Transdiagnostic Predictors of Early Clinical Trial Dropout Among Youth With Mental Illness: A Pooled Secondary Analysis of Three Adherence-Promotion Trials

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SUBMISSION DETAILS

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Methodological Issue Being Addressed Youth with serious mental illness are at high risk for early dropout from clinical trials, compromising statistical power, threatening internal validity, and obscuring interpretation of treatment effects. Identifying reliable transdiagnostic predictors of dropout is essential for improving trial design, participant engagement, and retention strategies. This secondary analysis examines predictors of early discontinuation across three prospective adherence-promotion trials, addressing a key methodological challenge in youth mental health research: retaining high-risk participants long enough to evaluate intervention efficacy.

Introduction Adolescence and young adulthood are the periods of greatest risk for the onset of many serious mental illnesses, bipolar disorder key among them. Although neurodevelopmental disorders, such as ADHD typically begin in childhood, they often persist into adolescence and early adulthood continuing to impair functioning and complicating clinical trial participation. Across these conditions, adolescents and young adults face substantial challenges that can interfere with sustained trial engagement, including developmental transitions, symptom burden, and structural barriers.

Retention difficulties in youth mental health trials reduce statistical power, limit the ability to detect intervention effects, and can bias conclusions. Prior work has suggested that demographic factors, clinical severity, and treatment complexity may influence dropout, but findings have been inconsistent. This pooled analysis examines transdiagnostic predictors of discontinuation across three adherence-promotion trials. We predicted that younger age, male sex, non-White race, greater number of prescribed medications, worse medication adherence at baseline, and higher disease severity would predict higher dropout. By integrating data across disorders with differing developmental onset patterns, this study aims to clarify which participant characteristics truly place youth at risk for dropping out of clinical research.

Methods A pooled sample (N = 71) of 3 prospective clinical trials testing a common adherence promotion intervention modified for the disease of interest were analyzed to evaluate factors that related to drop out in participants age 13-26. The IGNITE trial (bipolar disorder) included 6-months of follow-up, CAE-ADHD was a 12-week intervention study, and CAE-E (bipolar disorder) measured

primary outcomes at 6 months and followed participants for 12 months. Variables related to clinical trial drop out were assessed for this secondary analysis through 6 months. Dropout was defined as discontinuation of study participation before completing all scheduled study visits and follow-up assessments. Participants were classified as dropouts if they voluntarily withdrew, were lost to follow-up, or otherwise stopped participating prior to study completion. We evaluated clinical (diagnosis, disease severity, number of prescribed medications, medication attitudes, medication adherence [poor adherence was defined as missing more than 20% of prescribed medication doses]) and demographic (sex, age, race/ethnicity) variables in relation to drop out.

Results Mean sample age was 20.21 (2.67), 53 (74.6%) female, 18 (25.4%) non-White with diagnoses of BD (n = 56, 78.9%) and ADHD (n = 15, 21.1%). Interventions tested included customized adherence engagement (CAE) tailored to the specific mental health disorder. Among the dropouts (n = 21, 29.6%), most (n = 17, _81_%) of the drop-outs occurred at the < 12-week time-point. Age, race, biologic sex, and disease severity were not statistically significantly associated with drop out. Variables that were associated with drop out were less education (in years) and fewer prescribed medications, see table 1.

Conclusion Lower educational attainment emerged as the strongest predictor of early dropout across these three youth mental health trials, suggesting that literacy-related factors may play a more influential role in trial engagement than demographic or clinical characteristics. In contrast, variables often assumed to increase dropout risk—including age, sex, race, diagnosis, disease severity, medication adherence, and medication attitudes—were not associated with discontinuation, challenging common assumptions about which youth are most likely to disengage. Because most dropouts occurred early in the study period, these findings underscore the need for front-loaded retention strategies that support comprehension and engagement at the outset of participation. Overall, the results highlight the importance of designing study materials and procedures that are accessible to participants with varying educational backgrounds and incorporating clear, concise, and visually supported communication to enhance trial retention among adolescents and young adults with mental health conditions.

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