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Pilot RCT of Omega-3 and Individual-Family Psychoeducational Psychotherapy for Children and Adolescents with Depression

Mary A. Fristad, Ph.D., Anthony T. Vesco, Ph.D., Andrea S. Young, Ph.D., K. Zachary Healy, B.A., Elias S. Nader, B.S., William Gardner, Ph.D., Adina M. Seidenfeld, Ph.D., Hannah L. Wolfson, B.A., and L. Eugene Arnold, M.D.

All authors were affiliated with the The Ohio State University Wexner Medical Center Department of Psychiatry and Behavioral Health at the time of this work. Dr. Fristad has additional appointments with the Departments of Psychology and Nutrition at The Ohio State University. Dr. Vesco is now with Lurie Children's Hospital in Chicago, IL. Dr. Young is now with Johns Hopkins University in Baltimore, MD. Mr. Nader is now at the Center for Terrorism and Security Studies, University of Massachusetts Lowell, Lowell, Massachusetts. Dr. Gardner is now at the Research Institute, Children's Hospital of Eastern Ontario, Ontario Canada. Dr. Seidenfeld is now with the University of Delaware in Newark, DE

Abstract

Objective—To evaluate feasibility and estimate effect sizes of omega-3 fatty acids ($\Omega 3$), individual-family psychoeducational psychotherapy (PEP), their combination, and moderating effects of maternal depression and psychosocial stressors in youth with depression.

Method—In a pilot 2X2 randomized controlled trial, 72 youth (ages 7-14; 57% Caucasian, 57% male) with major depression, dysthymia, or depression not otherwise specified were randomized to 12 weeks of $\Omega 3$, PEP+placebo, $\Omega 3$ +PEP, or placebo. $\Omega 3$ vs. placebo was double-masked. Evaluators masked to condition assessed depressive severity at baseline (randomization), and 2, 4, 6, 9, and 12 weeks using the Children's Depression Rating Scale-Revised.

Results—Side effects were either absent or mild. PEP was administered with 74% fidelity. Remission was: 77%, $\Omega 3$ +PEP; 61%, PEP+placebo; 44%, $\Omega 3$; 56%, placebo. Intent-to-treat analyses found small-to medium effects of combined treatment ($d = .29$) and $\Omega 3$ monotherapy ($d = .42$), but negligible effect for PEP+placebo ($d < .10$), all compared to placebo alone. Relative to placebo, youth with fewer social stressors responded better to $\Omega 3$ ($p = .04$), PEP ($p = .028$), and their combination ($p = .035$), and those with maternal depression responded better to PEP ($p = .020$) than did those without maternal depression.

Conclusion—Remission rates were favorable compared to other studies of psychotherapy and comparable to an existing RCT of $\Omega 3$; results warrant further evaluation in a larger sample. $\Omega 3$ was well-tolerated. Active treatments show significantly more placebo-controlled depression improvement in the context of maternal depression and fewer stressors, suggesting they may benefit depression with a more endogenous than environmental origin.

Corresponding author: Mary A. Fristad, Department of Psychiatry and Behavioral Health, The Ohio State University Wexner Medical Center, 1670 Upham Drive Suite 460G, Columbus, OH 43210-1250.

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child & adolescent depression; omega-3; psychoeducational psychotherapy; maternal depression; psychosocial stress

Depression in youth is a significant public health concern. The prevalence of MDD in children 12 and under is about 2% and rises to 4-8% in adolescents. Approximately 0.6 to 1.7% of children experience dysthymic disorder with rates rising to 1.6-8% in adolescents. An additional 5 to 10% of youth experience subsyndromal symptoms with accompanying impairment (Angold & Costello, 2001; Bertha & Balázs, 2013; Birmaher et al., 1996; Fergusson, Horwood, Ridder, & Beautrais, 2005). Depression in youth is linked to significant functional impairment, including risk for disruptive behavior and substance use disorders (Birmaher et al., 1996). Recurrence rates are high: about 40% recur within 2 years and 70% within 5 years (Birmaher, Arbelaez, & Brent, 2002a; Kovacs et al., 1984).

The most common treatments for depression are medication and psychotherapy; but each has limited efficacy. Selective-serotonin-reuptake inhibitors (SSRIs) have a 2-fold increase (4% vs. 2%) in risk for suicidal behavior or ideation compared to placebo; this has led to an FDA black box warning (Food and Drug Administration, 2004). Bridge and colleagues (2007) found a smaller effect (<1%), but noted that increased treatment-emergent suicidality is still a concern. A recent reanalysis of the original paroxetine study led to warnings about safety (Le Noury et al., 2015). Only fluoxetine has been shown to be significantly better than placebo in children, and no medication-psychotherapy combination trials have included pre-teen children. Given concerns about treatment-induced suicidal ideation and behavior and questionable effectiveness of antidepressants in children, parents may seek other treatment options, such as psychotherapy or nutritional interventions.

Consumers are increasingly interested in complementary and alternative treatments (Barnes, Bloom, & Nahin, 2007). One promising intervention is omega-3 fatty acids (Ω3). Using international data, epidemiological studies have found significant negative correlations between national rates of mood disorders and fish consumption ($r = -.84$, $p < .005$ [Hibbeln, 1998] & $r = -.74$, $p < .0001$ [Noaghiul & Hibbeln, 2003]). Owen et al. (2008) posited four pathways through which Ω3 depletion may be linked to depression. First, ratios of docosahexaenoic acid (DHA; a type of Ω3) to other fatty acids affect membrane fluidity and enzyme functioning, ion channels, and receptor binding. Second, Ω3 concentrations modulate neuroplasticity and cell survival. Third, Ω3 concentrations affect gene expression. Fourth, Ω3 availability suppresses production of proinflammatory eicosanoids, which are elevated in depressed patients and inhibited by some antidepressants (Owen et al., 2008). High resolution structural MRIs show people with higher intake levels of Ω3 have greater gray matter volume in the anterior cingulate cortex, the right hippocampus, and the right amygdala. These brain areas are involved in emotional arousal and emotion regulation and are smaller in people with mood disorders (Conklin et al., 2007).

