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SHORT COMMUNICATION

Reduced mania and depression in juvenile bipolar disorder associated with long-chain ω-3 polyunsaturated fatty acid supplementation

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Long-chain ω-3 polyunsaturated fatty acid (LCn-3PUFA) supplementation may improve symptoms of depression in children and bipolar disorder (BD) in adults. No studies have examined the effectiveness of LCn-3PUFA supplementation in the treatment of mania and depression in juvenile BD (JBD) when given as an adjunct to standard pharmacological treatment. Eighteen children and adolescents with JBD received supplements containing 360 mg per day eicosapentaenoic acid (EPA) and 1560 mg per day docosahexaenoic acid (DHA) for 6 weeks in an open-label study. Intake and fasting red blood cell (RBC) LCn-3PUFA, mania, depression and global function were assessed before and after supplementation. RBC EPA and DHA were significantly higher following supplementation. Clinician ratings of mania and depression were significantly lower and global functioning significantly higher after supplementation. Parent ratings of internalizing and externalizing behaviours were also significantly lower following supplementation. A larger randomized controlled trial appears warranted in this participant population.
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Keywords: ω-3; EPA; DHA; children and adolescents; psychiatry; juvenile bipolar disorder

Introduction

The diagnosis of juvenile bipolar disorder (JBD) in children and adolescents is becoming increasingly accepted. The lifetime prevalence of JBD (approximately 1–2%) is similar to adults (Lewinsohn *et al*., 2000). The use of first-line mood-stabilizing medications, such as lithium and valproate, has been associated with adverse effects including gastrointestinal upset, thyroid effects, weight gain and increased triglycerides (Wozniak *et al*., 2007), leading to impaired quality of life and decreased medication compliancy. Safer and alternative treatments improving functioning or decreased requirements for standard mood-stabilizing medications are needed.

Supplementation with long-chain ω-3 polyunsaturated fatty acids (LCn-3PUFA) may improve symptoms of bipolar disorder (BD) in adults (Stoll *et al*., 1999) and depression in children (Nemets *et al*., 2006) when given as an adjunct to standard pharmacotherapy and may improve symptoms of mania in young children with BD when given as monotherapy (Wozniak *et al*., 2007). No studies have examined the effects of LCn-3PUFA supplements in the treatment of mania and depression in JBD when given as an adjunct to standard pharmacotherapy.

Methods

A total of 18 participants (12 female, mean age = 16.1 ± 0.81 years; 6 male, mean age = 13.0 ± 1.06 years) with JBD

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received three 1000 mg capsules containing tuna oil twice a day for 6 weeks in an open-label manner. Capsules contained 60 mg/g eicosapentaenoic acid (EPA) and 260 mg/g docosahexaenoic acid (DHA) and participants received a total dose of 360 mg per day EPA and 1560 mg per day DHA.

Participants were included in the study, if they met diagnostic criteria for BD I ($n=7$), BD II ($n=6$) or BD not otherwise specified ($n=5$) as specified in the *Diagnostic and Statistical Manual of Mental Disorders*, fourth edn, Text Revision and were prescribed mood-stabilizing medication (lithium = 9, valproate = 7 and quetiapine = 2). The mean time from diagnosis to study enrolment was 1.6 ± 0.3 years and 10 participants had at least one co-morbid diagnosis including psychosis, attention-deficit hyperactivity disorder or generalized anxiety disorder. Several participants received other medication in addition to a primary mood-stabilizer, with the most common being risperidone, dexamphetamine and selective serotonin re-uptake inhibitors. Details of inclusion and exclusion criteria have been described previously (Clayton *et al*., 2008). Participants had not taken LCn-3PUFA supplements within the previous 12 weeks and were not receiving any medications that affected lipid metabolism or blood coagulation.

