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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).

Methods—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

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ASY generated aims for the current analyses. AMS performed data analysis and interpretation. Testing, data collection, and data coordination were performed by KZH and ASY. LEA and MAF developed the study concept and design. ASY and AMS drafted the paper, and KZH, LEA, and MAF provided critical revisions. All authors approved the final version of the paper for submission.

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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.

Keywords

trial enrollment; randomized controlled trial; children; adolescents; mood disorders

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 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 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.

Method

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., 2016; Fristad et al., 2015). 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.

Procedures

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.

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).

Measures

Only screening assessment data were included in these analyses. Youth and their parent(s) were interviewed separately by graduate students pursuing a doctorate in clinical child psychology or by post-doctoral clinical researchers. The standardized assessment battery included semi-structured diagnostic interviews, rating scales and questionnaires, described below.

Demographics—At screen, parents provided information about the youth's sex, race, age, insurance status, family structure (number of siblings and the primary caregiver's relationship status), and primary caregivers' level of education and age. For the present study, primary caregivers' education was dichotomized (high school diploma or less [20%] vs. post-secondary education or training) as was parent relationship status (never-married, single-parent household [21%] vs. other).

Child clinical characteristics—Youth and parents participated in a semi-structured interview using the *K-SADS Depression Rating Scale (KDRS)* and *Mania Rating Scale (KMRS)* to assess youths' depressive and manic symptoms, respectively (Axelson et al., 2003; Chambers et al., 1985; Kaufman et al., 1997). The K-SADS has high interrater percent agreement (93–100%); test-retest reliability is excellent ($\kappa = 0.86 - 1.00$) for mood disorders. The Children's Interview for Psychiatric Syndromes—Child and Parent Forms (ChIPS/P-ChIPS), a reliable and valid measure also administered at screen, assessed comorbid DSM-IV diagnoses (Fristad et al., 1998b; Teare et al., 1998a, b; Weller et al., 1999a, b). ChIPS sensitivity was 0.70 and specificity was 0.84 when compared to discharge diagnoses (Fristad et al., 1998a); ChIPS/P-ChIPS have a negative predictive value of 0.96 (Weller et al., 2000). These aided in making mood diagnoses and determining study eligibility. The *Children's Global Assessment Scale (CGAS)* is a clinician rating of overall functioning at home, school and socially; scores range from 1 to 100 with higher scores indicating better function (Shaffer et al., 1983). The CGAS has demonstrated excellent inter-rater reliability (intraclass correlation [ICC] = .84) and good test-retest reliability (ICC = .69 – .95). CGAS scores were provided by the interviewer based on information from the semi-structured interview and were used as a measure of functional impairment in the current analyses.

Parent psychiatric history—Parents completed the *Family History Screen (FHS)* (Weissman et al., 2000), a semi-structured interview that collects information on symptoms

of 15 psychiatric disorders and suicidal behavior in the child's first- and second-degree relatives. The FHS has shown good agreement with best-estimate diagnoses made by independent clinicians, with a 15 month test-retest median kappa of 0.56 (Weissman et al., 2000). Only the primary caregiver's mood diagnoses (depression or bipolar disorders) were included in the current analyses.

Parent-child relationship—Expressed Emotion Adjective Checklist (EEAC) is a measure of expressed emotion (i.e., criticism, lack of warmth) as reported by an individual's relatives (Friedmann and Goldstein, 1993), and was completed by youths' parents. Parents rated on a scale of 1 (never) to 8 (always) the degree to which each of 20 adjectives described their behavior toward their child as well as the child's behavior toward the parent over the past three months. It has demonstrated validity (EEAC completed by mothers significantly predicted CGAS scores 12 months later) and reliability (internal consistency: alphas = 0.75) as a measure of expressed emotion in families of youth with mood disorders (Klaus et al., 2015). The EEAC includes both negative and positive items; however, only the negative scale is included in these analyses.

Data Analytic Plan

Twelve child demographic and clinical characteristics as well as family-level clinical/functional characteristics identified a priori were explored as potential predictors of enrollment. These independent variables included child age, child sex, functional impairment (CGAS), single parenting, number of siblings, parent education, Medicaid status, miles to the research facility, receipt of travel assistance, maternal history of mood disorder, and parent and child negative communication (the latter being two separate variables). All independent variables as well as the dependent variable of enrollment status were coded as dichotomous variables, with the exclusion of child age, functional impairment, number of siblings, miles to the research facility, and parent and child negative communication. Preliminary analyses examined the descriptive statistics and distribution of data by enrollment. Continuous variables were centered prior to conducting primary analyses.