Further, Ω3 has demonstrated an antidepressant effect in several studies of adults with mood disorders (Appleton, Rogers, & Ness, 2010; Lin & Su, 2007; Martins, 2009). In one RCT of Ω3 in 28 children aged 8 to 12 with MDD (Nemets, Nemets, Apter, Bracha, & Belmaker,

2006), 70% of the children who received $\Omega 3$ (380-400 mg EPA; 180-200 mg DHA, a 2:1 ratio) demonstrated greater than 50% reduction in depressive symptoms compared to no children who received placebo. Four out of 10 children on $\Omega 3$ achieved remission status compared to none on placebo. No participant reported adverse side effects, although mild gastrointestinal complaints have been reported in studies of youth with bipolar spectrum disorders (Clayton et al., 2009; Gracious et al., 2010; Wozniak et al., 2007). Thus, $\Omega 3$ shows promise in decreasing symptoms of childhood depression and may have fewer/milder side effects compared to medication. Further investigation of $\Omega 3$ for child depression appears warranted.

Regarding psychotherapy, two research groups have published open trials suggesting positive results in youth younger than age 15 (Kovacs et al., 2006; Tompson et al., 2007). In one study, 20 children aged 7-12 with dysthymic disorder received Contextual Emotion Regulation Therapy. About half of completers ($n = 15$) remitted fully at the end of the 10-month therapy. At 6- and 12-month follow-up, 79% and 92% of completers, respectively, achieved full remission (Kovacs et al., 2006). The second pilot study examined the impact of family-focused intervention on symptoms of MDD, dysthymic disorder, or depressive disorder not otherwise specified (NOS); nine youth ages 9-14 attended 12-16 sessions. At post-treatment, 66% demonstrated remitted depression increasing to 77% at 9-month follow-up. Preliminary data also suggested that changes in family functioning (i.e., reduced expressed emotion and increased cohesion) was a mechanism of change (Tompson et al., 2007). Although these small pilot studies show promise for prolonged symptom reduction, neither included a comparison group. In a recent pilot RCT of family-based interpersonal psychotherapy (IPT) for 7 – 12 year olds with depression, IPT showed significantly higher rates of remission from depression, greater decrease in severity, and lower post-treatment depressive severity relative to a supportive, nondirective treatment (Dietz, Weinberg, Brent, & Mufson, 2015).

Psychoeducational Psychotherapy (PEP) is a family-based cognitive-behavioral therapy (CBT) for mood disorders in youth that alternates parent and child sessions, with parents participating at the beginning and end of every child session. A multi-family group version (MF-PEP) improved mood in an RCT of 165 children (ages 8-12) with depressive or bipolar spectrum disorders (Fristad, Verducci, Walters, & Young, 2009). An individual-family version (IF-PEP) also demonstrated improved mood in a pilot RCT of 20 children with bipolar spectrum disorder (Fristad, 2006). Although PEP was originally developed for children aged 8-12, it has been implemented clinically with elementary and middle-school aged children, and, with minor adaptations, in adolescents; thus, it was selected for use in this study.

Biological and psychosocial treatments of depression are thought to target different mechanisms of change: inflammatory markers are associated with $\Omega 3$, whereas negative automatic thoughts, coping strategies, knowledge of mood disorders and family climate are associated with PEP. Thus, combined treatment may yield greater benefits than monotherapy. Although studies of combined pharmacologic and psychotherapeutic interventions have not been conducted in children with depression, randomized clinical trials for adolescent depression have demonstrated the superiority of combined anti-depressant

medication plus CBT over monotherapy on depression outcomes (Brent et al., 2008; Goodyer et al., 2007; March et al., 2004; TADS Team, 2007). In one of these trials, the Treatment for Adolescents with Depression Study (TADS), suicidal events were significantly more common with fluoxetine monotherapy than with CBT; combining CBT and fluoxetine ameliorated this safety concern (TADS Team, 2007).

Although a treatment may demonstrate small or insignificant treatment effects in an overall sample, clinically meaningful effects can be obscured for subsamples of a population, emphasizing the need for moderator analyses early in a treatment's evaluation process. Given the heterogeneous nature of depression, examination of treatment moderators and subgroups is important, because it is plausible that any particular treatment will not be effective for all youth with depression. Variable results found for the impact of $\Omega 3$ on depression may be due to differences in sample selection and unidentified factors that differentiate responders from non-responders. Little is known about for whom psychotherapy and/or $\Omega 3$ may work best, therefore moderator analyses may shed light on appropriate applications of these treatments (Appleton, Sallis, Perry, Ness, & Churchill, 2015).

Maternal depression and family stress have been associated repeatedly with youth depression, and are good candidates as moderators of treatment. Maternal depression may transmit to youth through biological and/or environmental factors (Birmaher, Arbelaez, & Brent, 2002b; Hammen, Burge, Burney, & Adrian, 1990; Tompson et al., 2010; Weissman, Warner, Wickramaratne, Moreau, & Olfson, 1997). The literature presents mixed findings on the role of maternal depression as a predictor of response to psychotherapy for adolescent depression (Brent et al., 1998; cf. Curry et al., 2006).

Family stress, such as stressful life events, trauma, and poor quality of parent-child relationships, also robustly predict youth depression (Birmaher et al., 1996; Suliman et al., 2009), particularly for those already at risk (Hammen, Brennan, & Shih, 2004; Jenness, Hankin, Abela, Young, & Smolen, 2011). However, limited research examines the impact of these factors on treatment outcomes. In a study of SSRI-resistant depression in adolescents, low family conflict was associated with greater treatment response across adolescents receiving combined treatment (CBT with medication change) or medication change alone (Asarnow et al., 2009). Similarly, psychosocial treatments of late-life major depression show faster, sustained treatment response when stress is low at baseline (Dew et al., 1997; Karp et al., 1993). Hence, an examination of maternal depression and family psychosocial stressors as moderators of treatment is warranted given the extant literature relating these factors to youth depression, and the lack of understanding of how these factors may impact treatment response in depressed youth.

