Exploring the Relationship Between NPI-C Psychosis Domains and CGI-S in Alzheimer's Disease Psychosis

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Methodological Issue Being Addressed Both the Neuropsychiatric Inventory–Clinician Rating Scale (NPI-C) and the Clinical Global Impression–Severity (CGI-S) are commonly used clinician-rated endpoints in Alzheimer's disease (AD) psychosis trials, yet their relationship has not been directly characterized. Clarifying how these measures align is important for evaluating convergent validity, interpreting treatment effects, and informing rater training and data quality monitoring.

Introduction The NPI-C expands the original Neuropsychiatric Inventory (NPI) through clinician synthesis of structured caregiver and patient interviews. NPI-C Psychosis (sum of Delusions and Hallucinations domains) has demonstrated convergent validity with clinician-rated psychosis measures such as the Brief Psychiatric Rating Scale (BPRS; de Medeiros et al., 2010). A similar association would be expected with CGI-S for psychosis, a global assessment of psychosis severity in AD; however, this association has not been empirically described. The current study examined the relationship between NPI-C Psychosis and CGI-S for psychosis using pooled data from two Phase 3 global AD psychosis trials.

Methods Data were pooled from two ongoing multicenter, global Phase 3 trials in Alzheimer's disease psychosis. Screening and end-of-treatment (EoT) data were analyzed. Screening data were evaluated separately because one study required a baseline CGI-S score ≥4, which could restrict the range of post-screening CGI-S scores. Within each visit, Spearman's rank correlation was used to assess the association between NPI-C Psychosis total scores and CGI-S psychosis ratings. To examine concordance across severity levels, a screening heatmap cross-tabulation (NPI-C Psychosis × CGI-S) was generated to visualize the joint frequency distribution and identify clustering patterns.

Results Descriptive statistics are presented in Table 1 (MMSE shown for contextualization of cognitive status). NPI-C Psychosis total scores were moderately and positively associated with CGI-S ratings at screening, $r_s(336) = .44$, $p < .001$, and strongly associated at EoT, $r_s(141) = .74$, $p < .001$. The screening heatmap (Figure 1) showed a diagonal concentration consistent with expected covariance; however, CGI-S ratings were highly concentrated at 4–5 (approximately 90% of observations), whereas NPI-C Psychosis totals spanned a broader range (1–40). The most frequent pairings occurred at NPI-C totals of 7–14 with CGI-S ratings of 4–5. Even among higher CGI-S ratings (6–7), NPI-C totals varied widely (12–38).

Conclusion This study examined the relationship between NPI-C Psychosis and CGI-S psychosis

ratings using pooled data from two global Phase 3 trials in Alzheimer's disease psychosis. As expected, NPI-C Psychosis total scores and CGI-S psychosis ratings were significantly associated, showing a moderate correlation at screening and a strong correlation at EoT.

Heatmap patterns also highlighted differences in score granularity: CGI-S ratings clustered predominantly in the mid-range, whereas NPI-C Psychosis scores were more widely distributed. This divergence likely reflects conceptual differences between the measures. CGI-S captures a global clinical impression that may be disproportionately shaped by one or a few salient or distressing symptoms, whereas the NPI-C provides a structured, symptom-level clinician rating within the Delusions and Hallucinations domains.

Taken together, these findings indicate that although NPI-C Psychosis and CGI-S psychosis ratings are moderately to strongly correlated, discordance between the two measures may be relatively common and, in isolation, should not be interpreted as a deviation or data quality concern. To enhance interpretability in AD psychosis trials, we recommend ongoing rater calibration, provision of CGI-S anchor guidance, and consistent adherence to standardized administration procedures (e.g., applying the correct evaluation timeframe and anchoring ratings to psychosis-specific symptoms rather than overall AD severity).

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Keywords

Keywords
NPI-C
Psychosis
Alzheimer's
CGI-S
Neuropsychiatric

Guidelines I have read and understand the Poster Guidelines

Disclosures All authors are employees of Signant Health with no conflicts of interest.