A Double-Blind, Placebo-Controlled Trial of Omega-3 Fatty Acids in Tourette's Disorder

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KEY WORDS

Tourette's disorder, omega-3 fatty acids, obsessive-compulsive disorder, double-blind, placebo-controlled

ABBREVIATIONS

ADHD—attention deficit/hyperactivity disorder
CDRS-R—Children's Depression Rating Scale – Revised
CGI-I—Clinical Global Impression-Improvement scale
CY-BOCS—Children's Yale-Brown Obsessive Compulsive Scale
DHA—docosahexaenoic acid
EPA—eicosapentaenoic acid
MASC—Multidimensional Anxiety Scale for Children
OCD—obsessive-compulsive disorder
O3FA—omega-3 fatty acid
NYU—New York University
TD—Tourette's Disorder
YGTSS—Yale Global Tic Severity Scale

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WHAT'S KNOWN ON THIS SUBJECT: Omega-3 fatty acids (O3FA) are commonly used as complementary treatments in pediatric psychiatric disorders, including Tourette's disorder (TD), and are well known to have anti-inflammatory properties. However, no studies to date have examined the effects of O3FA on pediatric TD.

WHAT THIS STUDY ADDS: This is the first double-blind, placebo-controlled clinical trial of O3FA in pediatric TD. The results indicate that O3FA supplementation may be beneficial in the reduction of tic-related impairment for some children and adolescents with TD, but not tics per se.

abstract

OBJECTIVE: Clinical observations have suggested therapeutic effects for omega-3 fatty acids (O3FA) in Tourette's disorder (TD), but no randomized, controlled trials have been reported. In a placebo-controlled trial, we examined the efficacy of O3FA in children and adolescents with TD.

METHODS: Thirty-three children and adolescents (ages 6–18) with TD were randomly assigned, double-blind, to O3FA or placebo for 20 weeks. O3FA consisted of combined eicosapentaenoic acid and docosahexaenoic acid. Placebo was olive oil. Groups were compared by using (1) intent-to-treat design, with the last-observation-carried-forward controlling for baseline measures and attention-deficit/hyperactivity disorder via (a) logistic regression, comparing percentage of responders on the primary Yale Global Tic Severity Scale (YGTSS)-Tic and secondary (YGTSS-Global and YGTSS-Impairment) outcome measures and (b) analysis of covariance; and (2) longitudinal mixed-effects models.

RESULTS: At end point, subjects treated with O3FA did not have significantly higher response rates or lower mean scores on the YGTSS-Tic (53% vs 38%; 15.6 ± 1.6 vs 17.1 ± 1.6 , $P > .1$). However, significantly more subjects on O3FA were considered responders on the YGTSS-Global measure (53% vs 31%, $P = .05$) and YGTSS-Impairment measure (59% vs 25%, $P < .05$), and mean YGTSS-Global scores were significantly lower in the O3FA-treated group than in the placebo group (31.7 ± 2.9 vs 40.9 ± 3.0 , $P = .04$). Obsessive-compulsive, anxiety, and depressive symptoms were not significantly affected by O3FA. Longitudinal analysis did not yield group differences on any of the measures.

CONCLUSIONS: O3FA did not reduce tic scores, but it may be beneficial in reduction of tic-related impairment for some children and adolescents with TD. Limitations include the small sample and the possible therapeutic effects of olive oil. *Pediatrics* 2012;129:e1493–e1500

Tourette's disorder (TD), a childhood-onset neuropsychiatric disorder, is characterized by multiple, waxing and waning motor and vocal tics. Converging lines of evidence suggest that the pathophysiology of TD entails alterations within the central monoamine system (eg, dopamine, serotonin) and in frontostriatal circuits.¹ More recently, the role of inflammatory processes has been linked to TD as well.² Although pharmacological treatments, such as α -adrenergic agonists and neuroleptics, are available, they either have limited efficacy, and/or are associated with significant adverse effects.¹ Consequently, there has been a surge in the use of complementary and alternative medications, such as omega-3 fatty acids (O3FAs), which are widely used in psychiatric disorders, including in TD.