The primary aim of the current study was to investigate feasibility and effect sizes for a family-based CBT protocol, Individual-Family Psychoeducational Psychotherapy (PEP), $\Omega 3$, and their combination (PEP+ $\Omega 3$) on depressive severity in 60 children with depression, a vulnerable yet understudied population. In addition, a secondary aim was to identify patient subgroups that were most likely to benefit from each intervention. Due to their robust associations with childhood depression in the extant literature (Birmaher et al., 2002a;

Hammen et al., 1990; Tompson et al., 2010; Weissman et al., 1997) and the family focus of PEP, family level factors measured by maternal depression and family psychosocial stressors were examined as moderators of treatment response.

Method

Participants

Participants were recruited between July 2011 and May 2014, primarily from community advertisements and clinician referrals within a large Midwestern city. Parents provided informed consent and youth provided assent per local Institutional Review Board (IRB) procedures.

Inclusion/Exclusion Criteria

Inclusion criteria were: 1) age 7-14 years (elementary/middle school); 2) diagnosis of DSM-IV-TR MDD, dysthymic disorder, or depressive disorder NOS; 3) clinically significant symptom severity (on the CDRS-R, ≥ 40); and 4) youth and at least one caregiver completed the screening assessment and were willing and able to participate in follow-up procedures. Age range was targeted at 7-14-year-olds to address the dearth of research on younger children with depression, and to adequately match the content of PEP to appropriate developmental stages (i.e., elementary and middle school-aged youth).

Exclusion criteria were: 1) inability to swallow capsules the size of the study supplement; 2) a major medical disorder; 3) DSM-IV-TR autistic disorder; 4) psychosis warranting anti-psychotic medication; 5) active suicidal concern (i.e., suicidal plans or recent attempt; passive suicidal ideation without plans/intent was permitted); 6) mental health intervention (psychotherapy or pharmacotherapy other than stable medication for attention deficit/hyperactivity disorder [ADHD] or a sleep aid) or ≥ 3 in the month preceding randomization; 7) intellectual disability (IQ < 70 and impaired adaptive functioning); and 8) lack of access to a phone.

Of 178 youth screened, 72 (37 [51%] with MDD; 5 [7%] with dysthymic disorder; 30 [42%] with depressive disorder NOS) were randomized in the current study, exceeding the targeted recruiting goal (N=60) by 20% (Figure 1). An additional 23 were randomized into a parallel study of youth with cyclothymic disorder or bipolar disorder NOS ([ClinicalTrials.gov](https://clinicaltrials.gov/ct2/show/study/NCT01341925) identifier: NCT01341925) reported elsewhere (Fristad et al., 2015).

Procedures

At the screening assessment, youth and parents participated in semi-structured diagnostic interviews. Youths also completed an intelligence screening test to establish diagnostic eligibility (see below for measures). Training in pill swallowing was offered as needed; six youth were deemed ineligible as they were unable to swallow pills following this training (see Figure 1). Physical examinations were conducted by a licensed physician or nurse practitioner to rule out major medical disorders.

Baseline assessments were scheduled at least one week later at a time convenient for eligible families, averaging 3.5 ± 1.8 weeks after the screening assessment (range = 0.9 – 8.0; see

Young, et al., in press for further details). Following the baseline assessment, eligible youth were randomized into one of four treatment arms: PEP+Ω3, n = 17; Ω3 monotherapy, n = 18; PEP+placebo (PBO), n = 19; or PBO alone, n = 18. This selected 2x2 design optimized treatment comparisons given the limited sample size in this pilot study: it permitted examination of the effects of combined therapy, and contrasts of PEP and Ω3. Families, regardless of randomized condition, participated in five follow-up assessments across 12 weeks of intervention at 2, 4, 6, 9, and 12 weeks following the baseline. Participants randomized into one of the two PEP conditions participated in two therapy sessions (one parent, one child) per week. Families received financial compensation for completing assessments. All treatments were provided free of charge; parking passes were provided and assistance with transportation was given to those in need.

Study Assessments

Trained graduate students or post-doctoral researchers interviewed youth and caregivers separately. Interviewer training included didactics, mock interviews, and observation and rating of videotaped and live interviews. Reliability was determined by calculating kappa statistics between raters for diagnosis on three independent interviews; intra-class correlation coefficients (ICC) assessed inter-rater reliability on continuous measures of depressive severity. Following each assessment, a consensus conference was completed to review symptoms and diagnoses with one of the co-principal investigators (a licensed and board-certified clinical child and adolescent psychologist or psychiatrist).

Individual-Family Psychoeducational Psychotherapy (PEP)

PEP is a family-based therapy incorporating psychoeducation and CBT techniques into weekly parent and youth individual sessions, each lasting 45-50 minutes. Parents join the beginning and end of each child session to review the prior week and take-home project and to learn the coming week's project. Content of sessions for children include: symptom identification, awareness of strengths, emotion recognition and regulation, understanding treatment components (medication, identifying school-based resources), development of coping strategies (including deep breathing and imagery), cognitive restructuring, problem-solving skills, and verbal and non-verbal communication. Parent sessions cover parallel content to the child sessions (at an adult level), and also include coverage of school advocacy, symptom management, and self-care. If relevant, a session with siblings and school professionals is provided. Parents are told explicitly that although they do not *cause* their child's depression, there are changes they can make that will affect its *course* (See Fristad, Goldberg Arnold, & Leffler, 2011 for additional details on session content.). Post-doctoral therapists conducted sessions in accord with the PEP manual (Fristad et al., 2011).

