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Moody Kids Years Later: Long-Term Outcomes of Youth from the Omega-3 and Therapy (OATS) Studies

Mary A. Fristad, PhD, ABPP[1,2], **Michelle E. Roley-Roberts, PhD**[3], **Sarah R. Black, PhD**[4], **L. Eugene Arnold, MD, MEd**[2]

[1]Nationwide Children's Hospital, Big Lots Behavioral Health Services and Division of Child and Family Psychiatry, Columbus, Ohio

[2]The Ohio State University Wexner Medical Center, Department of Psychiatry & Behavioral Health, Columbus, Ohio

[3]Creighton University, Department of Psychiatry, Omaha, Nebraska

[4]University of New Orleans, Department of Psychology, New Orleans, Louisiana

Abstract

Background.—This naturalistic follow-up study examines outcomes for youth with depression (n=25) or subsyndromal bipolar disorder (n=13) 2–5 years after participation in randomized clinical trials (RCTs) of omega-3 fatty acids (Ω3), individual family psychoeducational psychotherapy (IF-PEP), and their combination.

Methods.—Forty percent (38/95) of RCT families completed a follow-up assessment.

Results.—Relapse rates and conversion to bipolar disorder were consistent with published literature. Original treatment assignment did not impact current functioning. Overall, participants' mood severity, executive functioning, and global functioning continued to be better than at RCT baseline. Depressive symptoms increased significantly from end of RCT. Manic symptom severity, executive functioning, and global functioning remained comparable to end of RCT. The majority of parents and youth reported improved youth emotion regulation skills and family communication. They considered study participation beneficial, with increased understanding of mood disorders being the top reason. Half of youth commenced or continued Ω3 and 58%

Corresponding Author Contact Information: Mary A. Fristad, PhD, ABPP, 444 Butterfly Gardens Drive #3207, Behavioral Health Pavilion Suite 3C, Columbus, OH 43215, Mary.fristad@nationwidechildrens.org, 614-722-6872.

Contributors

The authors

CONFLICTS OF INTEREST

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commenced or continued psychotherapy post-RCT, suggesting some degree of consumer satisfaction; these youth had lower depression severity than other participants.

Limitations.—Only 40% returned to this naturalistic follow-up; they were less likely to have an African-American parent, were of higher income, and youth were more symptomatic at end of RCT than those who did not return.

Conclusions.—Improvement from RCT baseline continued although depressive symptom severity increased from end of RCT to follow-up. Meaningful improvements in youth and family functioning persisted 2–5 years later. Interventions that prevent relapse or conversion to BPSD are still needed for these vulnerable populations.

Few long-term studies have tracked treatment outcomes for childhood-onset depressive spectrum disorders (DSD) and bipolar spectrum disorders (BPSD) despite life-course mental health and functional impairments associated with these disorders (Axelson et al., 2006; Birmaher et al., 1996; Van Meter et al., 2012, 2013). Furthermore, it is difficult to attain sustained remission following treatment. While many youth recover, recurrent episodes are frequent in both DSD (80%; Blanz et al., 2006) and BPSD (62.5%; Goldstein et al., 2017). Regarding BPSD, high rates of progression from bipolar disorder-not otherwise specified or cyclothymic disorder (BP-NOS/CYC) to bipolar disorder type 1 or 2 (BD-1/−2) have been reported (Goldstein et al., 2017). Presence or absence of symptoms tells only a portion of the story; a focus on individual and family functioning outcomes may provide additional information about treatment impact.

In their 2017 review, Weersing et al. (2017) summarized findings around evidence-based treatments for depression in youth, considering child and adolescent RCTs separately. For adolescents, cognitive behavioral therapy (CBT) and interpersonal psychotherapy (IPT) were identified as “well-established” psychosocial treatments (e.g., Asarnow et al., 2005; Mufson et al., 2004; Mufson et al., 1999; Richardson et al., 2014). They also described family-based treatments as “possibly efficacious,” but cited heterogeneity in such interventions that may have obscured clear treatment effects of particular therapy techniques. Among children, however, no psychosocial interventions were described as “well-established.” The most effective interventions, CBT and behavior therapy, were described as “possibly efficacious,” primarily due to their lack of superiority to other active treatments (e.g., De Cuyper et al., 2004; Kahn et al., 1990; Weisz et al., 2009).

Fristad and MacPherson (2014) provided a similar review of evidence-based psychosocial interventions for BPSD in youth. The limited number of studies precluded separate investigation of childhood and adolescent interventions. Overall, no interventions were classified as “well-established,” but family psychoeducation plus skill building was considered “probably efficacious (Fristad et al., 2003, Fristad, 2006; Miklowitz et al., 2008, 2014).” Since then, additional studies have provided sufficient support to consider this class of interventions as “well-established” (Miklowitz et al., 2014; West et al., 2014). CBT was classified as “possibly efficacious” (e.g., Feeny et al., 2006), while dialectical behavior therapy (DBT) and interpersonal and social rhythm therapy were classified as “experimental” (e.g., Goldstein et al., 2007; Hlastala et al., 2010).