O3FAs are long-chain polyunsaturated fatty acids of 18 to 22 carbon atoms in chain length with the first double bond between the third and fourth carbon atoms (n-3). They are essential FA that must be obtained from dietary sources, because humans cannot synthesize them. Docosahexaenoic acid (DHA: 22 carbon atoms and 6 double bonds) and eicosapentaenoic acid (EPA: 20 carbon atoms and 5 double bonds) are main forms of O3FA mostly derived from fish. Although plant foods and vegetable oils lack EPA and DHA, some contain varying amounts of FA with fewer carbons, such as α -linolenic acid, which can be metabolized into the longer-chain EPA and DHA in the human body.

Accumulating evidence from animal and human studies documents that O3FAs affect central monoamine activity^{3–7} and have immunomodulatory properties,^{8–11} functions that are relevant to TD. In addition, O3FAs are central components of glial and neuronal membrane phospholipids and play critical roles in neuronal activity and synaptic transmission.^{12,13} Research indicates that O3FAs, specifically DHA, are critical

for fetal brain development,^{14–17} further suggesting a possible role in TD. One retrospective report of 10 children (ages 8–13 years) with a primary diagnosis of tic disorder, TD, and/or obsessive-compulsive disorder (OCD) receiving at least 6 consecutive weeks of 500 to 1500 mg/d of essential FA supplementation (fish or flax seed oil) reported that 6 of the 10 subjects (60%) experienced a 15% to 100% reduction in tic and anxiety symptoms after 6 weeks of treatment, and that the supplements were well tolerated.¹⁸ These observations suggest that O3FAs may be effective in TD.

To our knowledge, there has been no systematic study of O3FA efficacy in TD. The aim of the current study was to test the efficacy of O3FA (combined EPA+DHA ratio of 2:1) in a randomized, double-blind, placebo-controlled trial of children and adolescents (ages 6–18) with TD. We hypothesized that orally administered supplemental O3FA would reduce tic severity compared with a placebo (olive oil) in children and adolescents with TD as measured on the Yale Global Tic Severity Scale (YGTSS)-Tic. Secondary outcomes included YGTSS-Impairment and YGTSS-Global, and obsessive-compulsive, anxiety, and depressive symptoms, as well. We examined these in light of the high comorbidity between TD and mood and anxiety disorders, particularly with OCD, and the possibly linked pathophysiology.¹⁹

METHODS

Subjects

Thirty-three children and adolescents (6 through 18 years old) with a primary diagnosis of TD as defined in the *Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition, Text Revision*²⁰ were recruited from the greater New York metropolitan area, the Tics and Tourette's Clinical and Research Program at the New York University (NYU) Child Study Center, and

through referrals from the Tourette Syndrome Association.

All subjects were evaluated by a board-certified child and adolescent psychiatrist with expertise in TD and OCD (V.G. or B.C.) by using the Schedule for Affective Disorders and Schizophrenia – Present and Lifetime Version for Children,²¹ a semistructured diagnostic interview to establish psychiatric diagnoses. Tic and OCD symptom severities were rated on the YGTSS²² and the Children's Yale-Brown Obsessive Compulsive Scale (CYBOCS),²³ respectively. Baseline medical evaluation consisted of medical history, a physical examination, and laboratory studies (complete blood cell count, metabolic panel, liver and thyroid function tests, electrocardiogram, urine toxicology test, and urine pregnancy test for sexually active females). Laboratory data had to be within normal limits before treatment initiation.

To qualify for the study, subjects had to meet *Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition, Text Revision* criteria for TD and have a minimum YGTSS-Global Severity Score (YGTSS-Global) of 20, which indicates at least mild tic severity. We excluded subjects who had received immune-affecting medications (other than psychotropic medications) during the previous month, or who had an immunologic or hematologic disorder, Sydenham chorea, a significant medical or neurologic disorder, bipolar disorder, major depressive disorder, pervasive developmental disorder, intellectual disability, psychotic disorder, a substance-related disorder in the past 12 months, or a positive urine toxicology test, and, in females, a positive urine pregnancy test. Previous use of O3FA was also exclusionary. Concomitant psychotropic medication for tics or other current psychiatric disorders was not exclusionary, provided patients had clinically significant TD symptoms causing distress and/or impairment, had remained on a stable dose for at least 3

months before enrollment, and did not intend to alter their medication during the study.