Ω3

Ω3 supplements or placebo were provided to families in a pill box at each assessment following randomization. Both Ω3 and PBO capsules were provided by Omega Brite Corporation (www.omegabrite.com; Las Vegas, NV). Groups receiving Ω3 took two capsules of 500mg Ω3 each (350mg EPA: 50mg DHA, a 7:1 ratio; 68mg other Ω3) twice daily for a total daily dose of 1870mg Ω3. PBO groups received two placebo capsules twice daily matched to the Ω3 for odor and appearance. All participants were given a daily

multivitamin/mineral tablet to standardize micronutrition; no other nutritional supplements were permitted the month prior to randomization or during study enrollment.

Adherence was monitored by pill counts from returned pill boxes at each assessment. Parents were made aware of potential side effects of $\Omega 3$ (e.g., fishy burps, upset stomach), and were asked to report any side effects at each assessment via a Side Effects Review form.

Randomization

Block randomization was not contingent on any demographic or clinical variables. To facilitate near equal numbers of participants per randomized group, participants were randomized in sequential blocks of 16, 12, 12, 8, 4, 4, 4, and 12. Lab personnel not directly involved in the study generated the random allocation sequence and assigned participants a number linked with a treatment condition. These staff provided the appropriate study capsules to the family and notified the family if they were randomized to participate in PEP. Following their final assessment, each family was informed by a sealed letter whether the youth had received $\Omega 3$ or PBO capsules.

Study Masking

Participants, interviewers, therapists, coordinators, and other study staff who had contact with families were masked to $\Omega 3$ /PBO assignment. Interviewers completing study assessments were additionally masked to which participants were assigned to PEP.

Measures

Demographics Form—At screen, caregivers provided information about the youth's sex, age, family structure, socioeconomic status, caregivers' ages, and relationship to the youth. This information was used to characterize the sample.

Youth Diagnoses—A clinical interview inquiring about family history of psychiatric illness, history of psychiatric service use, mother's pregnancy and delivery of the participant, youth's early development, medical health, and functioning at home, at school, and with peers was completed. The K-SADS Depression Rating Scale (KDRS) and Mania Rating Scale (KMRS) (Ambrosini, Metz, Prabucki, & Lee, 1989; Chambers et al., 1985; Geller et al., 2001) assisted in diagnosing a *DSM-IV-TR* mood disorder. Interviewer inter-rater reliability (IRR) was excellent for the KDRS ($ICC = 0.89$) and KMRS ($ICC = 0.82$).

Comorbid psychiatric disorders were assessed when participants were screened using the Children's Interview for Psychiatric Syndromes Child and Parent Versions (ChIPS/P-ChIPS) (Weller, Weller, Rooney, & Fristad, 1999a, 1999b). These are structured psychiatric interviews designed to assess psychopathology according to *DSM-IV-TR* criteria among youth aged 6-18 years (Fristad, Cummins, et al., 1998; Fristad, Glickman, et al., 1998; Swenson et al., 2007). ChIPS/P-ChIPS assess 20 syndromes as well as psychosocial environmental stressors. IRR for diagnoses obtained from ChIPS/P-ChIPS was excellent ($\kappa = 0.86$). All diagnoses were finalized during a clinical consensus conference as described above.

Youth Depressive Symptom Severity—The Children's Depression Rating Scale-Revised (CDRS-R) measures depression in youth ages 6-17 years. It has 17 items, rated on a Likert scale indication of increasing severity. Scores range from 17 to 113 with a score of 40 indicating a clinical elevation and, consistent with previous research (e.g., Kennard, Silva, et al., 2009), scores ≥ 28 indicating remission status. Inter-rater reliability is excellent ($r = 0.86$), as is test-retest reliability over a 4-week interval ($r = 0.81$) (Poznanski et al., 1984). Study IRR for the CDRS-R was excellent ($ICC = 0.87$). The CDRS-R, the primary outcome measure, was completed at each study visit to assess functioning over the past two weeks.

Assessment of Intellectual Disability—The Kaufman Brief Intelligence Test, 2nd Edition (KBIT-2) (Kaufman & Kaufman, 2004) estimates verbal and nonverbal cognitive ability as well as aggregate composite IQ. The Vineland Adaptive Behavior Scales, 2nd Edition (VABS-II) (Sparrow, Cicchetti, & Balla, 2005) parent interview was administered if IQ fell between 65-70. One youth meeting all other study criteria had a measured IQ of 68 but had an adaptive behavior level of 104 and was consequently enrolled in the study. All other enrolled participants had IQ's ≥ 70 .

Maternal Depression—At the screening assessment, parents provided information regarding biological mothers' depressive symptoms via the Family History Screen (FHS). The FHS is a semi-structured interview with sound validity and reliability (Weissman et al., 2000). Maternal history of depression, operationalized categorically (present/absent), was determined if there was evidence of depressed mood or prolonged lack of energy and one or more additional depressive symptoms lasting ≥ 2 weeks currently or in the past.

Psychosocial Stress—Items from the Psychosocial Stressors section of the ChIPS (family illness, financial concerns, domestic conflicts, divorce/marital separation, substance use in the home, police involvement, and bereavement due to murder or bereavement due to accidental death/illness) were summed to result in a possible score from 0-8.

Side Effects Review—At each post-randomization interview, parents completed a Side Effects Review form about changes in the youth's health since the last interview. The 8-item questionnaire asks about side effects most associated with $\Omega 3$, such as intestinal/abdominal changes, appetite change, and increased burping and fishy breath. Side effects the youth may have experienced were rated from 0 (absent) to 6 (severe).

Therapy Fidelity Ratings

All undergraduate raters coding therapy videos participated in a weekly meeting to educate them about IF-PEP treatment components, instruct them on completing fidelity checklists, and provide them opportunity to ask questions about fidelity coding. Prior to completing fidelity coding for the study, raters were required to rate all the sessions of a training case and achieve adequate inter-rater reliability with a graduate student, experienced in IF-PEP, serving as a standard rubric for coding. A one-way, mixed ICC statistic was used to evaluate consistency between the rater and the standard for each treatment session checklist. For this

study, a consistency rating rather than absolute agreement was used. ICC can be interpreted as the degree of similarity in item scores on a given measure between independent raters.