Analyses focused on answering the following questions: 1) how much do these independent variables impact enrollment; 2) which of these predictor(s) are the most important when accounting for all proposed predictors; and 3) do these predictors interact to help explain study enrollment. Separate Mann-Whitney tests analyzed bivariate relationships between each potential predictor and trial enrollment; the success rate difference (SRD) provided an estimate of effect size (Kraemer, 2004; Kraemer et al., 1999; Kraemer and Kupfer, 2006). Next, a step-wise forward logistic regression with all independent variables entered simultaneously identified which of these predictor(s) explain the most variance in the model. This approach was supplemented by a Receiver Operating Characteristics (ROC) analysis using signal detection theory to obtain a hierarchy of predictors, which identifies interactive effects (Kraemer, 1992). ROC first identifies the most potent predictor, one that maximizes sensitivity and specificity using weighted kappa, and an optimal cut-point for that predictor. The total sample is then split into two arms based on that cut-point. The process is repeated

on these subsamples with the next most potent predictor until no additional variables significantly predict the outcome (see Owens et al. [2003] for an example).

Results

Screened youth had a mean age of 11.10 ± 2.30 , and primarily identified as Caucasian (66%). The full sample included 70 (58%) boys. There was no difference in enrollment by mood disorder diagnosis; that is, rates of enrollment were similar between youth with a depressive (79% enrolled) or a bipolar spectrum disorder (82% enrolled). Similarly, comorbid diagnoses of anxiety, ADHD, or DSM-IV Disruptive Behavior Disorder (DBD) were not associated with enrollment. Table 1 presents bivariate associations between target variables and enrollment (randomized vs. not). Travel assistance was largely skewed, such that, of those who received assistance, all but one family enrolled. It was, therefore, excluded from logistic regression and ROC analyses. Four families did not have family history data (maternal history of a mood disorder). Results did not change when maternal history of a mood disorder was excluded from analyses, so results present analyses with all proposed variables included. In bivariate analyses, only family structure was significantly associated with study enrollment; families whose primary caregivers were married, divorced or cohabitating (85.3% enrolled) were significantly more likely to enroll than never-married, single-parenting families (58.3% enrolled), $p < .01$.

Next, analyses identified the most important predictors from the proposed set of variables. A step-wise forward regression identified two predictors, single parenting, Wald $\chi^2(2, 115) = 6.50$, $b = -1.34$ odds ratio (OR) = 0.26 (95% Confidence Interval [CI] = 0.09–0.73), $p = .01$, and distance to study Wald $\chi^2(2, 115) = 3.94$, $b = -0.03$, OR = 0.97 (95% CI = 0.95–1.00), $p = .047$, as negatively predicting study enrollment. The model chi-square indicates that inclusion of single parenting and distance to study explains more model variance than the intercept only model, $\chi^2(2, 115) = 8.37$, $p < .05$. Nagelkerke's R^2 reveals that the model explains 10.9% of the variance in enrollment status.

The ROC analysis identified single parenting as the primary determinant of enrollment of the proposed variables, $\chi^2(1, 119) = 8.63$, $p < .05$, $k = .27$; demonstrating better sensitivity (0.85) than specificity (0.42). No interactive effects were identified.

Qualitative Information

Some minimal qualitative information was available from the phone logs of staff conversations with parents whose children were eligible, but who chose not to enter the treatment phase. Parents of three youth who did not enroll in the trial decided the youth should continue or initiate community-based services rather than be randomized into a treatment group. One child, who identified as vegetarian, was unwilling to take the study capsule because it contained fish oil; another experienced a family crisis shortly after the screening assessment. Surprisingly, only one family reported choosing not to enroll in the trial due to time/scheduling conflicts. Eighteen families either did not offer an explicit reason or were unreachable after the screening assessment.

Discussion

This study aimed to identify predictors of enrollment in a clinical trial for children and adolescents with mood disorders. To the knowledge of the authors, this is the first investigation of predictors of trial enrollment among this population. Previous research indicates that lack of interest, time, transportation, low SES, trial demands, clinical impairment, and parent-child relationships are associated with trial enrollment/engagement (Gul and Ali, 2010; Quinn et al., 2010; Riekert and Drotar, 1999). Thus, we explored whether socioeconomic, family, and clinical factors were associated with trial enrollment among youth with mood disorders. Results indicate significant group differences in sociodemographic characteristics, as anticipated and mostly consistent with previous findings in trial enrollment investigations (Gul and Ali, 2010). The most potent predictor of enrollment was primary caregivers' marital status, followed by distance between families' homes and the study site. Those who received travel assistance ($n = 19$; 16.0%) almost uniformly enrolled.

One potential explanation for the effect of parents' marital status on trial enrollment is that unmarried parents may have less social support and may feel more burdened by the time commitment of a 12-week trial. Though the study offered many resources to ease family burden, including childcare for other children, assistance with transportation, snacks, and monetary compensation, there was substantial time commitment that may have remained a burden to some families despite the resources provided. Surprisingly, Medicaid status was not significantly associated with study enrollment. Study incentives, the aforementioned accommodations, and access to study assessments, written diagnostic reports and the supportive environment offered by OATS staff may have facilitated study participation across SES. However, despite these accommodations, distance between study site and families' homes remained a significant barrier. While families were offered travel assistance (including gas reimbursement), longer travel times (and perhaps longer periods away from work, school, and other responsibilities) likely presented additional burden. Notably, distance was only significantly associated with enrollment after accounting for parents' marital status, indicating possible suppressor effects. This suggests that the part of distance that is independent of marital status, is significantly associated with enrollment; further research is needed to determine what factors (possibly access to public transportation or living in a rural area) account for this suppressor effect.

