

Enrichment based on speech latency enhances treatment effects in a Phase III study of brilaroxazine.

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Methodological Issue Being Addressed Can speech latencies, derived from a clinical interview, measure negative symptoms, and can they be used to enhance clinical trials as an enrichment tool?

Introduction Speech analysis offers an objective tool for quantifying negative symptoms. Speech latency, a measure of verbal response times, reflects a host of cognitive, social, and motivational abilities implicated in negative symptoms. Speech latency can be assayed directly from psychiatric interviews, which is advantageous for two reasons. First, the number of responses required of patients contributes to highly reliable speech latency estimates. Second, the nature of psychiatric interviews places a heavy, and relatively standardized, cognitive, social and motivational strain on patients.

We recently used speech latency analysis to enrich participants for an antidepressant clinical trial, resulting in nearly double the drug-placebo effects at half the sample size. Here we evaluate speech latency in a clinical trial of schizophrenia.

Methods Audio recordings from Positive and Negative Syndrome Scale (PANSS) interviews in a Phase 3 trial of brilaroxazine were evaluated. Recordings ($k = 2590$) for 408 participants from three countries representing eight languages were analyzed using an automated analytic pipeline. The speech latency measure, based on speaking turns, is the time elapsed between the rater's question and the study participant's response, corrected for the participants duration response.

We evaluated internal consistency, temporal stability, and convergence with clinical negative symptom ratings across three countries. To evaluate enrichment, we compared treatment response in patients that were Vocal BioMarker Negative (i.e., VBM-Neg; unremarkable latency) from Vocal BioMarker Positive (i.e., VBM-Pos; relatively long latency) during the screening session. VBM status was determined using a value derived from classifying asymptomatic from moderate/severe negative symptom in post-randomization interviews. This value was applied to pre-randomization data.

Results Speech latency showed excellent internal consistency, good temporal stability, and minimal convergence with potentially confounds. Patients high in negative symptoms showed longer speech latencies, with large effects sizes observed in every country (d 's from 1.00 to 1.47).

A speech latency value (AUC = 0.74) identified 179 and 229 participants as being VBM-Neg and positive respectively. Brilaroxazine, versus placebo, showed improved outcomes from baseline to end of treatment for the VBM-pos as compared to the VBM-neg group. Treatment effects were larger for VBM-Pos versus VBM-Neg patients in PANSS total scores (246% improvement), positive symptoms (193%), negative symptoms (1017%), Clinical Global Impressions (90%) and Personal and Social Performance scales (144% and 329%).

Conclusion Speech latency is a face-valid, objective biomarker of negative symptoms. It can be reliably and validly derived from natural speech during standard clinical assessments. As an enrichment tool, it can reduce sample size needs and enhance outcomes with minimal study burden.

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Keywords

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speech

enrichment

schizophrenia

negative symptoms

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Disclosures Alex S Cohen and Brian Kirkpatrick are officers of Quantic Innovations, Inc, a company developing digital phenotyping technologies for clinical trials.

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