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Research paper

Predicting enrollment in two randomized controlled trials of nonpharmacologic interventions for youth with primary mood disorders

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ABSTRACT

Background: As recruitment and retention are often challenging in randomized controlled trials (RCTs), this study sought to identify predictors of participation (i.e., trial enrollment).
Method: These analyses identified predictors of enrollment among 119 youth, ages 7–14, with a primary mood disorder, who screened eligible for the Omega-3 and Therapy pilot studies; 95 (79.8%) actually participated in the treatment.
Results: Youth who received some form of travel assistance (16.0%) almost uniformly enrolled in the treatment portion of the RCT. Youth who lived further away from the study site ($p = .047$) or whose primary caregiver never married ($p = .01$) were less likely to enroll. Of note, socioeconomic status (SES) variables (parent education and child insurance status) did not significantly predict enrollment, suggesting that study incentives or accommodations may have adequately addressed barriers commonly associated with SES.
Limitations: Due to the fairly high trial enrollment rate (approximately 80%), there likely was limited power to detect some differences between groups. Generalizability may be limited to youth with a primary mood disorder diagnosis.
Conclusions: Despite retaining a large proportion of the youth who screened eligible, participant self-selection is a limitation of any RCT. A silent inclusion criterion of any RCT is willingness to be randomized.

1. Introduction

Childhood mood disorders and interventions for them have increasingly been the focus of research (Goldstein et al., 2017). As researchers identify more evidence-based treatments for youth (Fristad and MacPherson, 2014; Weersing et al., 2017), understanding the applicability and generalizability of results of randomized controlled trials (RCTs) will be important. RCTs are essential to understand the effects of any intervention and necessary to identify empirically supported treatments (Chambless and Hollon, 1998). Interpreting RCT results requires considering the generalizability of treatment effects across populations. Samples that lack diversity can limit conclusions (Chambless and Hollon, 1998), whereas broad sample inclusion criteria permit identification of potential treatment moderators. For example, initial depression symptom severity and income have moderated treatment effects in previous RCTs for youth with mood disorders (Curry et al., 2006; Weinstein et al., 2015). However, recruitment and retention is a challenge for many RCTs (Gul and Ali, 2010; Rendell and Licht, 2007) and may be disproportionately difficult among some populations (Gul and Ali, 2010).

Because RCTs are the foundation of clinical science and the basis for treatment guidelines, identifying differences between families who express interest in a trial but do not continue with randomized treatment and those who do would have important implications for clinical research and practice. Often, clinical trials include multiple screening phases, which not only serve to determine eligibility, but also provide participants with many opportunities to withdraw their participation before starting randomized treatment. Thus, we need to understand both recruitment and retention factors that may impact randomized treatment.

A recent review of trial recruitment and retention barriers among adults indicates that lack of interest, time, and transportation, low

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socioeconomic status (SES), and trial demands are associated with trial refusal and attrition (Gul and Ali, 2010). Qualitative research has identified time commitment (Barratt et al., 2013), and, among African-American parents, stigma and long intervals between expressing interest and the first appointment as reasons for non-enrollment in research studies (Breland-Noble et al., 2011). In a study surveying attitudes about clinical trial recruitment, patients indicated equal interest in conventional and complementary intervention trials, but their interest in enrolling depended on receiving research findings, free parking, privacy and safety (Sood et al., 2009). These findings suggest that socioeconomic barriers as well as certain qualities of RCTs and their recruitment strategies may decrease patients' likelihood to enroll.

Most trial enrollment research has focused on adults, with only limited investigations into engaging youth with mental illness. In one trial of a family group intervention for aggressive middle school students, higher child levels of aggression and stronger parent-child bond were associated with fewer parent sessions attended (Quinn et al., 2010). In a youth diabetes research study, those who had poorer diabetes management prior to participation were less likely to complete the protocol (Riekert and Drotar, 1999), suggesting that youth with greater impairment in the behavior of interest may be less likely to enroll in research studies. Additionally, family dynamics likely play a large role in trial enrollment for youth compared to adults. To the authors' knowledge, no prior studies have investigated trial enrollment among families of youth with mood disorders.

Research on youth mental health service utilization in the community may help to inform trial recruitment and retention research in youth. Community-based services research has identified several predictors of youth mental health service attrition, including minority race/ethnicity, lower SES, older child age, less parent education, and living in a single-parent household (Alexandre et al., 2009; Fernandez and Eyberg, 2009; Gonzalez et al., 2011; Harrison et al., 2004; Kazdin et al., 1997; Pelkonen et al., 2000; Taylor et al., 2011). Child clinical characteristics, including externalizing problems (Kazdin and Wassell, 1998; Pelkonen et al., 2000; Taylor et al., 2011) and overall functional impairment (Pellerin et al., 2010), are associated with premature termination of treatment. Parental psychopathology history (Kazdin and Wassell, 1998; Pellerin et al., 2010) and negativity in parent-child relationships (Fernandez and Eyberg, 2009) also increases youths' risk of dropout. Thus, socioeconomic factors, family environment, and child clinical characteristics may be good candidates for investigating predictors of youth clinical trial enrollment.