Symptoms of mania (Young Mania Rating Scale, YMRS), depression (Hamilton Depression Rating Scale, HAM-D) and global functioning (Global Assessment Scale for Children, C-GAS) were assessed by clinicians, and internalizing and externalizing behaviour (Child Behaviour Checklist—Parent Report, CBCL-PR) were assessed by parents before and after supplementation. Fasting blood samples were collected at each assessment and red blood cells (RBCs) were separated from plasma for analysis of fatty acids using gas chromatography. Details of the assessment of mood, behaviour and RBC fatty acids have been described previously (Clayton *et al*., 2008).

All procedures were approved by the Hunter New England Area and University of Newcastle Human Research Ethics Committees. Parents/guardians gave written informed consent before the study. The study was registered with the Australian Clinical Trials Registry (www.actr.org.au) ACTRN: ACTRN012606000440527.

Changes in measures were analysed by repeated measures analysis using the MIXED Model procedure in the SAS program (Clayton *et al*., 2008). Percentage changes in psychological measures were correlated with baseline measures and changes in RBC LCn-3PUFA by Pearson correlation. Behaviour ratings could not be collected from one participant and RBCs could not be isolated from another participant after supplementation.

Results

Three participants withdrew during the study due to gastrointestinal disturbance (including bloating, increased flatulence and cramping). Supplement compliance (estimated by capsule count-back and interview with participants and parents/guardians) was 84.8 ± 4.1% for participants who completed the study. RBC EPA and DHA increased following supplementation (Figure 1). The ω-3 index (RBC EPA + DHA%, Harris, 2007) increased from 4.2 ± 2.1 to 7.8 ± 1.9.

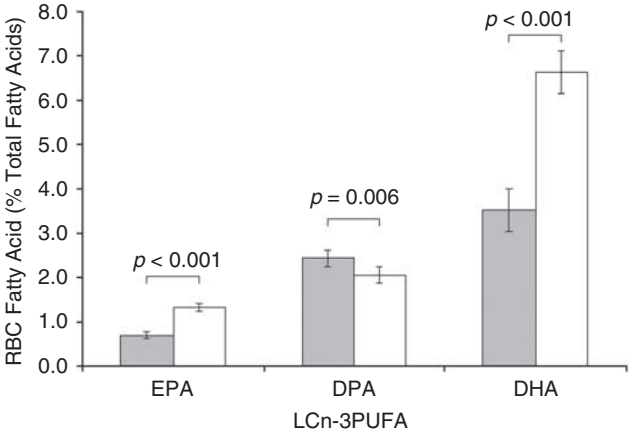

Figure 1 Change in red blood cell (RBC) eicosapentaenoic acid (EPA), docosapentaenoic acid (DPA) and docosahexaenoic acid (DHA) as a percentage of total fatty acids in participants with juvenile bipolar disorder (JBD) before (shaded bars) and after (unshaded bars) the consumption of 360 mg per day EPA and 1560 mg per day DHA for 6 weeks. Data are least-squares means ± standard error of the least-squares means.

Table 1 Clinician and parent ratings of mood and behaviour before and after the consumption of 360 mg per day EPA and 1560 mg per day DHA for 6 weeks by children and adolescents diagnosed with JBD

Scale/subscale[a]	*Baseline*	*Post intervention*	P-*value*
Clinician ratings			
Mania	13.1 (± 1.66)	6.3 (± 1.82)	0.004
Depression	12.0 (± 1.52)	5.6 (± 1.64)	0.002
Global functioning	50.8 (± 2.20)	65.0 (± 2.41)	<0.001
Parent ratings			
CBCL-PR—internal	71.2 (± 2.67)	65.7 (± 2.80)	0.009
CBCL-PR—external	67.3 (± 2.50)	62.5 (± 2.60)	0.014
CBCL-PR—total	71.6 (± 2.67)	64.8 (± 2.87)	0.010

Abbreviation: CBCL-PR, Child Behaviour Checklist—Parent Report.
[a]Mania, Young Mania Rating Scale (YMRS); Depression, Hamilton Depression Rating Scale (HAM-D); Global functioning, Global Assessment Scale for Children (C-GAS).