Data on follow-up effects from RCTs for child and adolescent depression are mixed. Among adolescents, Weersing et al. (2017) noted that 65% (22 of 34) of trials they reviewed included 12–24 month follow-up data. While most adolescents recovered over follow-up, specific treatment effects were not detected; in other words, distinctions between CBT, IPT, and other interventions faded over time. Among children, only 4 reviewed trials reported 1–12 month follow-up data. Evidence of long-term effects in children is mixed: while some trials reported superiority of the active treatment condition over control in follow-up (De Cuyper et al., 2004; Kahn et al., 1990), others demonstrated broad-based improvements in child depression symptoms regardless of intervention (Liddle & Spence, 1990; Trowell et al., 2007) while still others reported diminishing returns of treatment over time (Vostanis et al., 1998; Vostanis et al., 1996).

Follow-up studies of BPSD interventions are scant. Youth who received multi-family psychoeducational psychotherapy (MF-PEP) reported lasting improvement in mood severity over youth in a waitlist control (WLC) plus treatment as usual (TAU) group over an 18-month follow-up (Fristad et al., 2009). Individual-family psychoeducational psychotherapy (IF-PEP), a single-family adaptation of MF-PEP, showed similar efficacy over a 12-month follow-up (Fristad, 2006). Family focused treatment for adolescents (FFT-A), another family-based intervention, demonstrated similar efficacy to enhanced care (EC) over 2-year follow-up, but adolescents with bipolar disorder in FFT-A recovered from their depressive symptoms significantly quicker than youth in EC (Miklowitz et al., 2008). In another 2-year follow-up of youth at high risk for bipolar I or bipolar II due to having a major depression or BP-NOS and a family history of bipolar disorder, FFT-A was associated with longer intervals between depressive episodes, but not any other mood outcomes (Miklowitz et al., 2020).

There is a paucity of research regarding mechanisms of action in the treatments described above. The most effective application of CBT for adolescent depression occurred in the context of a primary care intervention (Asarnow et al., 2005; Richardson et al., 2014), which introduced other elements into treatment that may not be a part of standard CBT. Furthermore, behavioral and family-based treatments, which were classified as “possibly efficacious” for childhood and adolescent depression, were highly heterogeneous and included a variety of specific treatment techniques (Weersing et al., 2017). Therefore, it is difficult to isolate specific mechanisms of action in these treatments. Fristad and MacPherson further noted that only one RCT to treat pediatric BPSD has evaluated mediators (Fristad et al., 2009). Importantly, the lack of research regarding mechanisms of change may be especially pertinent to follow-up literature, considering that treatment effects for pediatric mood disorders, while enduring, are generally non-specific to particular treatment modalities (but may be specific to certain treatment techniques/mechanisms of action) over the long-term.

Research on medications for mood disorders in youth also has many limitations. RCTs of medication for DSD indicate that selective serotonin reuptake inhibitors (SSRIs) and serotonin-norepinephrine reuptake inhibitors (SNRIs) have small specific effects in youth, primarily due to large placebo response (Locher et al., 2017). In addition, patients taking SSRIs and SNRIs have significantly more treatment emergent adverse events, serious

adverse events, and study discontinuations compared to those on placebo (Locher et al., 2017). Medication studies of manic episodes indicate that multiple second-generation antipsychotics (SGAs) are effective but have undesirable metabolic side effects, while lithium carbonate has shown mixed effectiveness, and anticonvulsants (e.g., divalproex sodium, carbamazepine) are less effective than SGAs (Goldstein et al., 2017). In bipolar depression, two SGAs have FDA approval but are more likely to have undesirable metabolic and other side-effects (Patino & DelBello, 2019). Studies demonstrating long-term efficacy of medications for the treatment of DSD and BPSD are lacking.

Clearly, treatments that can provide sustained relief are needed. As noted above, Family Psychoeducation + Skill Building, a class of psychosocial treatments, is well established for acute symptom reduction in childhood BPSD (Fristad, 2016). One such treatment, Individual-Family Psychoeducational Psychotherapy (IF-PEP), has demonstrated short-term efficacy in randomized, controlled trials (RCTs) for youth with depression (Fristad et al., 2019) and BP-NOS/CYC (Fristad, 2006; Fristad et al., 2015), both alone and in combination with omega-3 fatty acid (Ω3) supplementation for depression in BP-NOS/CYC. The current study provides an examination of long-term naturalistic outcome data.

OATS Acute Trial: The Omega-3 and Therapy Studies (OATS) were two 2X2 randomized clinical trials with identical protocols, 72 in the depression trial and 23 in the BP-NOS trial. All participants were randomly assigned to either Omega-3 fatty acids (Ω3, 2g day) + active monitoring (AM), matched placebo+AM, IF-PEP+ Ω3, or IF-PEP+placebo. The only medications permitted were sleep aids or ADHD medications, and they had to be at a stable dose for the prior month. Intent-to-treat analyses from the depression trial revealed small to medium effects in decreasing depressive symptom severity of combined treatment (IF-PEP + Ω3; d=.29) and Ω3 + active monitoring (AM; d=0.42) compared to placebo + AM. Two treatment moderators were detected. Youth with fewer social stressors responded better to all three active conditions relative to placebo (Ω3, p<.04; IF-PEP, p<.03, combination, p<.04), and those exposed to maternal depression responded better to PEP (p=.02). In the BP-NOS/CYC trial, intent-to-treat analyses revealed significant improvement in depressive symptoms for those receiving IF-PEP + Ω3 compared to those receiving placebo + AM (p=0.01, d = 1.70). Manic symptoms improved over time, albeit without significant treatment effects. IF-PEP compared to AM had medium to large effect (d =.63–1.24), while the effect of Ω3 on depression was medium (d = 0.48).