The study was approved by the NYU Institutional Review Board. For participants age 18, written informed consent was obtained; those under age 18 provided assent and a parent provided written consent.

Study Treatment

Subjects were randomly assigned by the NYU investigational pharmacist to receive O3FA or placebo for 20 weeks. Investigators, subjects, and parents were blind to treatment assignment. Depending on age and ability to swallow capsules, children were prescribed small (500 mg) or large (1000 mg) capsules of O3FA or matching placebo. In all capsules, 20% of the mass was the inert capsule material. Of the remaining 80% of the O3FA capsules, 65% was O3FA, with an EPA:DHA ratio of 2:1 (ie, total 250 mg or 500 mg of EPA+DHA per capsule). In the placebo capsules, 70% of the remaining material was oleic acid (total 280 mg or 560 mg of olive oil per capsule). The remainder of the internal material was saturated fats (~10%), monounsaturated fats (~15%), and omega-6 fatty acids (~5%). Both O3FA and placebo capsules were identical in color (darkly colored) and were vanilla flavored and scented to minimize the chances of accurately guessing the drug assignment. All capsules were manufactured by Ocean Nutrition Canada Ltd. Ongoing testing was conducted by Siliker Canada Co. to ensure adequate levels and stability of O3FA and olive oil in the capsules, and by Research and Productivity Council to ensure the absence of any contaminants, including toxic substances. A combined product was selected based on studies in psychiatric patients that used an EPA:DHA ratio of 2:1.^{24–26} Notably, studies that used DHA alone had negative results, whereas results of the

studies that used the combined product were positive.^{24–29} In addition, evidence indicates that, although both EPA and DHA are implicated in TD, they putatively act through different mechanisms, with EPA more anti-inflammatory and DHA more neurotrophic. A relatively high maximum dose was selected to avoid a potentially ineffective low dose. The flexible dose titration, based on clinical response and side effects, reduced the likelihood of adverse events that may have been related to a higher dose. Furthermore, at the time of the study, high doses of O3FA were safely and effectively administered in adults and children with bipolar disorder.³⁰

The child and parent attended weekly visits during the first 4 weeks, biweekly during the following 8 weeks, and monthly thereafter (at weeks 16 and 20). Treatment was initiated at 500 mg/d O3FA or matching placebo (1 large capsule or 2 small capsules), and gradually titrated upward by increments of 1 small (250 mg) or 1 large capsule (500 mg) based on the appropriate capsule size, to a possible maximum dose of 6000 mg/d O3FA or 12 large placebo capsules. Dose titration depended on the subject's improvement since the initial visit. For instance, if the TD-Clinical Global Impression-Improvement scale (CGI-I)³¹ was very much improved or much improved, the dose remained unchanged; if ratings were minimally improved, no change, or worse, the dose was increased to the next level, but only in the absence of significant adverse effects. Subjects who were reluctant to increase the dose because of difficulty swallowing a large number of capsules were allowed to remain on the same dose. Analysis of CGI-I outcomes in the O3FA and placebo groups is presented in the Supplemental Information.

Study Measures

The YGTSS-Tic (Total Tic subscale) was selected as the primary outcome measure,

because it reflects domains of both vocal and motor tic severity such as number, frequency, intensity, complexity, and interference. As secondary outcomes, we also examined the YGTSS-Global and YGTSS-Impairment. The YGTSS-Global consists of 2 subscales: the YGTSS-Tic, and a tic-related impairment score (YGTSS-Impairment) that reflects tic-related impairment on self-esteem, school, and social and family functioning. These subscales are not redundant, because it is not unusual for children with high scores in frequency or complexity on the YGTSS-Tic subscale to have little tic-related functional impairment; conversely, children with low YGTSS-Tic scores may have significant functional impairment, if self-esteem, school, social, or family life are impacted significantly.³² The sum of the total tic and impairment scores, the YGTSS-Global, ranges from 0 to 100. OCD symptoms were rated on the CY-BOCS. Consistent with previous studies, treatment response for tic symptoms was defined a priori as a 30% or greater baseline-to-end point reduction in tic symptoms as measured on the YGTSS-Tic, YGTSS-Global, and YGTSS-Impairment scales,^{33,34} and, for OCD symptoms,³⁵ as a 25% or greater baseline-to-end point reduction on the CY-BOCS. The YGTSS and CY-BOCS were completed at each visit by a child and adolescent psychiatrist. Depressive and anxiety symptoms were assessed at baseline and end point by using the Children's Depression Rating Scale – Revised (CDRS-R) and Multidimensional Anxiety Scale for Children (MASC), respectively.

