

OMEGA-3 FATTY ACID SUPPLEMENTATION IN
THE TREATMENT OF ATTENTION DEFICIT/
HYPERACTIVITY DISORDER: A PILOT STUDY

WELDON BONNELL

Omega-3 Fatty Acid Supplementation in the Treatment of Attention Deficit/Hyperactivity Disorder: A Pilot Study

by

©Weldon Bonnell, MD FRCPC

A Thesis submitted to the School of Graduate Studies in partial fulfillment of the
requirements for the degree of

**Master of Science in Clinical Epidemiology
Faculty of Medicine**

Memorial University of Newfoundland

May 2013

St. John's

Newfoundland & Labrador

Abstract

Background and Purpose: Omega-3 fatty acids are essential for brain development but their dietary intake is low. Controlled trials of omega-3 fatty acids in Attention deficit/hyperactivity disorder (ADHD) suggest benefit but have limitations. The purpose was to conduct a small clinical trial to serve as a pilot study.

Methods: This was a randomized, double blind, placebo controlled trial, supplementing youth (6-17 years old) with ADHD, with an omega-3 fatty acid supplement or identical placebo for 6 months. The primary outcome measure was the Conners' ADHD scale.

Results: There were recruitment problems requiring inclusion/exclusion criteria revision. Seven (of 10) patients per group were recruited. Withdrawal was a problem; 57% of participants did not return following treatment assignment. One participant per group completed the study. Treatment assignment did not affect study withdrawal. Tolerability was a major reason for withdrawal in both groups. No differences in study outcomes were detected.

Conclusions: Several limitations and potential protocol enhancements were identified, including a change of supplement. No conclusions could be made regarding the efficacy of this supplement in the treatment of ADHD.

Acknowledgements

I would like to thank everyone that contributed to the completion of this research project and thesis. I will begin by thanking my masters' supervisor, Dr. Gerry Mugford, who served as a valuable resource throughout the process. Moreover, he was patient and willing to let me find my way with just the right amount of guidance. I wish to acknowledge the other members of my advisory committee, Drs. Terrence Callanan and David Craig. They too have been supportive and helpful while also patient with me throughout this process.

I thank the physicians and allied health professionals of the Department of Child and Adolescent Psychiatry at the Janeway Hospital. As the site for my study, these professionals made this research possible. I thank Drs. Leslie Wheeler, Chantelle Reid, Christine Snelgrove, Kim St. John, Tina McWilliam, Rajive Rajan and Hubert White for their enthusiastic participation and cooperation. I offer special thanks and recognition to the Outpatient Psychiatric and Research Nurse, Tanya Purchase, who provided invaluable assistance. I also thank the psychologists Drs. Christine O'Leary and Leah Puddister. I also thank my administrative assistant, Christine Powell, who's assistance with my academic and clinical responsibilities permitted me to focus on this project.

Finally, I am grateful to my family who have understood and supported me throughout this process.

Table of Contents

Abstract	ii
Acknowledgments	iii
Table of Contents	ix
List of Tables	xi
List of Figures	xiii
List of Abbreviations	xiv
1 Introduction	1
1.1 Attention Deficit/Hyperactivity Disorder	1
1.1.1 Description of the Condition	1
1.1.2 Aetiology	2
1.1.3 Diagnosis of Attention Deficit/Hyperactivity Disorder	2
1.1.4 Treatment for Attention Deficit/Hyperactivity Disorder	3
1.2 Omega-3 Fatty Acid Supplementation	4
1.3 Literature review	6
1.3.1 ADHD Subtypes	8
1.3.2 Concurrent Treatment	9

1.3.3 Outcome Measures	10
2 Purpose	11
2.1 Rationale	11
2.2 Scientific Question	12
2.2.1 Null Hypothesis	12
2.3 Alternate Hypothesis	12
3 Methods	13
3.1 Type of Research Design	13
3.1.1 Length of Study	13
3.2 Ethics Approval	14
3.3 Eligibility Criteria	14
3.3.1 Inclusion Criteria	14
3.3.2 Exclusion Criteria	15
3.3.3 Modification of the Inclusion/Exclusion Criteria	16
3.4 Study Enrolment	16
3.5 Sampling Methods/Recruitment	18
3.6 Randomization	19
3.7 Blinding	19
3.8 Sample Size Determination	20
3.9 Intervention	20
3.10 Measurements	22
3.10.1 Study Schedule	23
3.10.2 Conners' Rating Scales	23
3.10.3 Conners' Continuous Performance Test II	25
3.10.4 Clinical Global Impression	25