Limitations

These findings should be interpreted in light of several limitations. Due to small cell sizes and the fairly high trial enrollment rate (approximately 80%), there likely was limited power to detect some differences between groups. For instance, after identifying the single most potent predictor, ROC analyses identify predictors among subgroups of the sample, thus requiring a large initial sample size. In these analyses, subgroup n s were small, limiting power to detect a secondary predictor/moderator in the ROC analysis. Further, information on families' belief in the utility of nonpharmacologic interventions was not available and thus could not be investigated as a predictor of enrolling in the treatment portion of these RCTs. This study only included youth, ages 7–14, who had a primary mood disorder

diagnosis; thus, these findings may not generalize to youth of other ages or other primary diagnoses or other treatments. Additionally, subjective information about why families did not enroll in the treatment portion of the RCT was very limited. Finally, these analyses were exploratory, and thus identify hypotheses that should be considered and investigated in future studies.

Implications and Conclusions

These conclusions have several implications for RCTs and/or for translating findings from RCTs to community practice. Only family-level characteristics were significant predictors of trial enrollment. As such, trial recruitment/retention methodology should take into account potential barriers that families may face to participating in clinical trials. As Medicaid status was not associated with trial enrollment (contrary to the negative association between income and service use in the community), barriers associated with low income appear to have been adequately addressed by the assistance offered in these clinical trials. Likely due to monetary incentives and other strategies to improve participant access to the trial (e.g., transportation assistance, childcare), nearly 80% of screen-eligible families were retained in the randomized sample. Future RCTs may benefit from using such strategies to improve trial access for families.

Despite the high retention rate between screening and randomization, this study identified differences between families who elected to enroll in the treatment phase and those who did not. Sample biases limit the generalizability of clinical trial findings. As RCTs are often used to inform clinical practice in the community, it is essential that results of RCTs have solid external validity. More work is needed to better understand and identify predictors of trial enrollment. Whenever possible, clinical trials researchers should carefully assess whether and how eligible but non-randomized eligible participants differ from those randomized to ensure that the range of any variables key to the trial is not limited due to participant self-selection.

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Highlights

- Overall, high rate of enrollment of families of youth with mood disorders in a randomized controlled trial of psychotherapy and omega-3 supplementation.
- Family-level factors (including distance from study site and parents' marital status) appear to significantly impact enrollment.
- As RCTs are often used to inform clinical practice in the community, it is essential that results of RCTs have solid external validity.
- More work is needed to better understand and identify predictors of trial enrollment.

Table 1

Participant Characteristics by Enrollment Status: Bivariate Associations

Characteristic	Enrolled (<i>n</i> = 95) <i>n</i> (%)	Not enrolled (<i>n</i> = 24) <i>n</i> (%)	<i>U</i>	SRD
Child sex (male)	54 (57%)	16 (67%)	1028.0	−0.07
Parent marital status (single-parent)	14 (15%)	10 (42%)	833.0*	−0.27
Parent education (high school/GED)	15 (16%)	8 (33%)	940.0 ~~≠~~	−0.18
Travel assistance (yes)	18 (19%)	1 (4%)	971.5 ~~≠~~	0.18
Medicaid insurance	32 (34%)	7 (29%)	1088.5	0.03
Maternal mood history	55 (60%)	15 (63%)	1069.0	−0.01
Comorbid Anxiety	73 (77%)	16 (67%)	1024.0	−0.09
Comorbid ADHD	58 (61%)	17 (71%)	1028.5	0.07
Comorbid DBD	37 (39%)	7 (29%)	1028.5	−0.07
	Enrolled M ± SD	Not enrolled M ± SD	<i>U</i>	SRD
Child negativity	43.2 ± 13.4	48.6 ± 12.5	867.5 ~~≠~~	−0.24
Child age	11.3 ± 2.2	10.3 ± 2.6	890.5 ~~≠~~	0.22
Miles to study site	16.7 ± 15.5	21.6 ± 18.2	920.5	−0.20
Parent negativity	26.7 ± 12.0	29.4 ± 12.3	933.5	−0.18
Number of siblings	2.4 ± 1.1	2.4 ± 1.3	1094.0	−0.04
Functional impairment	50.2 ± 6.5	50.0 ± 4.9	1135.5	0

Note. Four families did not have family history data. ADHD = Attention Deficit/Hyperactivity Disorder; DBD = Disruptive Behavior Disorder; Child negativity = child negativity towards parent on the Expressed Emotion Adjective Checklist; Parent negativity = parent negativity toward child on the Expressed Emotion Adjective Checklist; SRD = Success Rate Difference. *U* = Mann-Whitney *U* test.

* $p < .01$,

~~≠~~ $p < .10$