The current study describes the naturalistic post-intervention follow-up of youth who participated in the acute OATS trials to assess their current functioning, ongoing service utilization (particularly use of Ω3 supplements and individual/family psychotherapy), and subjective evaluations of the impact of study participation on the child's and family's functioning several years post-study intervention.

Method

Participants

Youth (originally aged 7–14, aged 11–19 years at follow-up) who had been randomized into one of two pilot 2 × 2 randomized clinical trials (RCTs) (Clinicaltrials.gov Identifiers,

NCT01507753; NCT01341925) were recruited for this follow-up study. The original depression study (OATS-D) included 72 children who met Diagnostic and Statistical Manual, 4th Edition (DSM-IV-TR; American Psychiatric Association [APA], 2000) diagnostic criteria for depression (Major Depressive Disorder [MDD], Dysthymic Disorder [DD], or Depression Not Otherwise Specified [D-NOS]); the original bipolar study (OATS-B) included 23 children who met DSM-IV diagnostic criteria for either CYC or BPNOS. Participants in both OATS-D and OATS-B had been assigned to IF-PEP vs. AM and Ω3 vs. placebo (PBO) in a 1:1:1:1 distribution (i.e., participants were equally likely to have received IF-PEP + Ω3, IF-PEP + PBO, AM + Ω3, or AM + PBO). Both studies were conducted at an academic medical center in a Midwestern city that draws from both urban and rural catchment areas.

Procedures

Families were re-contacted by phone and invited to participate in the follow-up study between July 2016 and March 2017, 2.3 to 4.7 years after completing the RCT (M ±SD=3.5±0.7). Those who agreed were scheduled for a follow-up appointment. Parents provided written informed consent and youth provided written informed assent using documents approved by the local Institutional Review Board before beginning the follow-up assessment, which lasted ≤ 3 hours. Parents received a $40 gift card and youth a $25 gift card as compensation for their time. Youth and parents completed self-report questionnaires and were interviewed sequentially with semi-structured diagnostic interviews. Diagnostic interviews were conducted by two postdoctoral researchers and two advanced graduate research associates who were supervised by a licensed clinical psychologist. Interviewers had not been involved in the acute trial and were masked to original treatment condition. Self-report measures were administered by trained undergraduate research assistants. Global ratings and DSM mood diagnoses were based on all information obtained during the assessment (described below) without reference to original treatment assignment, and reviewed by the first author. Diagnoses of BP-NOS utilized additional criteria as established in two longitudinal studies of manic symptoms (Axelson et al., 2006; Findling et al., 2010).

Measures

Demographic Form.—Parents completed a demographic self-report form that documented the youth's sex, race/ethnicity, birthdate (to calculate the youth's age), and family socio-economic status.

Mental Health Services and Medication Grids (Mendenhall et al., 2010).: Parents provided information on the youth's medical and mental health interventions from the end of OATS treatments to follow-up assessment. The Mental Health Services and Medication Grids have demonstrated convergent validity with youth patient medical charts (r_s = .92, p < .01; r_s = .99, p < .01; Mendenhall et al., 2010).

Young Mania Rating Scale (YMRS; Young et al., 1978).: The YMRS is an 11-item semi-structured interview of youth mania symptoms. Total scores range from 0 (no manic symptoms) to 60 (severe manic symptoms; Young et al., 1978); it has good reliability (α = 0.91; Youngstrom et al. 2002) and discriminant validity (r = 0.83, p < 0.0001; Fristad et al.

1992; Fristad et al. 1995; Youngstrom et al. 2003). The YMRS was administered at each assessment in the acute trial and follow-up; it assessed symptoms of hypomania and mania over the past two weeks.

The Children's Depression Rating Scale-Revised (CDRS-R; Poznanski et al., 1984).: The CDRS-R is a semi-structured depressive symptom severity interview for youth ages 6–17 that includes 21 items, each rated on a 1–5 or 1–7 point scale in the direction of increasing severity. Scores can range from 17 to 113; interrater reliability is good (r =.86), as is test-retest reliability over a 4-week interval (r =.81; Poznanski et al. 1984). The CDRS-R was administered at each assessment in the acute trial and follow-up; it was used to assess depressive symptoms over the past two weeks.

Behavior Rating Inventory of Executive Functioning (BRIEF; Gioia et al., 2000).: The BRIEF is a 138-item parent-report of youth's ability to complete tasks requiring executive functioning skills (Inhibition, Shift, Emotional Control, Initiation, Working Memory, Planning, Organization of Materials, and Monitoring). Age and sex-normed t-scores, based on a standardization sample (N = 1,419) of youth, were used; higher t-scores indicate greater impairment. Test–retest reliability is adequate (r=0.58) and internal consistency is high: Cronbach's α = 0.96. The BRIEF was completed at acute trial screen and endpoint, and at follow-up.

Children's Global Assessment Scale (CGAS; Shaffer et al., 1983).: The CGAS is a clinical rating scale used to document children's current functioning at home, school, and with peers. Scores range from 1 (severely impaired) to 100 (superior functioning). It has excellent reliability (Rey et al., 1995) and construct validity (Bird et al., 1987). Ratings were made after completion of each study visit during the acute trial and follow-up.