3.10.5	Thirst/Skin Questionnaire	26
3.10.6	Adverse Effect Inquiry	26
3.10.7	Baseline Characteristics	26
3.11	Study Schedule	27
3.12	Statistical Analysis	29
3.12.1	Baseline Data	29
3.12.2	Planned Analyses	29
4	Results	30
4.1	Demographics	30
4.1.1	Age	30
4.1.2	Gender	31
4.1.3	ADHD Subtype	31
4.1.4	Comorbidities	33
4.1.5	Number of Medications	36
4.2	Baseline Characteristics	38
4.2.1	ADHD Severity Measures	38
4.2.1.1	Conners Continuous Performance Test II	38
4.2.1.2	Conners 3: Teacher Report	39
4.2.1.3	Conners 3: Parent Report	43
4.2.1.4	Conners 3: Teacher and Parent Reports Compared	47
4.2.2	Signs of Omega-3 Fatty Acid Deficiency	47
4.3	Study Completion	51
4.3.1	Reasons for Withdrawal	52
4.3.2	Cox Proportional Hazards Regression	53
4.3.3	Tolerability/Adverse Effects	54
4.3.4	Compliance	56

4.4	Outcomes	56
4.4.1	ADHD Severity Measures	56
4.4.1.1	Conners Continuous Performance Test II	56
4.4.1.2	Conners 3: Teachers and Parent Reports	59
4.4.2	Clinical Global Impression Scale	59
4.4.3	Signs of Omega-3 Fatty Acid Deficiency	61
5	Discussion	64
5.1	Demographics	64
5.1.1	Age	64
5.1.2	Gender	64
5.1.3	ADHD Subtype	65
5.1.4	Comorbidities	65
5.1.5	Number of Medications	66
5.2	Baseline Characteristics	67
5.2.1	ADHD Severity Measures	67
5.2.1.1	Conners Continuous Performance Test II Confidence Index	67
5.2.1.2	Conners 3: Teacher and Parent Reports	68
5.2.1.3	Comparison to Related Research	70
5.2.2	Signs of Omega-3 Fatty Acid Deficiency	70
5.3	Study Completion	71
5.3.1	Comparison to Similar Studies	71
5.3.2	Frequency of Follow-up	73
5.3.3	Inter-visit Telephone Contact	73
5.3.4	Length of Study	74
5.3.5	Participant Characteristics	74

5.3.5.1	Severity of ADHD	75
5.3.5.2	Oppositionality	75
5.3.5.3	Comorbidities	76
5.3.6	Caregiver Characteristics	77
5.3.7	Implications as a Pilot Study	78
5.3.8	Survival Curves	78
5.3.9	Reasons for Withdrawal	79
5.3.10	Tolerability/Adverse Effects	79
5.3.11	Supplement Formulation	80
5.4	Outcomes	80
5.4.1	ADHD Severity Measures	81
5.4.1.1	Conners Continuous Performance Test II	81
5.4.1.2	Conners 3: Teacher & Parent Reports	81
5.4.2	Clinical Global Impression Scale	81
5.4.3	Signs of Omega-3 Fatty Acid Deficiency	82
6	Conclusions	83
6.1	Outcomes	83
6.1.1	Primary Outcomes	83
6.1.2	Secondary Outcomes	83
6.1.3	Survival Analysis	84
6.2	Patient Characteristics	84
6.2.1	ADHD Symptomatology	84
6.2.2	Comorbidities	85
6.2.3	Signs of Omega-3 Fatty Acid Deficiency	85
6.3	Study Protocol	86
6.4	Limitations	86

6.4.1	Dropout	86
6.4.2	Inability to Conduct Planned Analyses of Data	86
6.4.3	Change in Protocol	87
6.4.4	Study Site	87
6.4.5	Failure to Recruit Full Complement for Study	87
6.4.6	Last Observation Carried Forward	88
6.5	Role as a Pilot Study	88
6.5.1	Study Site	88
6.5.2	Recruitment	89
6.5.3	Inclusion/Exclusion Criteria	90
6.5.4	Sample Size	90
6.5.5	Study Length	90
6.5.6	Choice of Supplement	91
6.5.7	Frequency of Follow-Up	91
6.5.8	Outcome Measures	92
6.6	Summary	92
A Clinical Global Impression Scale		94
B Adverse Effect Inquiry Form		95
C Thirst Skin Questionnaire		96
D Omega-3 Fatty Acid Supplement		97
Bibliography		100

List of Tables

3.1	Study Schedule	24
4.1	Age	31
4.2	Attention Deficit Hyperactivity Disorder Subtypes	33
4.3	Comorbidities	35
4.4	Conners 3: Teachers Report (Baseline)	41
4.5	Conners 3: Parent Report (Baseline)	45
4.6	Baseline Conners 3: Teacher and Parent Reports Compared	48
4.7	Thirst-Skin Questionnaire Initial Responses	50
4.8	Study Completion	52
4.9	Reasons for withdrawal from study	53
4.10	Cox Proportional Hazards Regression Analysis of Factors Affecting Study Withdrawal	54
4.11	Adverse Effects	55
4.12	Conners Continuous Performance Test II Confidence Index	57
4.13	Clinical Global Impression Scale (Last Observation Carried Forward)	59
5.1	Comparison of Loss to Follow-up Among Polyunsaturated Fatty Acids versus Placebo Clinical Trials	72
D.1	Genius Liquid Kids And Teens - Omega-3: Formulation Per 5 mL Serving	97