Given the paucity of research on recruitment/retention of youth in RCTs (and the absence of such research on children and adolescents with mood disorders) and its potential to impact generalizability, this study sought to identify predictors of enrollment of youth with primary mood disorders in randomized treatment in two RCTs of psychoeducational psychotherapy (PEP), a child/family-based cognitive-behavioral intervention, and omega-3 supplementation (the Omega-3 and Therapy Studies [OATS]). Trial enrollment was operationalized in this study as participating in a treatment arm of the trial after passing an initial eligibility screening assessment. These analyses examined demographic (minority race, lower SES, older age, travel distance) and clinical factors (functional impairment, maternal mood history, parent-child relationship) that previous research has identified as being negatively associated with trial enrollment and/or mental health services utilization.

2. Method

2.1. Participants

Data for the current study came from two OATS pilot trials of PEP and omega-3 supplementation, one for youth with depressive spectrum disorders, the other for youth with bipolar disorder not otherwise specified (BP-NOS) or cyclothymic disorder. Both studies were conducted at an academic medical center in a city in the Midwest. Methodology in the two OATS trials was identical (Fristad et al., 20162015). This sample included all youth identified as eligible for the treatment phase of the trials whether they eventually enrolled or not. Participants were primarily recruited from clinician referrals (46.2%) and community advertisements (e.g., newspaper ads, fliers) (35.3%), with 18.5% recruited from some other source (e.g., school, word of mouth). Families were compensated $55 for the screening visit and up to a total of $235 for completing all study visits. Inclusion criteria at the screening assessment were: 1) diagnosis of a mood disorder (bipolar disorder NOS [BP-NOS], cyclothymic disorder, major depressive disorder, dysthymic disorder, or depressive disorder NOS); 2) age 7–14 years; 3) full-scale IQ ≥ 70. Exclusion criteria were: 1) a major medical disorder; 2) autism; 3) schizophrenia or other psychotic states warranting anti-psychotic medication; 4) active suicidal concern (passive suicidal ideation without plans/intent was permitted); 5) three or more "marked" or "severe" mood symptoms on the Kiddie Schedule for Affective Disorders and Schizophrenia (K-SADS); 6) mental health intervention (pharmacotherapy and/or psychotherapy, excluding stimulants or sleep aids) in the month preceding the baseline assessment; 7) enrollment in the 9th grade or higher. Of 178 youth screened, 119 were eligible (66.8%). Of these, 95 (79.8%; 23 with BP-NOS or cyclothymic disorder, 72 with a depressive disorder) were randomized; 24 (20.2%) were eligible but did not enroll in the treatment phase of the study.

2.2. Procedures

2.2.1. Eligibility screening

Families who expressed interest after hearing a brief description of study methodology, including randomization (with a one in four chance of receiving no active treatment, only ongoing monitoring and referrals, as needed, at the end of the study), and who met preliminary criteria after a phone pre-screening were invited for a four to six hour in-person assessment. Parents provided written informed consent, and children gave written assent to participate prior to the screening assessment, as approved by the Institutional Review Board. This visit included a detailed explanation of the clinical trial procedures followed by a diagnostic clinical interview to determine eligibility. We included many components previous studies have suggested to improve retention, such as providing parking or cab vouchers (Gul and Ali, 2010; Sood et al., 2009), detailed feedback sessions following the screening/eligibility assessment (Sood et al., 2009), and baseline assessments available within one to two weeks following an eligible screening assessment (Breland-Noble et al., 2011). Parents and youth were financially compensated for participating, and childcare for siblings was available as needed. Interviewers reminded participants and their parents that eligible youth would be equally likely to be randomized into any of four treatment cells (including the possibility of receiving no active treatments, only ongoing assessment and referral at end-of-study). Participants were notified of their eligibility by phone or mail within approximately one week of their screening assessment. If eligible participants who were successfully contacted via phone elected to discontinue their participation, staff documented reasons for termination on a phone log.

2.2.2. Clinical trial

Participants who were eligible and agreed to enroll in the study's treatment phase were invited to participate in a baseline assessment, then were block-randomized into a 12-week clinical trial of omega-3 monotherapy, individual-family psychoeducational psychotherapy (IF-PEP) (Fristad et al., 2011) monotherapy, combination therapy, or a placebo condition using a 2 × 2 design (see Fristad et al. (2015) and Fristad et al. (2016) for more details about treatments and study design).