The OATS Family Experience Assessment – Child and Parent Report (FEA).— Self-report measures designed for this study were used to assess parent (20-item) and youth (18-item) opinions of the utility and potential mechanisms of change of OATS interventions. Questions asked about changes in child and family functioning beyond symptom reduction (e.g., peer relations, family communication) as a result of study participation, study-related components that parents and children believed were related to changes in functioning, and whether families began or continued taking Ω3 or other psychotropic medication (stimulants or sleep aids that had been prescribed a month or more prior to enrollment and had been permitted in the acute trial), and began or continued individual/family psychotherapy after the acute trial ended. Parents and children also rated how helpful the study was in providing tools to families (1 = least desirable to 7 = most desirable, or non-applicable).

Data Analytic Plan

Descriptive statistics, ANOVA, and chi-square tests were utilized to characterize the sample, report on participants' evaluation of the acute trial, and assess for possible demographic differences between the follow-up sample and original treatment groups. Three main timepoints were compared: 1) baseline-this followed the RCT screening visit and was the point of randomization; 2) end of RCT—this was after 12 weeks of treatment; 3) follow-up

—this was 2–5 years after study enrollment. *T*-tests comparing baseline to follow-up and RCT end to follow-up means were performed to examine whole sample differences on the outcome variables (CDRS-R, YMRS, BRIEF, C-GAS). Missing data for *t*-tests were handled using listwise deletion. Effect size was determined by Cohen's d where a small effect = 0.2, a medium effect = 0.5, and a large effect = 0.8 (Cohen, 1998). Linear mixed effects models (LME; Diggle et al., 2002) were fit to each outcome variable using SPSS v. 22 to assess impact of initial treatment group assignment (IF-PEP + Ω3, IF-PEP + PBO, or AM + Ω3 versus AM + PBO) on mood trajectories. As no participants from the original OATS-D study converted to a BPSD in this follow-up study, the YMRS was only analyzed for those who had BPSD in the acute study.

Random effects were intercept and slope, which provides a personalized linear response to treatment for each participant. Fixed effects were treatment group (dummy coded relative to placebo plus active monitoring) X time (weeks since randomization) interaction, which measured systematic rate of change differences. Finally, to determine if long-term results differed by treatment subsequent to acute RCT (i.e., therapy or not, Ω3 or not after OATS participation), LME models were utilized as above. The assumption of a common initial mean for all participants was adopted because participants originally were randomized into specific treatment groups. The major advantage of LME is that participant effects can be estimated using incomplete data as LME does not rely on a balanced group design; thus imputation of missing values was not needed because data were assumed to be missing at random (Gardner et al. 1995). Effect sizes were examined with the treatment X time slopes method (Feingold, 2009), rather than relying on statistical significance as this was a pilot follow-up study.

Results

Sample Characteristics

Thirty-eight of 95 families (40%) from the acute trial participated in the follow-up study; in 3 cases, only parents participated. Follow-up occurred 3.5±0.7 (range = 2.3–4.7) years after the acute trial. Follow-up participants (*M* age = 14.6, *SD* = 2.5) were 63% male; 76% non-Hispanic Caucasian, 16% Biracial/Black, 3% Asian; 5% Latinx. Follow-up participants, compared to those who did not return, were more likely to have: completed the acute RCT [92%; χ^2 (1, 95) = 8.82, p = .003]; a non-Black/Biracial caregiver [χ^2 (1, 95) = 7.09, p = .008]; annual family income of $80–100K [$\chi^2$ (1, 95) = 10.10, p = .001]; and less improvement in manic symptoms at RCT end-point [YMRS; t (17) = 3.16, p = .006]. Age, race, and sex did not differ between those who did versus did not return for follow-up. The proportion assigned to each of the four original OATS treatment groups did not differ significantly among follow-up participants: Ω3 + PEP, n=11 (29%); PBO + PEP, n=10 (26%); Ω3+ AM, n=7 (18%); and PBO + AM, n=10 (26%).

Diagnostic Changes

Eleven (44%) of 25 youth initially diagnosed with depression ([MDD, n = 13; D-NOS, n = 9; DD, n = 3) were in remission. Of the remaining 14 (56%), nine (36%) had MDD, three (12%) had DD, and two (8%) had D-NOS at follow-up. Five (38%) of 13 youth initially

diagnosed with BP-NOS or CYC had converted to BD-1 (n = 3) or BD-2 (one depressed type, one mixed type, n = 2). Of the remaining eight (62%), one continued to have BP-NOS and six persisted with CYC. One youth initially in the BPSD group had an unspecified mental disorder (the parent was sole informant and had insufficient information to make a precise diagnosis).

Impact of Original Treatment Condition

Original treatment assignment (IF-PEP + Ω3, IF-PEP + PBO, and AM + Ω3 compared to AM + PBO) did not significantly impact mood ratings or global functioning at follow-up (group X time CDRS-R, p=.75; YMRS, p=.74, CGAS, p=.45).

Baseline to Follow-Up Comparisons for the Entire Sample

Baseline, end of RCT, and follow-up mood ratings, executive functioning, clinical global impressions, and overall functioning appear in Table 1. Compared to baseline depressive symptoms, participants had significantly lower CDRS-R scores at follow-up, with a small effect size. For those from OATS-B, compared to baseline manic symptoms, participants at follow-up had lower YMRS scores by a large effect size. Executive functioning was improved significantly from baseline with a medium effect size. Compared to baseline, participants were functioning better at follow-up (i.e., higher CGAS scores) with a medium effect size.