At each visit, the child and adolescent psychiatrist completed a TD-CGI-I scale to rate improvement of tic symptoms specifically. The CGI-I is a 7-point clinical rating scale with lower values reflecting more favorable responses (ie, 1 or 2 = very much improved and much improved; 3 or above = minimally improved, no change and worse).

Adverse effects were systematically assessed at each visit and recorded on the Safety Monitoring Uniform Report Form. Heart rate, blood pressure, and weight were also obtained at each visit. Because increased bleeding time has been associated with high doses of O3FA, we monitored platelet count, prothrombin time, and partial thromboplastin time.

Statistical Analyses

To examine whether treatment groups differed significantly at baseline, Fisher exact tests were applied to dichotomous measures (ie, attention-deficit/hyperactivity disorder [ADHD] and OCD diagnoses, medication status, gender), and exact Mann-Whitney tests to continuous variables (ie, age, YGTSS-Tic, YGTSS-Global, YGTSS-Impairment, CY-BOCS, CDRS-R, MASC). Within-treatment group differences relied on Wilcoxon signed rank tests that compared baseline and end point scores (with last observation carried forward to week 20).

An intent-to-treat design, with last observation carried forward, compared O3FA with placebo via (a) analysis of covariance comparing end point outcome scores as the dependent variable and treatment group as a nominal predictor variable, with baseline values as covariates. Analyses were repeated while controlling for any potential confounders identified above; (b) logistic regression comparing the percentage of responders on the primary (YGTSS-Tic) and secondary (YGTSS-Global, YGTSS-Impairment, CY-BOCS) outcome measures, controlling for baseline values and any potential confounder identified above; (c) in addition, the 2 groups were compared by using longitudinal mixed-effects models analysis (described in detail in the Supplemental Information).

Statistical significance was defined as a 2-sided P value $\leq .05$. SAS version 9.0 (SAS Institute, Cary, NC) with SAS

Proc MIXED and GENMOD, and StatXact version 6.0 (Cytel Software Corporation, Cambridge, MA) were used.

RESULTS

Sample Characteristics

Clinical and demographic profiles are presented in Table 1. The rate of ADHD was significantly lower in the O3FA than the placebo group (41% vs 81%, respectively; $P = .03$); therefore, analyses were repeated while controlling for ADHD in addition to baseline measures (presented in Supplement Information). Of the 33 subjects enrolled, 8 (24%) did not complete the full 20 study weeks: 3 from the O3FA and 5 from the placebo group (reasons for dropout are detailed in the Supplemental Information). Of the 33 subjects, 25 (76%) remained on psychotropic medication throughout the study (17 with one, 6 with two, and 1 with three medications, detailed in the Supplemental Information).

Mean end doses of O3FA were 4074 mg/d of EPA+DHA; and 4865 mg/d of oleic acid in the placebo group. Responders on O3FA were receiving 3778 mg/d and nonresponders were receiving 4406 mg/d. In the placebo group, responders were receiving 4536mg/d and nonresponders were receiving 5015mg/d.

Within Treatment Groups Changes From Baseline to End Point

Both groups showed significant reductions on the YGTSS and CY-BOCS over time. (Means and standard deviations of severity scores at baseline and end point are presented in Table 2.)

Comparing End Point Scores Between Groups

Primary Outcome

Our hypothesis that subjects treated with O3FA compared with placebo would have fewer tics at end of study was not supported, because the groups did not differ on the YGTSS-Tic end point scores (15.6 ± 1.6 vs 17.1 ± 1.6 , $P > .1$).

