PANSS AND CGI-S: TEN YEARS LATER – A FURTHER EXAMINATION OF THEIR RELATIONSHIP

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BACKGROUND

- The Positive and Negative Syndrome Scale (PANSS)[1] and Clinical Global Impressions-Severity (CGI)[2] scale are frequently used as endpoints in schizophrenia clinical trials[3].
- Although both measures are clinician-reported outcome measures (ClinRO), the PANSS examines the schizophrenia symptomatology and general psychopathology, whereas the CGI provides a global assessment of overall functioning.
- The CGI, comprised of three items, measures illness severity (CGI-S) and improvement (CGI-I), and contains a single item related to drug treatment effects (i.e., efficacy index).
  - Each CGI item is designed to be rated separately, there is no composite score.
  - Clinicians are permitted access to all collateral patient information and expected to rate subjects relative to their past experience with other schizophrenia patients[2].
  - Many clinical trials require that the CGI be administered last to consider all collected information when making the global rating(s).
- The CGI, however, has been criticized for its psychometric limitations[4-7] and susceptibility to expectancy bias when administered following the PANSS[3].
- Leucht and colleagues in 2005[3] explored the relationship between these scales and clinical meaningfulness of the PANSS in relation to the CGI.
  - This seminal work pooled patient data from seven randomized, double-blind, placebo controlled schizophrenia trials (N = 4,091, at baseline) and found a baseline correlation of 0.56 between the two measures.
  - It also observed a correspondence between the two scores, where mildly ill (CGI-S 3) corresponded to a total PANSS score of 58, “moderately ill” (CGI-S 4) to a PANSS score of 75, “markedly ill” (CGI-S 5) to a PANSS score of 95, and “severely ill” (CGI-S 6) to a PANSS score of 116.
- A significant amount of clinical trial data has been collected on these scales in schizophrenia since Leucht et al. published more than a decade ago. Further examination of the relationship between these scales seems prudent given their importance in the field.

OBJECTIVES

- The objectives of the present study were to:
  1. Replicate and expand upon Leucht et al. using a large dataset spanning multiple clinical trials.
  2. Examine the level of agreement when both measures are administered by the same centralized and calibrated clinical trial raters.

METHODS

- Aggregated data from seven global clinical trials of schizophrenia in which both the PANSS and CGI-S were administered. There were 3,070 subjects across the studies, a total of 12,476 PANSS/CGI-S assessments.
- Both scales were administered by a cohort of remote centralized clinicians who were blinded to protocol requirements, visit number, and prior knowledge of subject, a methodology that has been shown to help standardize assessments and eliminate scoring bias[8].
- The centralized clinicians completed the PANSS and CGI-S ratings, after which they examined alignment between the scores according to the guideline provided by Leucht et al. Misaligned scores were noted but initial scores remained unchanged.

References

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RESULTS

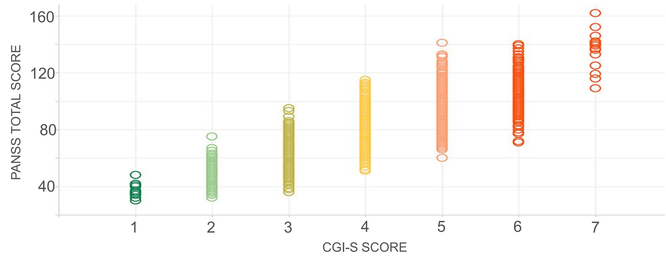
- Table 1 shows the mean PANSS total and CGI-S scores for each of the seven studies. Pooled means across the studies were 81.5. (SD=16) and 4.3 (SD =0.9) for the PANSS total and CGI-S scores, respectively. This corresponds to a ‘moderately’-to-‘markedly ill’ aggregate population[3].

Table 1. Cohort Characteristics

	Study 1	Study 2	Study 3	Study 4	Study 5	Study 6	Study 7	Overall
# Subjects	262	473	738	334	418	422	423	3,070
# PANSS/CGI-S Assessments	1,031	2,068	3,583	1,581	1,338	1,900	975	12,476
Mean PANSS (SD)	82.2 (15.73)	81.9 (14.93)	79.9 (14.0)	80.2 (15.42)	70.1 (15.99)	88.2 (16.66)	90.8 (13.58)	81.5 (16.01)
Mean CGI-S (SD)	4.4 (0.88)	4.3 (0.83)	4.2 (0.78)	4.3 (0.87)	3.7 (0.95)	4.7 (0.9)	4.8 (0.75)	4.3 (0.89)

- The distributions of PANSS total scores at each CGI severity stage are shown in Figure 1.
- The mean (SD) PANSS total scores at each of the seven stages all fell within range of the Leucht et al. findings: 37.2 (4.3), 47.1 (5.8), 59.9 (5.9), 76.4 (6.6), 92.9 (6.7), 109.4 (8.6), and 136.3 (12.7), respectively.

Figure 1. Relationships between PANSS and CGI-S scores



- Importantly, we observed a strong and significant correlation between PANSS total and CGI-S scores, r = .91, p < .0001. The Pearson correlation coefficients for each of the studies within the cohort are shown in Table 2, and ranged from .80 to .92 (versus 0.56 to 0.73 reported by Leucht et al.[3]).

Table 2. Correlations between PANSS total scores and CGI-S scores

	Study 1	Study 2	Study 3	Study 4	Study 5	Study 6	Study 7
Pearson Correlation Coefficient *(r)*	0.922*	0.918*	0.906*	0.924*	0.858*	0.892*	0.798*

** Correlation is significant at the 0.01 (2-tailed) level*

- Misalignments were very low, and observed in only 1,159 (9%) of PANSS/CGI-S scores.

CONCLUSIONS

- The present study utilized a large dataset spanning multiple global schizophrenia studies, replicated and expanded upon the original 2005 work of Leucht and colleagues, and provided additional evidence for substantial agreement between PANSS total score and CGI-S.
- This study, however, found much higher correlations (r = .91, p < .0001), likely attributable to implementation of assessments by highly calibrated central clinicians.
- As noted in the methods, raters were blinded to the study protocol, treatment arm and visit, which appeared to reduce bias (therapeutic alliance, expectancy, etc.) that often occurs in clinical trials and can compromise ratings.
- Less bias and associated variance translates to potentially increased power to detect a therapeutic effect.
- The substantial overlap and significant shared variance between the two scales (i.e., 83 percent) brings into question the additional value of CGI-S administration, as this scale has already been shown to have several limitations, including expectancy bias, ceiling effects, and lack of data with regards to reliability and validity[3-7].
- The present study also had limitations, particularly those inherent in aggregate data, such as selection of studies and potential bias in the design of individual studies. It is noteworthy, however, that despite such limitations, correlations remained robust.
- Considering the complementary nature of the PANSS and CGI-S and the significant correlations between these measures, researchers should carefully consider the risk-benefit of including both on the chance they do not align and/or consider implementing a blinded centralized review (over-read) of all collected data.

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