End of Study to Follow-Up Comparisons for the Entire Sample

Compared to end of RCT depression scores, CDRS-R scores were higher at follow-up with a medium effect size. YMRS score did not change significantly. There was a marginal (non-significant small effect) improvement in executive functioning. Global functioning (C-GAS) remained similar from end of RCT to follow-up.

Utilization of Ω3, Medication, and Therapy after the Acute Trial

Families received sealed envelopes after their acute trial participation that contained information regarding their treatment assignment (i.e., Ω3 or placebo) and where they could purchase the same or a comparable Ω3 to that used in the study. All families who requested psychotherapy referrals were provided with such at their final assessment; families whose children remained symptomatic were offered referrals as standard practice.

Fifty-eight percent of the follow-up sample reported being in therapy after the OATS study. Those assigned to IF-PEP (71%) were more likely to meet with a (non-study) therapist than those assigned to active monitoring (41%; $\chi 2 = 6.43$, $p < .05$).

Fifty percent of the sample reported taking Ω3 after the OATS study (59%, Ω3 group; 43%, placebo group; $\chi 2 = 0.26$, $p = .61$). Parents whose children did not take Ω3 reported multiple reasons, including: child did not want to take it (n = 5; 17%); other treatments were enough (n = 5; 17%); wanted to try conventional medicine (n = 5; 17%); did not think it would be helpful (n = 4; 13%); too expensive (n = 3; 10%); child refused (n = 3; 10%); child didn't like the pills (n = 2; 7%); got better without them during the study (n = 1, 3%); did not know where to purchase (n = 1; 3%); or unknown reason (n = 1; 3%). Youth who did not take Ω3

reported a variety of reasons, including: did not know why/just did not take Ω3 (*n* = 4; 25%), did not need (*n* = 3; 19%), parents didn't know where to purchase (*n* = 3; 19%), didn't think it would be helpful (*n* = 2; 13%), and didn't like Ω3, unwilling to take, parent did not want to make child take, and didn't like taste (*n* = 1; 6% each).

At some point during the follow-up period, a majority of youth (63%, 24 of 38) had taken medication other than for ADHD or a sleep aid (both of which had been permitted in the acute trial if the child had been on a stable dose for a month or longer): 61% mood stabilizer; 37% anti-obsessional; 21% anti-depressant; 3% anti-psychotic. Medication utilization did not vary by original treatment group (χ^2=3.18, p=.365). At the time of follow-up, 50% were on medication (48% mood stabilizer; 38% antidepressant; 5% anti-obsessional; 5% anti-psychotic). Scores on all outcomes measures (i.e., CDRS-R, YMRS, BRIEF, and C-GAS) did not differ based on medication status at follow-up (t scores ranged from .023 to 1.164).

Impact of Treatment after the RCT

Those who continued or initiated Ω3 after the acute OATS trial had significantly lower CDRS-R scores at follow-up compared to those who did not take Ω3 (see Table 2), as did those who continued or initiated therapy after the acute OATS trial compared to those who did not (see Table 2). There were no differences in YMRS scores between those who took Ω3 or participated in therapy after the acute trial compared to those who did not. As none of the depressed group converted to a BPSD, a sensitivity analysis was conducted to examine manic symptom trajectories for the 13 youth with BP-NOS/CYC from the acute trial; results were comparable to the full dataset.

Family Evaluation of Study Impact

Parental report of study impact.—The majority of parents reported that their child's and their family's functioning improved during the acute trial (84% child; 87% family) and maintained improvement after the acute trial ended (82% and 74%, respectively; Table 3). For example, half or more of parents endorsed that their child had improved their ability to cope with stress, that family communication had improved, and that they felt more hopeful. Nearly all (95%) would recommend the study to other families. Overall, parents liked being in the OATS study (6.0±1.0 on scale of 1 to 7). Parents rated several aspects of study participation quite favorably, in particular, obtaining knowledge and skills, school-based consultation and referrals at study end (see Table 4). Reasons to which parents attributed improvement appear in Table 5. For questions about study pills and therapy, endorsements were repored only for those who received the active intervention in question (i.e., therapy skills for those in IF-PEP, study pills for those assigned to Ω3). All endorsements were pooled for study interviews. Parent and child skill building, study pills, and increased understanding (through therapy and interviews) were endorsed by at least half the parents.

Youth report of study impact.—The majority of youth also reported that their functioning as well as their family's functioning improved during the acute trial (82% and 79%, respectively) and maintained improvement after the acute trial ended (68% for both child and family functioning; Table 6). For example, half or more of youth endorsed that

they felt better about themselves, were more calmed down, that they learned new coping strategies, and that their family communicated better. A majority (59%) would recommend the study to others. Overall, youth liked being in the OATS study (5.9±1.3). As with the parents, they reported increased understanding of symptoms, improved skills, school-based interventions, and post-study referrals; they also listed improved family life as benefits (see Table 4). Reasons to which youth attributed improvement appear in Table 7. Endorsements were tallied by intervention received (i.e., therapy skills for those in PEP, study pills for those assigned to Ω3). All endorsements were pooled for study interviews. Parent and child skill building, caring therapists, study pills, and increased understanding through therapy were endorsed by at least half the youth.