Secondary Outcome Measures (YGTSS-Global and Impairment)

There was a significant advantage for children and adolescents on O3FA compared with placebo on the YGTSS-Global scores (postadjusted means: 31.7 ± 2.9 vs 40.9 ± 3.0 , $t = 2.14$, $df = 30$, $P = .04$, Fig 1, Table 2), and a trend in favor of O3FA on the YGTSS-Impairment scales (16.9 ± 2.1 vs 23.0 ± 2.2 , $t = 1.92$, $df = 30$, $P = .06$). No significant differences were found between the O3FA and placebo groups on any of the scales at weeks 6, 10, and 16.

TABLE 1 Demographic and Clinical Characteristics of Children and Adolescents with Tourette's Disorder in the O3FA and Placebo Treatment Groups

	O3FA (n = 17)	Placebo (n = 16)	P
Characteristic			
Age, y	11.9 $\pm$ 3.6	10.6 $\pm$ 2.3	>.1
Gender (female/male)	3/14 (18/82%)	3/13 (19/81%)	>.1
Psychotropic medication status (medication-free/medicated)	5/12 (29/71%)	3/13 (19/81%)	>.1
Baseline assessment scores			
YGTSS-Global, mean $\pm$ SD (range)	49.3 $\pm$ 9.1 (35–68)	44.8 $\pm$ 7.4 (34–70)	>.1
YGTSS-Tic, mean $\pm$ SD (range)	21.1 $\pm$ 5.7 (11–33)	20.4 $\pm$ 4.3 (9–30)	>.1
YGTSS-Impairment, mean $\pm$ SD (range)	28.2 $\pm$ 5.3 (20–40)	24.4 $\pm$ 6.3 (10–40)	>.1
CY-BOCS, mean $\pm$ SD (range)	9.7 $\pm$ 8.8 (0–27)	8.1 $\pm$ 7.2 (0–18)	>.1
CDRS-R, mean $\pm$ SD (range)	19.0 $\pm$ 2.5 (17–26)	19.9 $\pm$ 2.5 (17–27)	>.1
MASC, mean $\pm$ SD (range)	42.4 $\pm$ 11.9 (21–57)	48.9 $\pm$ 17.9 (20–86)	>.1
Current comorbid disorders			
Attention deficit hyperactivity disorder	7 (41%)	13 (81%)	<.05
OCD	8 (47%)	10 (63%)	>.1
Any non-OCD anxiety disorder	5 (29%)	4 (25%)	>0.1

TABLE 2 Mean Values at Baseline and Posttreatment in O3FAs and Placebo Groups

Measure	O3FA (n = 17)					Placebo (n = 16)					Treatment Differences Between Groups	
	Mean ± SD			Within-Group Difference		Mean ± SD			Within-Group Difference			
	Baseline	End Point ^a (CI)	Decrease ^b (%) ^c	Z	P	Baseline	End Point ^a (CI)	Decrease ^b (%) ^c	Z	P		
GTSS-Global	49.3 ± 9.1	31.7 ± 2.9 (25.7–37.7)	14.9 ± 12.1 (36)	9.54	<.0001	44.8 ± 7.4	40.9 ± 3.0 (34.7–47.1)	6.7 ± 11.6 (9)	9.53	<.0001	2.14	<.05
GTSS-Tic	21.1 ± 5.7	15.6 ± 1.6 (12.4–18.8)	5.2 ± 7.3 (26)	8.73	<.0001	20.4 ± 4.3	17.1 ± 1.6 (13.8–20.4)	3.6 ± 5.6 (16)	8.99	<.0001	0.69	>.1
GTSS-Impairment	28.2 ± 5.3	16.9 ± 2.1 (12.5–21.2)	9.7 ± 8.6 (40)	8.05	<.0001	24.4 ± 6.3	23.0 ± 2.2 (18.5–27.5)	3.1 ± 8.3 (6)	8.60	<.0001	1.92	.06
Y-BOCS	9.7 ± 8.8	5.9 ± 1.1 (3.6–8.3)	3.3 ± 5.3 (39)	2.90	.01	8.1 ± 7.2	4.4 ± 1.2 (2.0–6.8)	4.1 ± 6.3 (46)	3.77	.002	−0.90	>.1

An intent-to-treat analysis was used with the last observation carried forward. CI, 95% confidence interval.

^a Adjusted for baseline assessment scores.

^b Within-subject decrease.

^c Calculated by using adjusted end point scores.

