A General Theory of Construct Enrichment: Inclusion Criteria for Symptom Structure Not Severity

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What is the Methodological Issue Being Addressed? In clinical trials there are currently no methods to ensure that the construct reliability of any given scale is maintained by enrolling subjects having the symptom construct. Here we sought to enrich for subjects having high degree of variance explained on known symptom constructs as inclusion/exclusion criteria for clinical trials.

Introduction In psychiatric drug development, there is a lack of symptom-based, data-analytical approaches to relate properties of individual subjects at study entry to the known heterogeneity of the disorder. The construct reliability and validity of assessment scales used in schizophrenia and bipolar depression are largely based on the relationship between the variance explained by individual items and the underlying symptom constructs of the disorder. It is often that psychiatric scales are used as enrollment criteria in clinical trials and total severity of symptoms scores are believed to guard against patient heterogeneity. However, accuracy of the psychometric instrument for the specified construct is compromised by using severity alone, and allows heterogeneity to be introduced from related constructs.

Methods Screening and baseline MADRS and PANSS assessments registration trials in schizophrenia (N=4,868), bipolar depression (N=2,026) and MDD with mixed features (N=208) were used to test indices of heterogeneity. Indices of heterogeneity were created for specific symptom constructs using variance-covariance and difference matrices of selected items belonging to that construct, using only screening and baseline assessments prior to randomization. Separately composite heterogeneity indices were defined, for each of PANSS and MADRS scales, to identify a subpopulation of subjects that maximally expressed the 5-factor PANSS construct, and the 4-factor MADRS construct.

Results Each of the 5 Marder PANSS symptom constructs, and each of the 4 factors of MADRS, demonstrated reliable indices of heterogeneity that could sort individual subjects by adherence to each of the pre-specified constructs. Variance explained, among subject subgroups binned by heterogeneity in each of the targeted symptom constructs, tracked with each respective heterogeneity indices for all the PANSS- and MADRS-based constructs. For each of the selected constructs, thresholds of heterogeneity identified subpopulations with greater variance explained, internal reliability, and thus excellent fits to each of the predefined factor models, based on confirmatory factor analysis.

Conclusion The ability to identify subjects to enrich for a trial population whose variance in a specified symptom domain is well-described by the selected instrument (PANSS, MADRS), improves the reliability of clinical trials. Optimizing the match between instrument, trial population, and endpoint will increase the validity and power of clinical trials. Enriching for symptom structure and not severity may lead to more effective testing of new treatments, and is in keeping with existing categories of enrichment strategies as discussed in FDA guidance documents.

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Disclosures Seth C. Hopkins, Sasagu Tomioka, and Kenneth Koblan are employees of Sunovion Pharmaceuticals, Inc.

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