Clinician ratings of mania and depression were significantly lower and global functioning significantly higher following supplementation (Table 1). Parent ratings of internalizing and externalizing behaviours were also significantly improved after treatment. Following a secondary intention-to-treat analysis using the last observation carried forward procedure, symptom change over time was still significant (data not shown).

Correlational analyses revealed a positive association between participant age and improvement in parent ratings of internalizing symptoms ($r = 0.59$, $P = 0.045$) and number of years between diagnosis and study enrolment and improvement in parent ratings of externalizing symptoms ($r = 0.56$, $P = 0.046$). Change in parent rated externalizing symptoms was diminished when participants received antipsychotic medication directed to agitation or aggression ($n = 3$) compared with all other participants ($n = 11$, symptom change $= 2.2 \pm 3.9$ versus $-9.6 \pm 2.2\%$, $F = 7.00$, $P = 0.023$). Changes in mood or behaviour were not significantly related to gender, primary diagnosis, mood-stabilizing medication or changes in RBC LCn-3PUFA.

Discussion

Although improvements in mania in this study did not reach 50%, indicating a relatively small clinical response, depression change was greater than 50%. Forty percent of participants also had 'Much' or 'Very much' improved symptoms according to the Clinical Global Improvements scale, similar to LCn-3PUFA supplementation as monotherapy (Wozniak *et al*., 2007). Current changes were in addition to improvements that may have occurred with previous pharmacological treatment, as participants were stabilized on their usual medication for at least 6 weeks before the study. Parent ratings of internalizing and externalizing behaviour on the CBCL also improved following supplementation, similar to research with aggression (Itomura *et al*., 2005) and, were significantly related to age and time between diagnosis and study enrolment, respectively, which may be indicative of spontaneous improvement rather than a specific response to LCn-3PUFA supplementation. Changes in symptoms, however, were not significantly correlated to changes in RBC LCn-3PUFA. These findings should be interpreted with caution, however, owing to the small sample size.

Although the direct link between LCn-3PUFA and decreases in mania and depression cannot be elucidated from the current open-label design, supplementation significantly increased EPA and DHA in RBC membranes. EPA and DHA are selectively incorporated into the phospholipid fraction of RBC membranes (Galloway *et al*., 1985) and, as neurotransmitter receptors are affected by the fluidity of phospholipid membranes, receptor 'function' could be changed in 6 weeks following LCn-3PUFA supplementation. Increased membrane fluidity following LCn-3PUFA supplementation is associated with a general dampening of signal transduction pathways. These and other mechanisms linking LCn-3PUFA supplementation with improvement in BD have been reviewed previously (Clayton *et al*., 2007).

LCn-3PUFA supplementation in conjunction with standard pharmacotherapy may lead to additive improvements in membrane function, as lithium and valproate treatment is associated with decreased AA turnover without altering DHA turnover (Chang *et al*., 2001). Although symptom improvement in this study was not related to primary mood-stabilizing medication, changes in parent rated externalizing symptoms were diminished when participants without a co-morbid diagnosis of psychosis received antipsychotic medication. Further studies should determine whether improvements are consistent for different medications or whether medication dose could be decreased to reduce side effects, while maintaining similar symptom improvement.

There are obvious limitations to conducting an open-label study, including a lack of blinding and clinician and parent bias. Therefore, the improvement in symptoms in this study may be due to factors other than LCn-3PUFA. Despite these limitations, given the improved RBC LCn-3PUFA and reduced symptoms of JBD, together with previous results in adults, there appears to be enough evidence to warrant a large prospective randomized controlled trial in this participant population. Future studies should also consider using more concentrated forms of LCn-3PUFA to reduce the burden of taking the supplements in addition to standard medications.

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