FIGURE 1

Yale Global Tic Severity Scale (YGSS)-Global unadjusted means at each visit within each treatment arm over 20 weeks.

Obsessive-Compulsive, Depressive, and Anxiety Symptoms

There were no significant differences between the groups on CYBOCS, CDRS-R, and MASC scores.

Response Rates on O3FA and Placebo

Primary Outcome

There were no significant differences in response rates between O3FA and placebo on the YGTSS-Tic score with and without controlling for comorbid ADHD (53% vs 38%, $\chi^2 = 1.03$, $df = 1$, $P > .1$).

Secondary Outcome Measures

Significantly more subjects were considered responders (as defined above) in the O3FA-treated group than the placebo group on the YGTSS-Global scores (53% vs 31%, $\chi^2 = 3.79$, $df = 1$, $P = .05$), and on the YGTSS-Impairment scores

(59% vs 25%, $\chi^2 = 3.94$, $df = 1$, $P < .05$). Findings are summarized in Table 3.

Longitudinal Mixed Effects Models Analysis (Between-Groups Comparisons)

Although there were no significant differences on any of the outcome measures, moderate effect sizes were found in favor of O3FA on the YGTSS-Global (0.75) and the YGTSS-Impairment (0.89). Findings are detailed in Table 4.

Adverse Events

No significant treatment differences were found in adverse events, assessed at every visit on the Safety Monitoring Uniform Report Form. The treatment-related events most frequently reported in the O3FA group were headache ($n = 4$; dosages = 500, 1250, 3000, and 3000 mg/d), nausea/stomachache ($n = 4$; dosages = 1000, 2500, 5000, and 6000 mg/d), and diarrhea/loose stool ($n = 2$,

TABLE 3 Response Rates for Tic and Obsessive-Compulsive Symptom Ratings in the O3FAs and Placebo Groups

Measure	Response Rates			
	O3FA (n = 17)	Placebo (n = 16)	χ^2 ^a	P
YGSS-Global	53% (9/17)	31% (5/16)	3.79	.05
YGSS-Tic	53% (9/17)	38% (6/16)	1.03	>.1
YGSS-Impairment	59% (10/17)	25% (4/16)	3.94	<.05
CY-BOCS	47% (8/17)	50% (8/16)	0.16	>.1

YGSS response was defined as $\geq 30\%$ baseline-to-end point reduction. CY-BOCS response was defined as $\geq 25\%$ baseline-to-end point reduction. An intent-to-treat analysis was used with the last observation carried forward.

^a Adjusted for baseline assessment scores.

TABLE 4 Longitudinal Mixed-Effects Models Comparing - O3FAs and Placebo Groups

Measure	O3FA (n = 17) Mean ± SE				Placebo (n = 16) Mean ± SE				Treatment Group Differences			
	Baseline	End Point	Decrease	P	Baseline	End Point	Decrease	P	Decrease Difference	Effect Size	P	Power
YGTSS-Global	48.5 ± 2.5	35.8 ± 4.1	12.7 ± 3.3	.0001	44.5 ± 2.5	38.2 ± 4.2	6.2 ± 3.4	.06	6.4 ± 4.5	0.75	>.1	0.64
YGTSS-Tic	20.3 ± 1.2	16.2 ± 1.7	4.2 ± 1.5	<.01	18.5 ± 1.3	14.9 ± 1.8	3.6 ± 1.6	.02	0.5 ± 2.1	0.10	>.1	0.05
YGTSS-Impairment	27.9 ± 1.7	19.2 ± 2.9	8.7 ± 2.6	<.001	24.7 ± 1.7	21.4 ± 2.9	3.3 ± 2.7	>.1	5.4 ± 3.6	0.89	>.1	0.73
CY-BOCS	9.0 ± 1.8	6.5 ± 1.6	2.5 ± 1.3	.05	7.8 ± 1.9	3.4 ± 1.6	4.4 ± 1.3	.001	−2.0 ± 1.8	−0.24	>.1	0.13

Means and standard errors are adjusted and derived from the longitudinal mixed effects models used in the analysis.

dosages = 1000 and 1000 mg/d). All were tolerable and self-limited. One subject in the O3FA group experienced several nosebleeds and bruised easily (dosage = 1000 mg/d), and 1 subject in the placebo group had elevated clotting times at the midstudy blood draw (dosage = 3500 mg/d); however, all follow-up laboratory test results were within normal limits.