Discussion

DSD and BPSD are disorders noted for their chronic and/or recurrent presentations. No long-term treatment studies of pharmacotherapy or psychotherapy have demonstrated ongoing symptomatic relief as defined by sustained remission without relapse. Findings from this study are consistent with these earlier reports. Rates of depression recurrence for the DSD group and conversion from BP-NOS/CYC to BP-I/II from the BPSD group were consistent with data from other longitudinal studies (Axelson et al., 2011; Birmaher et al., 2009; Geller et al., 2008; Shankman et al., 2009; Wozniak et al., 2011). Interventions that provide sustained remission of mood symptoms in youth are still very much needed.

Participants, regardless of original treatment group, continued to do better than they had at RCT baseline regarding depressive and manic symptom severity, executive functioning, and global functioning. Manic symptom severity, executive functioning, and global functioning remained comparable to end of RCT. Depressive symptoms increased significantly from end of RCT for the overall group although still significantly better than baseline. However, the 50% of families who commenced or continued Ω3 and the 58% who commenced or continued psychotherapy post-RCT had lower depressive symptom severity at follow-up compared to those who did not.

Two to almost five years after participation in the acute trial, the 40% of participants who returned for follow-up attributed some improved individual and family functioning to study participation. The majority of parents and youth reported improved youth emotion regulation skills and family communication. They considered study assessments beneficial, with increased understanding being the top reason. Among those who had received IF-PEP, the most common reasons for improvement reported by both parents and youth included learning new skills, improved parent-child interactions, increased understanding, and feeling cared about/supported. Among those who had received Ω3, study pills also were acknowledged as useful. Interestingly, participation in study assessments themselves were considered beneficial, particularly by parents, with increased understanding being the top reason stated, lending further credence to the impact thorough assessments had on participating families. This is consistent with findings from our acute trials, in which the impact of a thorough assessment at screening was linked to improved outcomes at the baseline assessment for some participants (Young et al., 2019).

This discrepancy between lack of overall sustained improvement in mood symptoms despite indication of improved child and family functioning is consistent with other reports in the literature that focus on what "good outcome" means to consumers of mental health care (De Smet et al., 2020; Oldehinkel, 2019). In a study of 47 adults with major depression who had completed an RCT, participants reported that "good outcomes" included feeling empowered and finding personal balance, rather than symptom reduction, per se (DeSmet et al., 2020). In reviewing definitions of mental health, Oldenhinkel (2019, pp. 825–826) includes: 1) "a state of well-being in which individuals realize their own abilities and can cope with the normal stresses of life, work productively, and can contribute to their community"; and 2) "mental well-being…[which consists of] perceived personal effectiveness and happiness"; he specifically negates the absence of symptoms as a meaningful definition of mental health.

Slightly over half of families either commenced or continued with psychotherapy and half of the families commenced or continued with Ω3 following the acute trial. In addition, half of youth were on medication at the time of this follow-up. These numbers suggest relatively high rates of apparent consumer satisfaction when compared to drop-out rates in acute trials, particularly for pharmacotherapy, which are around 32% in 6–12 week trials of anti-depressants (Rutherford et al., 2013). Significantly more of those originally assigned to PEP were getting psychotherapy than those not so assigned (71% vs. 41%) and nominally more of those originally assigned to Ω3 were taking it than those assigned to placebo. Thus, families tended to continue with what they had been "introduced to" in the RCT. This is consistent with follow-up findings from the Multimodal Treatment study of ADHD (MTA Cooperative Group, 2004). In the MTA 10-month follow-up, >85% of those originally assigned to medication continued it while only 44% originally assigned to behavioral treatment alone were taking medication despite a recommendation at RCT end to start medication.

Limitations

There are several clear limitations to this study. Importantly, less than half of acute trial participants attended this follow-up 2–5 years later. Sample size for youth with BPSD was particularly small. Second, those who did attend were more likely to have completed the acute trial, were less likely to have an African-American parent, were of higher income, and the child was more symptomatic at the end of the acute study. It may be that families who were more pleased with their acute trial participation were more likely to return, but we would have expected those who were more symptomatic at the end to be less pleased. These families may also have had more overall resources and support, leading to a better outcome, or they may have believed they would achieve additional benefit from participating once again in a follow-up of the treatment study, all of which could bias these results. Third, half of participants were prescribed psychotropic medication at the follow-up visit, which likely impacted some outcomes. Finally, contextual variables other than those assessed in this study could have contributed to stability or improvement in functioning during this time period. For example, both those youth who started or continued in therapy and those who started or continued taking Ω3 were doing better at follow-up. Perhaps families who continued to actively seek intervention had other intangible (or at least unmeasured by this

study) characteristics, such as hope in improvement or ongoing encouragement and engagement in the child's life that enhanced recovery.

However, this study also has several notable strengths. First, it is one of the longest naturalistic follow-up studies available for youth with DSD or BPSD (mean follow-up was 3½ years). Second, it tracked outcomes for participants in the first combined trial of Ω3 and psychotherapy for youth with mood disorders. Third, as recommended by The President's New Freedom Commission on Mental Health (2003), functional outcomes beyond symptom remission were measured.

