * [\text{SCORE}]_{(30x7)} = [\text{Transformed Factor Data}]_{(Nx7)}$

  where $[\text{PANSS Data}]_{(Nx30)}$ is a matrix with N observations and 30 columns for 30 PANSS items that will be transformed; $[\text{SCORE}]_{(30x7)}$ is a matrix with 30 observations and 7 columns for 7 transformed factors

  $[\text{Transformed Factor Data}]_{(Nx7)}$ is the transformed matrix with N observations (same as before transformation) and 7 columns for 7 transformed factors
- The MATLAB code to multiply matrices PANSS and SCORE is shown as follows:

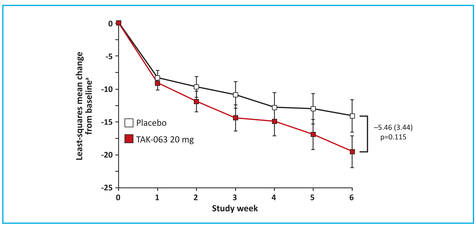
  TRANSFORMEDFACTORS = PANSS * SCORE

  where SCORE and PANSS are variables in MATLAB workspace of data type double

Results

- Primary results of study TAK-063_2002 have been reported elsewhere (the least-squares mean difference in change from baseline between TAK-063 and placebo was 5.46 points on the total PANSS score with a standard error of 3.44, p=0.115 and effect size 0.308) (**Figure 1**).[3]

Figure 1. Change From Baseline in PANSS Total Score by Study Week



Abbreviation: PANSS, Positive and Negative Syndrome Scale.
[a]Points indicate least-squares (LS) mean change from baseline at weeks 1-6 of the treatment period. Numbers at week 6 report LS mean difference (standard error). P-values were derived from the LS mean difference between TAK-063 and placebo, which was obtained using a mixed model for repeated measures with baseline PANSS total score as a covariate, and pooled center, week, and treatment as fixed factors. Unstructured covariance was assumed.

- The mixed model for repeated measures (MMRM) analysis of total PANSS and PANSS Marder factors are reported in **Table 1**.

Table 1. MMRM Analysis of Total PANSS and Marder Factors at Week 6

Parameter		LS mean (SE)			P-value	Effect size
		Placebo	TAK-063 20 mg	Difference		
Total PANSS		-14.08 (2.47)	-19.54 (2.41)	-5.46 (3.44)	0.115	0.308
PANSS Marder Factors	Positive	-5.33 (0.800)	-7.23 (0.778)	-1.90 (1.119)	0.092	0.330
	Negative	-3.38 (0.681)	-4.11 (0.662)	-0.73 (0.940)	0.441	0.150
	Disorganized	-1.90 (0.579)	-3.16 (0.565)	-1.26 (0.804)	0.119	0.305
	Hostility	-1.16 (0.476)	-2.28 (0.462)	-1.12 (0.653)	0.088	0.334
	Anxiety/ Depression	-3.66 (0.460)	-4.34 (0.447)	-0.68 (0.635)	0.288	0.207

Abbreviations: LS, least-squares; MMRM, mixed model for repeated measures; PANSS, Positive and Negative Syndrome Scale; SE, standard error.
LS means, differences, and P-values were obtained using a mixed model for repeated measures with baseline score for the indicated parameter as covariate and pooled center, week, and treatment as fixed factors. Unstructured covariance was assumed.

- The Pearson's correlations among the Marder scores (change from baseline to endpoint) were generally above 0.40 and generally similar to the correlations reported by Loebel et al (**Table 2**).
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Table 2. Correlations Among Marder PANSS Factor Scores (Week 6 Change From Baseline)

Marder PANSS Factors						
Positive	1.00					
Negative	0.46	1.00				
Anxiety/ Depression	0.55	0.45	1.00			
Disorganized	0.65	0.50	0.50	1.00		
Hostility	0.46	0.23	0.47	0.41	1.00	
PANSS Total	0.85	0.71	0.76	0.80	0.66	1.00

Abbreviation: PANSS, Positive and Negative Syndrome Scale.
Pearson's correlations
1.0 0.6 ≤0.3

- The transformed factors corresponded well to their respective Marder factors and between factor correlations were reduced compared to non-transformed values and were generally similar to those reported by Loebel et al (**Table 3**).