DISCUSSION

To our knowledge, this is the first randomized, double-blind, placebo-controlled trial that examines the efficacy of O3FA in children and adolescents with TD. Findings give some, but not strong, support to potential benefits of O3FA in ameliorating tic-related impairment, but not tics per se in children and adolescents with TD. Thus, significantly more patients treated with O3FA compared with placebo were responders at the end of the trial on the YGTSS-Global severity scale, as well as on the YGTSS-Impairment scale, but tic scores on the YGTSS-Tic subscale were not improved by O3FA. Similar results were found when we compared end point severity scores. With the use of the longitudinal mixed-effects models analysis, we did not detect significant group differences; however, we found moderate effect sizes in favor of O3FA on the YGTSS-Global and YGTSS-Impairment. Because the YGTSS-Global scale incorporates tic severity and functional impairment, and because we did not detect any significant differences with respect to tic severity per se, findings most likely were driven by a reduction in tic-related

impairment and an improvement in well-being. This finding may be related to O3FA therapeutic effects on depressive symptoms, for which there is some supportive clinical evidence.^{36,37} However, in our study, depressive and anxiety symptoms were not significantly improved in the O3FA arm. Nonetheless, follow-up studies in TD indicate that the functional impairment associated with TD is a key aspect of illness severity and, therefore, an essential target for treatment.³⁸

At the same time, although improvements in tic scores were not significantly different between the O3FA and placebo groups, the percent mean improvement of YGTSS-Tic scores for the O3FA group was 26%, which is consistent with results of other TD randomized controlled trials with risperidone (29%) and guanfacine (29.5%).^{39,40} This suggests that O3FA may have potential as an alternative treatment of tics as well. Percent mean improvement of YGTSS-Tic scores on placebo for other TD randomized controlled trials ranged from 0% to 7%, compared with 16% in this study.^{40–42} In addition, baseline tic severity scores in our sample of children and adolescents with TD are similar to those reported by others, suggesting that this clinical sample closely resembles those in other pediatric clinical TD samples. The small sample size may have contributed to our inability to detect treatment differences in tics. Another possible reason is the use of olive oil as the placebo. Olive oil has antioxidative properties and, as such, may have an independent therapeutic effect in TD.⁴³ Furthermore,

dietary olive oil intake can increase production of O3FA in the body⁴⁴ and increase the ratio of O3FA to omega-6FA in tissues, especially the brain, possibly leading to similar effects as with an O3FA-enriched diet.⁴⁵

The lengthy 20-week study was designed to allow for a slow upward dose titration. There were no significant treatment differences in outcome at weeks 6, 10, or 16, suggesting that extended exposure to O3FA may be required to yield therapeutic benefit. It is unclear whether this is a function of time or dose, and findings might differ with more rapid titration. Finally, results do not support the expectation that O3FAs are effective in the reduction of OCD symptoms in children and adolescents with TD. This finding is consistent with a preliminary study of EPA alone in adults with OCD.⁴⁶

The study has several limitations. The small sample size may have reduced the possibility of detecting treatment differences, such as in tic scores. The study had a 24% dropout rate, which is relatively high, but does not appear excessive given the lengthy 20-week duration of the trial. Another concern is that we did not monitor weekly intake of O3FA from food consumption, which could have confounded our findings. However, studies have indicated that children and adolescents consume only ~30% of the recommended O3FA daily allowance.⁴⁷ Furthermore, the randomization process would have addressed possible differences in O3FA intake.

Finally, most patients (76%) were receiving concomitant psychotropic medication. However, medications had

been stable for 3 months before enrollment and throughout the study, minimizing the confounding effect of intervening medication. At the same time, we did not test the efficacy of O3FA as a monotherapy.

Whereas these findings require replication in larger samples with the use of a placebo that does not possess putative therapeutic properties, our study indicates that O3FA supplementation is tolerable for children and adolescents

with TD and may be a rational consideration, especially for patients who experience high levels of impairment and/or do not obtain satisfactory results from currently established medications.

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