According to Cicchetti (1994), an ICC value greater than 0.40 is considered “fair,” above 0.60 is considered “good,” and a value above 0.75 is considered “excellent.” A student rater was deemed passably reliable when they achieved an average ICC = 0.60 on training videos. The overall mean fidelity ICC rating across undergraduate raters was 0.61 (SD = 0.05; Range: 0.50 – 0.68). For undergraduate raters who had an ICC below 0.60, further instruction was given and ratings relative to the standard were revealed and discussed in an individual meeting. After students passed the training or were given further instruction via an individual meeting, they were assigned a set of cases to code. Ten percent of each undergraduate rater’s coded videos were evaluated by another reliable rater, and an ICC was calculated. This served as a continued reliability check to assess rater drift. The mean ICC for the 10% sample of videos was 0.58 (SD = 0.31; Range: –0.15 – 0.94). Overall, the mean ICC for the 10% drift sample is considered fair.

Statistical Analyses

Descriptive statistics, ANOVA, and χ^2 tests were used to characterize the sample and analyze differences in demographic characteristics by treatment group. Linear mixed effects (LME) modeled depressive severity trajectories as measured by CDRS-R scores using intent-to-treat (ITT) analyses. Model fixed effects were treatment group (dummy-coded with placebo as the reference category), time (weeks) from randomization, and group-by-time interactions. Moderator analyses additionally included the main effect of the moderator and moderator-by-group, moderator-by-time, and moderator-by-group-by-time interactions. Number of stressors was analyzed as a mean-centered, continuous moderator. The interaction was probed at one standard deviation above and below the mean to characterize low and high environmental stress. This was used to obtain simple slopes and intercepts. Participant-level intercepts and slopes were modeled as random effects, accounting for correlations among observations from the same participant. Cohen’s *d* effect sizes were calculated for each of the three treatment groups relative to placebo (Feingold, 2009). Additional analyses collapsed the two groups receiving $\Omega 3$ (PEP+ $\Omega 3$ combined and $\Omega 3$ monotherapy groups) and compared them to the two groups who received placebo (PEP +PBO and PBO groups); then collapsed the two groups receiving PEP (PEP+ $\Omega 3$ and PEP +PBO groups) and compared them to the two groups assigned to no psychotherapy ($\Omega 3$ monotherapy and PBO groups). This pilot study emphasized effect sizes to guide interpretation of results; α was set at 0.05 without correction for multiple tests.

Results

Participants

Although the original goal was to recruit 60 participants, 72 enrolled in the study. Slightly over half of the participants were white and male; as a group they demonstrated average intellectual ability. Two-thirds (67%) were aged 12 or younger ($M_{age} = 11.6 \pm 2.1$ years); 25% were aged 9 or younger. The most common comorbid disorders were anxiety (including specific phobia, generalized anxiety, social anxiety, separation anxiety, and

anxiety NOS), ADHD, and disruptive behavior disorders. Participating parents were mostly middle-aged mothers. Families were mostly lower to middle socioeconomic status (median income \$40,000 – \$60,000) and almost evenly split between married and single caregivers. There were no statistical differences between randomized groups on demographic or clinical characteristics at baseline (Table 1).

Three participants dropped out of the study after randomization but before their first follow-up assessment; two randomized to $\Omega 3$ monotherapy were lost-to follow-up and one randomized to PEP+PBO withdrew due to time burden (see Figure 1). Thus, baseline data are reported for all 72 participants but outcome analyses are based on 69 youth, as LME modeling requires 2 observations per participant.

Therapist Fidelity, PEP Attendance and Pill Adherence

All sessions for which families provided consent/assent were recorded to determine therapist fidelity to the PEP manual. Fidelity was moderate to high ($M = 74.4 \pm 9.7\%$) among the 10% of sessions randomly selected for rating. Families randomized into PEP+PBO attended an average of 16 ± 6 sessions (range: 4-24); families randomized to PEP+ $\Omega 3$ attended an average of 14 ± 7 sessions (range: 2 - 22). Families had the option of up to four “in-the-bank” sessions (i.e., extra sessions in addition to the scripted sessions). Over half of the families (57%) utilized these: of these, 45% had one additional session, 15% had two additional sessions, and 40% had three or more additional sessions. This flexible session structure most commonly allowed for additional content review with the child, addressing additional family stressors, support for the parent, incorporating a second parent into treatment, or addressing school advocacy or sibling issues beyond the content routinely provided in regular sessions. $\Omega 3$ monotherapy adherence ranged from 48 to 100% ($M = 86 \pm 15\%$) and $\Omega 3$ adherence from the $\Omega 3$ + PEP group ranged from 55 to 100% ($M = 86 \pm 15\%$). Similarly, placebo adherence ranged from 37 to 100% ($M = 81 \pm 19\%$) when occurring with PEP and from 48 to 100% ($M = 89 \pm 14\%$) within the non-active treatment group. Treatment group differences in pill adherence were nonsignificant.

Side Effects

No significant differences were noted between youth receiving $\Omega 3$ and PBO capsules on any of the eight monitored side effects: constipation, diarrhea, stomachache, increased appetite, decreased appetite, burping, fishy breath or nausea. Mean scores on the Side Effects Review form for each symptom at any assessment were all 1 on a 0-6 scale of severity.

Depression Scores over Time

Table 2 presents depression symptom severity (CDRS-R) at screen, baseline, and endpoint and remittance rate across treatment groups. Youth on average demonstrated severity of depressive symptoms within the clinical range at baseline ($M = 42$, clinical cut-off 40), which was a decrease from initial screen assessment ($M = 47$). By the end of treatment, average depression symptom severity fell within typical remission status (i.e., 28) in the combined group ($M = 26$; 77% remission rate), but not for PEP ($M = 30$; 61% remission rate) and $\Omega 3$ ($M = 31$; 44% remission rate) monotherapies or PBO alone (without any active treatment; $M = 31$; 56% remission rate).

