

Enrichment for canonical symptom presentation in Generalized Anxiety Disorder

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What is the Methodological Issue Being Addressed? Clinical trials in psychiatry are challenged by heterogeneous patient populations and uncertainty in measuring neuropsychiatric constructs with symptom rating scales. Conventional inclusion criteria specify symptom severity, but do not determine whether an individual subject's item-level symptom presentation is well-suited to the psychometric structure of the selected instrument. Variance-covariance difference (VCD) methods were previously developed to identify canonical versus anomalous symptom structure at the individual-subject level, with the goal of reducing nondrug-related variability and increasing the ability to detect a drug effect if one is present. This analysis evaluates whether this symptom-structure enrichment concept can be applied to the Hamilton Anxiety Rating Scale (HAM-A).

Introduction The HAM-A is widely used in anxiety clinical trials, but total score severity may obscure important differences in item structure. We hypothesized that subjects whose screening and baseline HAM-A item patterns conform more closely to a prespecified psychic/somatic anxiety construct would provide greater measurement certainty than subjects with anomalous HAM-A item structure. In effect, this method reframes the usual question of "what instrument is best for my study?" as "what symptom presentation is best for my instrument?"

Methods This retrospective analysis used HAM-A 14-item scores from 635 subjects across 3 studies, using screening and baseline assessments. For each subject, HAM-A item scores from the 2 visits were encoded as a 287-element VCD vector comprising item-level variances across visits, between-item covariances, within-visit item differences at screening and baseline. Isolation Forest derived VCD-based anomaly scores quantifying disparities in HAM-A item-structure distribution. Subjects were stratified into canonical and non-canonical groups using percentile-based anomaly-score definitions. Psychometric validity was evaluated using confirmatory factor analysis (CFA) of a prespecified 2-factor HAM-A model representing correlated but distinct psychic and somatic anxiety domains. Items 1–6 and 14 loaded on a psychic anxiety factor, the remaining items on a somatic anxiety factor. Validation was based on degradation of CFA fit indices. Fit indices included Comparative Fit Index (CFI) and Root Mean Square Error of Approximation (RMSEA).

Results Subjects classified as canonical consistently demonstrated better fit to the prespecified 2-factor HAM-A model than non-canonical subjects. Canonical groups had higher CFI and lower RMSEA, whereas non-canonical subjects showed systematic fit deterioration. For example, using a 0%–70% canonical interval, canonical subjects (N=445) demonstrated CFI=0.743 and

RMSEA=0.087, compared with CFI=0.626 and RMSEA=0.113 in non-canonical subjects (N=190). Similar directional results were observed for 0%-60% canonical subjects (N=381; CFI=0.754, RMSEA=0.086) versus non-canonical subjects (N=254; CFI=0.653, RMSEA=0.107). The canonical side of the anomaly-score distribution better preserved the prespecified HAM-A factor structure, indicating that the HAM-A VCD representation contains construct-validity information at the individual-subject level.

Conclusion These findings support the utility of VCD symptom-structure enrichment in HAM-A to identify subjects whose anxiety symptoms better conformed to a prespecified psychic/somatic HAM-A construct. The method is not intended as responder-enrichment or a diagnosis classifier; rather, it is an instrument-validity enrichment strategy designed to reduce nondrug-related variability by selecting subjects whose symptom presentation is more canonical for the rating scale used as an endpoint.

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Keywords

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