Prevalence and Severity of PANSS Worsening Across Schizophrenia Clinical Trial Populations: An Analysis of 33 Studies.

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What is the Methodological Issue Being Addressed? How do worsening rates, operationalized via PANSS deterioration thresholds, differ by trial population in schizophrenia clinical trials?

Introduction Clinical trials in schizophrenia typically emphasize mean symptom improvement as the primary measure of efficacy. However, a meaningful and heterogeneous subset of participants worsens during trials, irrespective of treatment assignment, and this proportion is rarely reported. In this retrospective analysis of a large pooled dataset, we estimated the prevalence of worsening using progressively stringent PANSS-based thresholds and assessed differences across three patient populations: acutely exacerbated, predominant negative symptoms, and suboptimally controlled.

Methods Data were pooled from 33 double-blind, placebo-controlled trials (21 acute exacerbation, 8 negative symptom, 4 suboptimally controlled), comprising 15,204 subjects. Worsening was defined as an increase of ≥1, ≥10, ≥13 (commonly proposed relapse threshold), or ≥20 points in PANSS total score from baseline at any time during the primary treatment period. For each threshold, mixed-effects logistic regression models were fitted with fixed effects for study type, baseline PANSS total, centered study start year, and proportion of planned follow-up completed. A protocol-level random intercept accounted for between-study heterogeneity. Models were estimated using residual pseudo-likelihood with containment-based degrees of freedom.

Results In acute exacerbation trials, mean proportions meeting worsening thresholds (≥1, ≥10, ≥13, ≥20) were 33%, 10%, 7%, and 3%, respectively. Corresponding rates in negative symptom trials were 33%, 7%, 4%, and 1%, and in suboptimally controlled trials were 23%, 3%, 2%, and <1%. Protocol-level random effects were consistently significant, indicating substantial between-study heterogeneity. For the ≥10-point threshold, both acute and negative symptom studies showed higher odds of worsening compared with non-acute trials (OR = 3.04, 95% CI: 1.73–5.34, p = 0.0001; OR = 2.42, 95% CI: 1.30–4.50, p = 0.0057). Similar patterns were observed for ≥13 and ≥20 thresholds. Baseline PANSS total showed a non-significant trend toward lower odds of worsening, and no temporal trend was observed by study year.

Conclusion Although mild deterioration is relatively common, clinically meaningful worsening during the primary treatment period is infrequent. This is somewhat unexpected in acute exacerbation trials, where greater deterioration might be anticipated. Lower worsening rates in suboptimally controlled populations—despite longer follow-up—likely reflect study design, as these trials evaluated adjunctive treatments added to stable antipsychotic therapy rather than

monotherapy. A similar pattern was observed in negative symptom trials, with higher worsening rates in monotherapy designs. Higher worsening rates in acute versus negative symptom trials may also reflect differences in patient selection, with acute trials enriching for positive symptoms and instability, versus relative stability in negative symptom populations.
Key limitations include lack of treatment assignment, precluding arm-level comparisons, and absence of sensitivity analyses imputing dropouts as worsened, which may underestimate true deterioration rates. Strengths include the large pooled sample and use of mixed-effects models to account for protocol-level variability.
Overall, clinically meaningful worsening appears relatively infrequent in schizophrenia trials and influenced by design features. Routine reporting of worsening rates alongside mean improvements would provide a more complete and clinically relevant assessment of treatment outcomes.

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Keywords

Keywords
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Guidelines I have read and understand the Poster Guidelines

Disclosures Alan Kott and Xingmei Wang are employees of Signant Health and may hold shares of Signant Health. David Daniel is an Executive Advisor to Signant Health.

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