Linear Mixed Effect Models (LME) of Depression Trajectories

Table 3 displays the LME model results. Depression scores decreased significantly over time for all groups, but without statistically significant differences between treatment groups. Combined treatment and $\Omega 3$ monotherapy demonstrated small-medium effects beyond that of placebo ($d = 0.29$ and $d = 0.42$, respectively). In the contrast comparing $\Omega 3$ groups (monotherapy and combined) to the placebo groups, there was marginal benefit of $\Omega 3$ ($p = .079$), with a small effect ($d = .39$). The contrast comparing PEP groups (PEP+PBO and combined) to the no psychotherapy groups was not significant and effect size was negligible ($d < .10$).

Moderator Analysis: Family Social Stress and Maternal Depression History

Over one-third of participants (38%) had a history of maternal depression; youth endorsed 2.0 ± 1.4 family environmental stressors on average (range 0-5 out of a possible 0-8). History of maternal depression and family environmental stressors were not significantly associated [$t(66) = 0.07$, $p = 0.948$]. Neither maternal depressive history [$\chi^2(3) = 2.36$, $p < 0.5$] nor family environmental stressors [$F(3,64) = 2.31$, $p = 0.085$] significantly differed by randomization group. Significant three-way interactions (time by treatment group by moderator) were found on the CDRS-R for both of the proposed moderators (Table 2, Figure 2).

Number of family stressors significantly moderated the effects of each active treatment vs. placebo ($p = .028$ to $.04$). A greater number of family environmental stressors was associated with a significant decline in depressive severity across all treated groups without significant differences between nonplacebo groups. When families reported fewer psychosocial stressors, placebo demonstrated little impact on depressive severity and each active study intervention demonstrated a significant decline in depressive severity with medium to very large placebo-controlled effect sizes ($d = 1.07$, 0.73 , and 1.38 for combined, PEP + PBO, and $\Omega 3$ monotherapy, respectively).

A history of maternal depression significantly moderated the effects of PEP+PBO vs. PBO ($p = 0.02$) but not the placebo-controlled effects of combined or $\Omega 3$ alone. All treatment groups, including placebo, demonstrated a significant decline in depressive severity in the absence of maternal depression without group differences. Youth with a history of maternal depression responded to PEP+PBO but not to PBO alone, with large placebo-controlled effect of PEP ($d = 0.84$).

Additional Exploratory Analyses

Given the variability of adherence among the four groups and the distribution of depression diagnoses in the sample, the potential moderating effects of both adherence and depression subtype were examined. Neither was significant.

Discussion

This study examined feasibility and effect sizes of two non-pharmacologic treatments for depression in youth. Six youth were unable to swallow capsules the size of the $\Omega 3$

supplement; this represents 7.7% of the otherwise eligible youth. Nevertheless, recruitment goals were exceeded by 20%. The combined treatment group had the largest percentage of remitters, 77% compared to 56% for placebo. This compares favorably to remission rates reported in studies of children with depression treated in open-label psychotherapy studies (53%, Kovacs et al., 2006; 66%, Thompson et al., 2007), psychotherapy RCTs (66%, Dietz et al., 2015; 64%, Kennard et al., 2009), and combination medication/psychotherapy RCTs (39% at 24 weeks, Emslie et al., 2010).

Nevertheless, PEP and Ω 3, alone or in combination, did not significantly impact depressive trajectories compared to placebo alone in this pilot study, although small-medium effects were noted for Ω 3 monotherapy and combined treatment relative to placebo. The small to medium effect of Ω 3 monotherapy is consistent with literature demonstrating that Ω 3 decreases symptom severity, but does not fully alleviate depression (Appleton et al., 2015). When the two groups that received Ω 3 were combined and compared to the two groups who received placebo (with or without PEP), the difference was still nonsignificant but marginal, suggesting that the small sample size may have limited power to detect a significant effect. Of note, the remission rate reported in this study for the Ω 3 alone condition was comparable to that reported by Nemets et al. (2006), 44% versus 40%, respectively, although different doses and EPA/DHA ratios were used in the two studies.

All children in this pilot study improved, consistent with literature indicating that children show a strong placebo response to treatment for depression (Bridge et al., 2007). Thus, identifying situations in which placebo is not effective while other treatments are effective provides important clinical information. History of maternal depression and lower levels of environmental family stressors moderated treatment response significantly by modifying placebo response.

Youth who were depressed in the context of a greater number of environmental stressors improved over time regardless of treatment assignment. However, youth whose depression occurred with a minimal number of environmental stressors (possibly a more endogenous depression) responded more robustly to all the active treatments than to placebo. A wealth of literature supports environmental stressors such as divorce, bereavement, and family discord as predictors of youth depressive symptoms (Stark et al., 2012). When families of these youth are linked with resources that may assist them with managing and relieving their stress (e.g., information on food, housing, financial assistance, school advocacy, parental mental health referral sources), depressive symptoms may also be relieved as stressors are removed. In the present study, parents received information about the aforementioned resources if requested or if study staff observed an apparent need, regardless of treatment assignment. Provision of such information was frequent in the study across all conditions. This could explain lack of specificity of treatment response among randomized groups in the context of high stress, as all groups were receiving such referrals and support when necessary.