Conclusions

The search for treatments that ameliorate depressive and bipolar spectrum disorders in youth continues. This study suggests that intervention with Ω3 and/or IF-PEP has some consumer appeal and may provide some broad-based benefits beyond symptom severity reduction. Manic symptoms, executive functioning, and global functioning remain comparable to end of acute treatment. While depressive symptom severity increased for the overall sample from end of acute treatment to follow-up, those who persisted in utilizing Ω3 and/or psychotherapy had lower depressive symptom severity than those who did not utilize these interventions. Meaningful improvements in child and family functioning persist 2–5 years post-acute intervention with Ω3 and/or IF-PEP in the 40% of families who returned to this follow-up. These findings underscore the importance of assessing functioning in addition to symptom severity in clinical practice. A large multisite investigation with a long-term follow-up is needed to confirm these findings; extended follow-up should be an integral part of that study, with a consent process setting the expectation of returning to improve the follow-up rate. Finally, it must be emphasized that the field remains in need of interventions that provide sustained remission of mood symptoms in youth.

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HIGHLIGHTS

- Depression and bipolar disorder in youth have high rates of relapse and conversion.
- Long-term follow-up studies of interventions for depression and bipolar disorder in youth are very limited.
- Psychoeducational psychotherapy (PEP) and omega-3 fatty acids (Ω3) show promise for clinical improvement over time in youth with mood disorders.
- Improvements in overall functioning, not just reductions in symptom severity, are relevant outcomes.

Table 1.

Follow-Up Mood and Functioning Scores Compared to Baseline and End of RCT

	Means			Change from Baseline			Change from RCT End		
	Baseline	**End of RCT**	**Follow-up**	***t***	***p***	***d***	***t***	***p***	***d***
CDRS-R	40.6	29.1	35.4	−2.13	.040	−.35	7.69	.002	.71
YMRS	24.2	19.2	17.5	−1.91	.080	−.72	.496	.629	−.18
BRIEF	70.3[†]	66.8	64.5	−4.07	.000	−.60	−1.06	.297	−.21
CGAS	50.6	59.3	59.2	3.89	.000	.63	−.194	.848	−.03

Note. CDRS-R = Children's Depression Rating Scale-Revised. YMRS = Young Mania Rating Scale. BRIEF = Behavior Rating Inventory of Executive Functioning. CGAS = Children's Global Assessment Scale

[†]Measure given at Screen, not Baseline.

Table 2.

Linear Mixed-Effects Model Results for Use Omega-3 and Psychotherapy after the Acute Trial on Mood Symptoms

Measure	Source	Estimate	df	t	Sig.
CDRS	Intercept	66.79	134.66	2.83	.005
	Ω3After OATS (Reference: No 03)				
	Ω3	−36.54	126.33	−.387	.699
	Timepoint (Reference: Endpoint)				
	Follow-up	527.6	209.99	13.05	.000
	Tx*Time Interactions (Time = Follow-up; Reference: No Ω3*Time)				
	Ω3*Time	−520.56	209.99	−3.17	.002
CDRS	Intercept	80.86	93.44	3.30	.001
	Tx After OATS (Reference: No Tx)				
	Tx	−53.771	106.60	−1.17	.246
	Timepoint (Reference: Endpoint)				
	Follow-up	708.87	239.83	20.77	.000
	Tx*Time Interactions (Time = Follow-up; Reference: No Tx*Time)				
	Tx*Time	−702.42	239.84	−11.33	.000
YMRS	Intercept	18.13	11.08	8.37	.000
	Ω3 After OATS (Reference: No 03)				
	Ω3	−4.13	15.43	−1.84	.156
	Timepoint (Reference: Endpoint)				
	Follow-up	−2.56	13.42	−1.84	.088
	Tx*Time Interactions (Time = Follow-up; Reference: No Ω3*Time)				
	Ω3 *Time	1.06	13.40	.563	.583
YMRS	Intercept	17.78	1E.21	7.76	1.00
	Tx After OATS (Reference: No Tx)				
	Tx	−1.70	56.99	−.594	.555
	Timepoint (Reference: Endpoint)				
	Follow-up	−1.11	1.E+23	−.495	1.00
	Tx*Time Interactions (Time = Follow-up; Reference: No Tx*Time)				
	Tx *Time	−1.61	1.E+23	−.614	1.00

Notes. CDRS = Children's Depression Rating Scale. YMRS = Young Mania Rating Scale. Tx = Psychotherapy. Ω3 = Omega-3.

Table 3.

Parent Report of Symptom and Family Functioning Improvements.

Parent Report - Child's Functioning Improved	**%**	**Parent Report - Family Functioning Improved**	**%**
Ability to cope with stress	50%	I felt more hopeful	63%
Ability to get along	28%	Family communication	58%
School - grades/behavior	21%	My child and I argued less	29%
Eating habits	13%	My children argued less	21%
Sleep habits	11%	My own mood improved	18%
Exercise habits	8%	Other[b]	16%
Aggression	8%	My family engaged in more fun activities together	13%
Other[a]	3%	My partner and I argued less	8%
Any type of improvement endorsed during RCT	**84%**	**Any type of family function improvement endorsed during RCT**	**87%**
Any type of improvement endorsed after RCT	**82%**	**Any type of family function improvement endorsed after RCT**	**74%**

Note.

[a]1 each responded - Started counseling; worries.