Table 3. Correlations Between Marder Versus Transformed PANSS Factor Scores[a] (Week 6 Change From Baseline)

Marder PANSS Factors	POS	DIS	AA	DE	HOS	ANX	DEP	TOT
Positive	0.81	0.30	0.30	-0.04	0.22	0.43	0.42	0.82
Disorganized	0.38	0.64	0.26	0.15	0.20	0.36	0.32	0.70
Negative	0.30	0.02	0.75	0.64	0.08	0.24	0.37	0.72
Hostility	0.19	-0.02	0.01	-0.06	0.94	0.28	0.28	0.60
Anxiety/Depression	0.33	-0.04	0.34	-0.03	0.27	0.77	0.82	0.82
PANSS Total	0.56	0.24	0.45	0.18	0.43	0.54	0.57	0.96

Abbreviations: AA, negative apathy/avolition; ANX, anxiety; DE, negative deficit of expression; DEP, depression; DIS, disorganized; HOS, hostility; PANSS, Positive and Negative Syndrome Scale; POS, positive; TOT, total.
Pearson's correlations
1.0 0.6 ≤0.3
[a]Pearson's correlation coefficients between all subjects' Marder factor scores and transformed factor scores.

- With transformation, the Pearson's correlations among the transformed scores were considerably less than among the Marder factor correlations (**Table 4**).

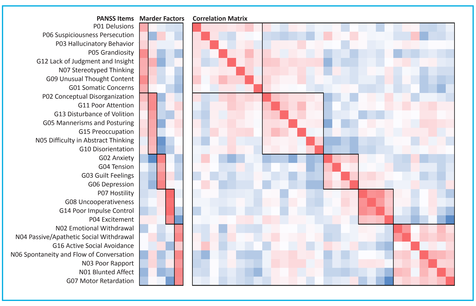
Table 4. Correlations Among the Transformed PANSS Factor Scores (Week 6 Change From Baseline)

Transformed PANSS Factors							
Positive	1.00						
Disorganized	0.07	1.00					
Apathy/Avolition	0.18	-0.07	1.00				
Deficit of Expression	-0.02	-0.07	0.15	1.00			
Hostility	-0.01	-0.13	-0.15	-0.02	1.00		
Anxiety	0.28	0.01	0.24	-0.18	0.44	1.00	
Depression	0.29	-0.16	0.29	0.06	0.09	0.36	1.00
PANSS Total	0.59	0.14	0.50	-0.23	0.38	0.61	0.65

Abbreviation: PANSS, Positive and Negative Syndrome Scale.
Pearson's correlations
1.0 0.6 ≤0.3

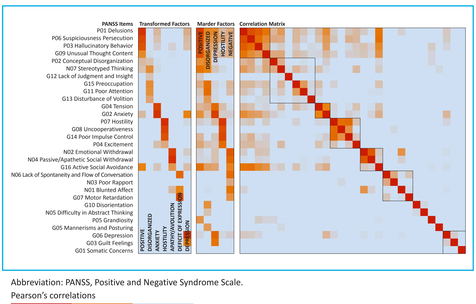
- A correlation matrix heat map of PANSS item scores for all subjects at baseline in TAK-063_2002 is shown in **Figure 2**.
- A correlation matrix heat map of PANSS items scores change from baseline in TAK-063_2002 is shown in **Figure 3**.

Figure 2. Structure of Schizophrenia Symptoms at Baseline



Abbreviation: PANSS, Positive and Negative Syndrome Scale.
Pearson's correlations
1.0 0.6 0.3 0.0 -0.3
Correlation matrix heat map of PANSS item scores for all subjects at baseline (N=164). Each row corresponds to an item of the PANSS and correlations between each item and Marder factor (left columns) and PANSS items (right columns).

Figure 3: Change From Baseline Correlation Matrix by Marder Factor and PANSS Item



Abbreviation: PANSS, Positive and Negative Syndrome Scale.
Pearson's correlations
1.0 0.6 ≤0.3

Conclusions

- Utilizing the transformation method to PANSS factors from the TAK-063_2002 study yielded results similar to those reported by Loebel et al for a drug with a different mechanism of action.
- The correlations between Marder factors showed high levels of correlations between factors.
- The correlations between transformed scores and Marder factors were considerably less.
- The correlations among the transformed PANSS factors were considerably smaller than those seen on the Marder factors.
- Reducing the correlations between factor scores may be a more accurate representation of antipsychotic effects.

References

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2. Loebel T, Hopkins S. A new PANSS factor analysis intended to reduce pseudospecificity among domains and enhance understanding of symptom change in antipsychotic-treated patients with schizophrenia. Poster presented at: 13th Annual Scientific Meeting of the International Society for CNS Clinical Trials and Methodology (ISCTM); February 21-23, 2017; Washington, DC.
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Disclosures

F. Ogrinc is an employee of Takeda Development Center Americas, Inc., Deerfield, IL, USA. A.R. Mahableshwarkar and T.A. Macek were employees of Takeda Development Center Americas, Inc., Deerfield, IL, USA, at the time of this study.
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