Consistent with the psychosocial stress findings, in the absence of maternal depression, youth depression improved regardless of treatment assignment; that is, placebo worked as well as active treatment in the absence of maternal depression. However, youth whose mothers had a history of depression did not respond to placebo. While all active treatments

appeared to decrease depressive symptom severity, only PEP+PBO demonstrated a significant decline in symptom severity statistically greater than placebo. This suggests active psychotherapeutic elements are needed to address depressive symptoms in youth whose mothers have a history of depression. Although it is not clear which specific factors are mediating this effect, results suggest the importance of family therapy as provided by PEP. PEP provides considerable support for parents in the parent-only sessions, which may be especially important for mothers with a depression history. This support may translate into improved parenting, which could lead to improved functioning in the child. PEP aims to decrease parental guilt and to increase parental empowerment by distinguishing *cause* from *course* of illness. Parents are reminded that they did not get to choose the genes they have nor the ones they have passed on to their children. They are taught strategies to help their child, both by modeling healthy behavior and by coaching their child to engage in healthy behavior. They are also encouraged to practice self-care. While more research is needed to determine whether parent involvement in therapy is the active component for families with a history of depression, it is clear that treating these youth requires actual specialized treatment, not just placebo.

Cumulatively, this suggests that youth with what might be considered endogenous depression (i.e., occurring despite minimal psychosocial stressors and/or in the context of a positive family history) benefit uniquely from the study's active treatment elements. In contrast, youth who are depressed in the context of significant psychosocial stress or without a history of maternal depression improve with the tincture of time, attention (from the assessments and assistance to families, as described above), and from participation in a clinical trial that increases parent-child interaction and provides a forum for improved understanding of the child's symptoms.

Limitations and Strengths

The sample and design of this pilot RCT poses some limitations on study conclusions. Multiple analyses were completed on a small sample. Interpretation of statistical models did not include correction for multiple tests, as this was a pilot study. Additionally, the effects of $\Omega 3$ may not be generalizable to fish oil supplements that differ in dose or EPA/DHA ratio. The most beneficial EPA to DHA ratio for youth with mood disorders is currently unknown; a 7:1 EPA/DHA formulation was used in this trial. Similarly, the optimal dose for youth is unknown and because this was a fixed dose study, our results do not answer that important question.

Reliability of therapy video ratings was acceptable but not strong. Undergraduate raters were challenged by the sophistication needed to rate subtle therapeutic content that occurred across sessions. Finally, youth with active suicidality or severe psychosis were excluded from participating in this pilot trial for safety reasons; thus, results may not be generalizable to youth with severe presentations of depression. Although at screen all youths' depression symptom severity fell within the clinical range (CDRS-R range= 40-76), at baseline, participants demonstrated mild depressive symptoms as indicated by mean CDRS-R scores of 42, just above the standard clinical cutoff for this measure of depressive severity. Initial assessment procedures appear to have impacted improvement (Young et al., in press).

Nevertheless, this pilot study is unique in having tested the separate and combined impact of a nutritional intervention with a family-based psychosocial intervention.

Conclusions

Results of this study are novel and the moderator analyses, in particular, provide guidance for future clinical and research efforts. PEP and $\Omega 3$ appear to be safe and palatable, with good therapist fidelity and treatment adherence; results support the potential feasibility of a larger trial. While main effects of treatment were nonsignificant, $\Omega 3$ with and without PEP demonstrated small to medium effects, which suggests that a large multi-site trial is warranted. Youth who are depressed in the absence of major psychosocial stressors and/or whose mothers have experienced depression may be more likely to respond to more specific and intensive treatment, including $\Omega 3$ and PEP. Those without maternal depression but with high environmental stressors may respond to empathic support, attention to pragmatic issues (e.g., the lowest rung of Maslow's hierarchy (Maslow, 1943)), and the passage of time. Future research should consider maternal depression and number of stressors as inclusion/exclusion criteria and/or build in moderator analyses to determine if the current findings are replicable. These findings, although not conclusive, cohere with previous evidence supporting the effectiveness of $\Omega 3$ and PEP.

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Figure 1.

CONSORT diagram illustrating participant enrollment, randomization allocation, and study completion status. PEP = Psychoeducational Psychotherapy. PBO = Placebo.

Figure 2.

Plots of CDRS-R scores on time from randomization (measured in weeks) as effects of maternal depression and psychosocial stress. Simple slopes (b_{simple}) of the 3-way-interaction were calculated for each treatment group. Depressive severity trajectories by treatment group (A) in the absence of maternal depression; (B) in the presence of maternal depression; (C) greater number of psychosocial stressors (one standard deviation above the mean count of stressors); (D) lower number of psychosocial stressors (one standard deviation below the mean count of stressors).

Table 1

Participant demographics and clinical characteristics

	Total (<i>N</i> = 72)	Combined (<i>n</i> = 17)	PEP Only (<i>n</i> = 19)	Q3 Only (<i>n</i> = 18)	PBO (<i>n</i> = 18)
<i>M ± SD or n (column %)</i>					
Youth Age	11.6 ± 2.1	11.3 ± 2.2	11.7 ± 2.1	12.3 ± 1.8	11.1 ± 2.4
Youth Sex: Male	41 (56.9)	10 (58.8)	9 (47.4)	9 (50.0)	13 (72.2)
<i>Youth Race</i>					
White	41 (56.9)	11 (64.7)	11 (57.9)	7 (38.9)	12 (66.7)
Black/African American	22 (30.6)	5 (29.4)	5 (26.3)	8 (44.4)	4 (22.2)
Asian	0	0	0	0	0
Biracial	9 (12.5)	1 (5.9)	3 (15.8)	3 (16.7)	2 (11.1)
Youth Ethnicity: Hispanic	7 (9.7)	4 (23.5)	2 (10.5)	0	1 (5.6)
Youth Insurance: Medicaid	23 (31.9)	3 (17.6)	4 (21.1)	9 (50.0)	7 (38.9)
<i>Comorbid Disorders</i>					
Anxiety Disorder	54 (75.0)	12 (70.6)	15 (78.9)	13 (72.2)	14 (77.8)
ADHD	41 (56.9)	7 (41.2)	12 (63.2)	9 (50.0)	13 (72.2)
DBD	22 (30.6)	5 (29.4)	6 (31.6)	5 (27.8)	6 (33.3)
PTSD	7 (9.7)	1 (5.9)	3 (15.8)	1 (5.6)	2 (11.1)
Number of diagnoses	3.4 ± 1.2	2.9 ± 1.0	3.4 ± 1.1	3.3 ± 1.2	3.8 ± 1.4
Full Scale IQ	103 ± 15	106 ± 14	103 ± 16	99 ± 16	104 ± 15
Parent Age	41.8 ± 8.1	42.8 ± 9.3	41.1 ± 6.4	40.7 ± 6.5	42.4 ± 10.1
<i>Parent Relationship</i>					
Mother	66 (91.7)	17 (100)	19 (100)	15 (83.3)	15 (83.3)
Father	4 (5.6)	0	0	3 (16.7)	1 (5.6)
Grandmother	2 (2.8)	0	0	0	2 (11.1)
<i>Family Structure</i>					
Married parents	25 (34.7)	8 (47.1)	7 (36.8)	5 (27.8)	5 (27.8)
Single parent	28 (38.9)	5 (29.4)	8 (42.1)	8 (44.5)	7 (38.9)
Step Family	7 (9.7)	1 (5.9)	2 (10.5)	3 (16.7)	1 (5.6)
Other	12 (16.7)	3 (17.6)	2 (10.5)	2 (11.1)	5 (27.8)