[b]1 each responded - Receiving diagnosis of ODD was eye-opening/helped us understand child more; I understand my child more; my spouse understands our child more; child is more hopeful; the parenting tools I learned for one child applied to the whole family; I learned the importance of communication and counseling.

Table 4.

Parent and Youth Report of Tools Gained from Participating in the Study.

Informant	Item	Mean±SD*
Parent		
	Better understanding of mood disorders	5.5±1.7
	Better able to manage child's feelings and behaviors	4.5±1.7
	Overall helpfulness of participation for the family	4.6±1.5
	Better able to talk to their child's school about their child's needs	5.0±1.9
	**Linked their child to appropriate referral sources following the study	4.4±1.7
	*Linked parents to mental health services for themselves either during or after the study	3.8±1.5
	*Located appropriate services for other family members	3.1±1.4
Youth		
	Better understanding of mood disorders	5.2±1.4
	Better ability to manage their feelings and behaviors	5.2±1.5
	Improvement in family life	4.7±1.4
	*Helped with talking to their school about their needs	4.3±2.0
	*Linked them to appropriate referral sources following the OATS study	4.9±1.7

Notes.

*1–7 Scale, 7 most desirable;

**If marked not applicable, no score was assigned.

Table 5.

Parent Report of Reasons for Improvements.

Child Functioning Improved - Active Treatment Reasons‡	**%**	**Child Functioning Improved - Study Interviews Reasons**	**%**
My child learned new skills	76%	Child's understanding of him/herself increased	50%
Study pills†	59%	My child felt supported	44%
My understanding of my child improved	52%	Understanding of my child increased	42%
I learned new ways to interact with my child	48%	I learned new ways to interact w my child	34%
My child felt supported in therapy	43%	Multivitamin	11%
Staff helped me communicate my child's needs to school	33%	Other[a]	13%
Family Functioning Improved - Active Treatment Reasons ‡	**%**	**Family Functioning Improved - Study Interviews Reasons**	**%**
My understanding of my child improved	71%	My understanding of my child increased	47%
My family learned new skills	71%	My family felt supported	42%
I learned new ways to interact with my child	67%	I learned new parenting strategies	26%
I learned new coping skills	57%	New ways to interact with my child	26%
My family felt supported	48%	I learned new coping skills	24%
I learned new parenting strategies	43%	My family learned new skills	21%
Staff helped me communicate my child's needs to school	33%	Decreased family stress	8%
Study pills†	18%	Other[b]	8%
		Multivitamin	5%

Note.

‡Includes only those in the relevant active treatment condition (i.e., skills-in IF-PEP; study pills-in Ω3).

†Includes only those in the active Ω3 condition.

[a]1 each responded - Filling out mood questionnaires may have helped my child be more aware of his/her moods and help him/her self-regulate; Parent saw areas where she/he needed to change approach toward child; child felt happy coming to OATS visits; child felt like others cared about him/her; my child started taking Omega-3s after study completion.

[b]1 each responded - my child felt more support; my child was exercising more; the time that I spent with my child was fun.

Table 6.

Child Report of Child and Family Functioning Improvements.

Child Functioning Improved	**%**	**Family Functioning Improved**	**%**
Calmed down	59%	My family communicated better	50%
Felt better about myself	56%	My parents and I argued less	38%
Learned new coping strategies	50%	My parents felt better	29%
Got along better with others	32%	I argued less w my brother(s)/sister(s)	26%
Did better in school	29%	My family did more fun things together	21%
Ate healthier/ healthier amounts	21%	My parents argued less	9%
Slept better, Exercised more (each endorsed)	15%	Other[b]	6%
Other[a]	9%		
Any type of symptom improvement endorsed	**82%**	**Any type of family function improvement endorsed**	**79%**

Note.

[a] 1 each responded - felt more comfortable, learned strategies to cope with fears, mood swings.

[b] 1 each responded with – I got along with people a bit better; fun experience, was uplifting in some ways.

Table 7.

Child Report of Reasons for Improvements.

Child Functioning Improved - Active Treatment Reasons ‡	**%**	**Child Functioning Improved - Study Interviews Reasons**	**%**
I learned new skills	84%	I learned more about myself	35%
I learned new ways to talk and behave with my parents	79%	I learned new skills	29%
Therapist cared about me	58%	Interviewer cared about me	29%
Study pills †	47%	Parents treated me differently	29%
I learned more about myself	42%	I learned new ways to talk and behave with my parents	24%
Staff helped me/my parent(s) get school help	11%	Multivitamin	3%
Family Functioning Improved - Active Treatment Reasons ‡	**%**	**Family Functioning Improved - Study Interviews Reasons**	**%**
I learned new ways to talk and behave with my parents	93%	I learned more about myself	29%
My family learned new skills	73%	I learned new coping skills	29%
I learned more about myself	67%	My family learned new skills	27%
Our therapist cared about my family	53%	My family was less stressed	27%
Study pills †	47%	Our interviewer cared about our family	21%
Staff helped me/my parent(s) get school help	20%	I learned new ways to talk and behave with my parents	21%
		My parents treated me differently	20%
		Other [a]	9%
		Multi-vitamin	3%

Note.

† Includes only those in an active Ω3 condition.

‡ Includes only those in the relevant active treatment condition (i.e., skills-in IF-PEP; study pills-in Ω3).

[a] 2 responded – I don't know; 1 responded with "MF PEP".