Alternative Thresholds for Negative and Positive Symptoms in the CATIE Trial:

Implications for Negative Symptom Clinical Trials

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Background – Negative Symptoms

- Negative symptoms are an important target for schizophrenia drug development, however clinical trial patient selection remains challenging.
  - Restrictive criteria are needed to avoid confounding (pseudospecific) effects of change in positive, depressive or extrapyramidal symptoms
  - Subjects with negative symptoms experience apathy and avolition, which further limits ability to engage them in clinical research

- Guidance has been developed to minimize pseudospecific treatment effects:
  - NIMH-MATRICS [1] : "…clinically stable patients whose negative symptoms persist with adequate antipsychotic drug treatment."
  - EMA negative symptoms guidance [2]: "Subjects with predominant and persistent negative symptoms… …and who have stable condition of schizophrenic illness…"
  - Both recommend exclusion of subjects whose negative symptoms may be secondary to depressive or extra-pyramidal symptoms (EPS)

Background – Negative Symptoms

- Despite the consensus on the need for symptoms to be stable and persistent, there is little agreement on optimal symptom severity thresholds for inclusion in clinical trials
  - Tight negative and positive symptom thresholds yield clinical samples where treatment effects on negative symptoms would not be considered pseudospecific.
  - However, tight thresholds lead to small eligible subject pools: A recently published analysis of NEWMEDS dataset of short-term, placebo-controlled trials found that tighter criteria for patient selection lead to only a small fraction remaining eligible for trial inclusion [3]

- This presentation aims to evaluate effects on sample characteristics and treatment effects on the CATIE study dataset
  - Negative and positive symptom inclusion criteria evaluated in the NEWMEDS dataset will be used [3]

Objective

- To evaluate the impact of multiple operational definitions of negative and positive symptom criteria on:
  - Eligible population sample size
  - Baseline negative and positive symptom severity
  - Negative and positive symptom change scores
  - Correlations between negative and positive symptom change scores

Analysis Definitions

- An initial subset of stable subjects was identified:
  - No symptom exacerbations during the preceding 3 months
  - With at least minimal scores (>1) on the PANSS items N1 (blunted affect), N4 (apathy/avolition) and N6 (decreased conversation flow).
  - Confounding effects from depressive symptoms were limited by excluding patients with a PANSS item G6 (depression) score >4 (moderate severity).
- Six alternative criteria (from broad to restrictive) based on PANSS subscale scores that enrich for negative symptoms and limit positive symptoms were evaluated:
  - Negative subscale > positive subscale *
  - Negative subscale score ≥21 and ≥1 point over positive subscale score [Riedel 2005] [6] *
  - Negative subscale: at least three items with a score ≥4, or at least two items with a score ≥5 [Kinon 2006] [7] +
  - Negative subscale score ≥6 points over positive subscale score [Olie 2006] [8] *
  - Negative subscale: at least three items with a score ≥4, or at least two items with a score ≥5, and a positive subscale score <19 [Stauffer 2012] [9] *
  - Negative subscale: items N1 and N6 scores >3 and at least one third of items with a score >3; positive subscale: maximum of two items with a score >3 [Moller 2004] [10] +

* Predominant
+ Prominent

Summary Results and Conclusions

- Varying the PANSS-based criteria used to define entry criteria for negative symptom trials yields large differences in eligible population size
- More restrictive criteria yield gradual increases in baseline negative symptom severity and generally lower baseline positive symptom severity
- Change from baseline in both positive and negative symptoms increase with increased baseline severity. However, when adjusted for baseline score or change from baseline in positive symptoms, there is a comparable change from baseline across subsets
- Correlations between negative and positive symptom change was modest and comparable across subsets.
- Overall, in a stable subset of CATIE participants with at least minimal baseline negative symptoms, varying negative and positive symptom severity thresholds had large impact on sample size and limited impact on observed treatment effects.
- The need for restrictive positive and negative symptom study entry criteria in negative symptom trials warrants further research

References

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