	<i>M ± SD or n (column %)</i>				
	Total (<i>N</i> = 72)	Combined (<i>n</i> = 17)	PEP Only (<i>n</i> = 19)	Q3 Only (<i>n</i> = 18)	PBO (<i>n</i> = 18)
<i>Household Annual Income</i>					
<\$20,000	13 (18.3)	3 (18.8)	1 (5.3)	6 (33.3)	3 (16.7)
\$20,000 - 40,000	19 (26.8)	4 (25.0)	4 (21.1)	5 (27.8)	6 (33.3)
\$40,000 - 60,000	13 (18.3)	0	5 (26.3)	3 (16.7)	5 (27.8)
\$60,000 - 80,000	8 (11.3)	3 (18.8)	3 (15.8)	0	2 (11.1)
\$80,000 - 100,000	3 (4.2)	1 (6.3)	2 (10.5)	0	0
>\$100,000	15 (21.1)	5 (31.3)	4 (21.1)	4 (22.2)	2 (11.1)

Note. No significant differences on any demographic or clinical characteristics existed between randomization groups. ADHD=Attention-deficit/Hyperactivity Disorder; DBD=Disruptive Behavior Disorder; PEP = Psychoeducational Psychotherapy; PTSD= Post-Traumatic Stress Disorder.

Table 2

Mood Symptoms, Severity by Treatment Group and Screen, Baseline, and Endpoint

Treatment Group	Screen		Baseline		Endpoint		Remitted
	M±SD	Range	M±SD	Range	M±SD	Range	%
COMB	44±5	40-59	38±9	20-56	26±10	17-57	76.5%
PEP	47±7	40-64	42±9	26-57	30±9	18-52	61.1%
Q3	49±6	40-60	44±12	27-75	31±9	19-55	43.8%
PBO	49±8	40-76	44±13	28-72	31±11	21-69	55.6%

Note. N=69. Scores are from the Child Depression Rating Scale-R. Remittance cut-score 28.

Table 3

Linear mixed effects models of primary analysis and treatment moderation of psychosocial stressors and maternal depression history on CDRS-R scores

Moderator	Parameter	Estimate	p-value
None	Intercept	38.01	< 0.001
	Treatment Group (reference: Placebo)		
	Combined	-2.84	0.355
	PEP+placebo	1.18	0.690
	Ω3 monotherapy	3.65	0.231
	Time (weeks)	-0.94	< 0.001
	Treatment Group X Time		
	Combined X Time	-0.25	0.344
	PEP+placebo X Time	0.04	0.880
	Ω3 monotherapy X Time	-0.38	0.175
Presence of Maternal Depression	Intercept	38.84	< 0.001
	Treatment Group (reference: Placebo)		
	Combined	-2.73	0.454
	PEP+placebo	-3.13	0.411
	Ω3 Monotherapy	4.53	0.241
	Time (weeks)	-1.27	< 0.001
	Presence of Maternal Depression	-2.90	0.543
	Combined X Presence of Maternal Depression	0.08	0.991
	PEP+placebo X Presence of Maternal Depression	10.32	0.106
	Ω3 Monotherapy X Presence of Maternal Depression	-0.81	0.901
	Combined X Time	-0.17	0.584
	PEP+placebo X Time	0.42	0.161
	Ω3 Monotherapy X Time	-0.29	0.417
	Time X Presence of Maternal Depression	1.07	0.005
	Combined X Time X Presence of Maternal Depression	-0.41	0.444
	PEP+placebo X Time X Presence of Maternal Depression	-1.17	0.020
	Ω3 Monotherapy X Time X Presence of Maternal Depression	-0.60	0.273
Psychosocial Stressors	Intercept	37.85	< 0.001
	Treatment Group (reference: PBO)		
	Combined	-3.61	0.307
	PEP+placebo	1.49	0.637
	Ω3 Monotherapy	4.60	0.163
	Time (weeks)	-0.80	< 0.001
	Number of Stressors	3.05	0.079
	Combined X Stressors	-4.92	0.067
	PEP+placebo X Stressors	-1.74	0.442
	Ω3 Monotherapy X Stressors	-5.16	0.056

Moderator	Parameter	Estimate	p-value
	Combined X Time	−0.35	0.253
	PEP+placebo X Time	−0.13	0.636
	Ω3 Monotherapy X Time	−0.55	0.065
	Time X Stressors	−0.42	0.004
	Combined X Time X Stressors	0.48	0.035
	PEP+placebo X Time X Stressors	0.41	0.028
	Ω3 Monotherapy X Time X Stressors	0.52	0.040