D.2 Genius Liquid Kids And Teens - Omega-3: Polyunsaturated Fatty Acid

Content Per 5 mL Serving	99
------------------------------------	----

List of Figures

1.1	Eicosapentaenoic Acid (EPA) Structure. From “Eicosapentaenoic acid structure,” by K. Harrison, 2007, http://www.3dchem.com/molecules.asp?ID=380 . Copyright 2007 by Karl Harrison.	5
1.2	Docosahexaenoic Acid (DHA) Structure. From “Docosahexaenoic acid structure,” by K. Harrison, 2006. http://www.3dchem.com/molecules.asp?ID=238 . Copyright 2006 by Karl Harrison.	6
4.1	Histograms of Age	32
4.2	Bar Chart of the Number of Comorbid Diagnoses Among Treatment Groups	34
4.3	Bar Chart of the Number of Medications Prescribed Per Patient Among Treatment Groups	37
4.4	Mean Initial Conners Continuous Performance Test II: Confidence Index (CCPT-CI) Results (95% Confidence Intervals)	40
4.5	Mean Conners 3: Teachers Reports Subtest Scores (95% Confidence Intervals)	42
4.6	Mean Conners 3: Parent Reports Subtest Scores (95% Confidence Intervals)	46

4.7	Mean Conners 3: Teacher and Parent Reports Subtest Scores (95% Confidence Intervals)	49
4.8	Mean Conners Continuous Performance Test II: Confidence Index (CCPT-CI) Results (95% Confidence Intervals): First and Last Observations	58
4.9	Mean Clinical Global Impression Scale Scores (Last Observation Carried Forward) (95% Confidence Intervals)	60
4.10	Mean Thirst Skin Questionnaire (TSQ) Scores: First and Last Observations (95% Confidence Intervals)	62
C.1	From "Omega-3 fatty acids in boys with behavior, learning, and health problems," by Stevens et al., 1996, <i>Physiology and Behaviour</i> , 59, p. 916.	96
D.1	Genius Liquid Kids And Teens - Omega-3. From "Genius Liquid Kids And Teens - Omega-3," by Nutripur, 2013, http://www.nutripur.com/ . Copyright 2013 by Nutripur.	98

List of Abbreviations

ADHD	Attention Deficit/Hyperactivity Disorder
AEI	Adverse Effect Inquiry Form
C3P	Conners Third Edition: Parent Report
C3P-T	Conners Third Edition: Parent Report: Global Index: Total Score
C3T	Conners Third Edition: Teacher Report
C3T-T	Conners Third Edition: Teacher Report: Global Index: Total Score
CCPT-CI	Conners Continuous Performance Test II Confidence Index
CCPT-II	Conners' Continuous Performance Test II
CGI	Clinical Global Impression
<i>CI</i>	Confidence Interval
DHA	Docosahexaenoic Acid
DSM-IV TR	Diagnostic and Statistical Manual of Mental Disorders: Fourth Edition, Text Revision
EPA	Eicosapentaenoic Acid

LOCF	Last Observation Carried Forward
<i>M</i>	Mean
<i>Mdn</i>	Median
PUFA	Polyunsaturated Fatty Acid
<i>SD</i>	Standard Deviation
<i>SMD</i>	Standardized Mean Difference
TSQ	Thirst/Skin Questionnaire

Chapter 1

Introduction

1.1 Attention Deficit/Hyperactivity Disorder

1.1.1 Description of the Condition

Attention deficit/hyperactivity disorder (ADHD) is the most common developmental disorder of childhood, with prevalence estimates ranging from 4% to 15% for school age children [1, 2, 3, 4, 5]. ADHD is characterized by sustained problems with age-inappropriate levels of inattention, hyperactivity and/or impulsivity in a variety of settings [5]. There are three subtypes of ADHD: a predominantly inattentive subtype, a predominantly hyperactive-impulsive subtype, and a combined inattentive and hyperactive-impulsive subtype [5]. There is little information available regarding the proportions of ADHD subtypes within non-clinical and clinical populations [1, 2, 4]. Anecdotally, the majority of cases are the combined subtype, with a roughly equal number of inattentive and hyperactive/impulsive subtypes. ADHD is more prevalent in boys. The gender ratios range from 2:1 (Males:Females) to 9:1 [5].

Challenges associated with ADHD can include academic struggles, social dysfunction and poor self esteem [1, 2]. Youth with ADHD often have comorbid diagnoses, including learning disabilities, disruptive behaviour disorders, tic disorders, anxiety disorders and major depression [1, 2]. The diagnosis is associated with a higher risk of negative outcomes, such as substance abuse, delinquency, school withdrawal and motor vehicle accidents [1, 2]. Between 50% and 75% of youth with ADHD will have sufficient symptoms to warrant continued diagnosis with ADHD as adults [1, 2].

1.1.2 Aetiology

Evidence suggests that several factors contribute to the development of the diagnosis of ADHD, including genetic factors, neuroanatomical abnormalities, psychosocial factors, pregnancy and delivery complications, and environmental factors, such as prenatal exposure to cigarettes or alcohol [2, 1]. Heritability is believed to account for approximately 75% of the aetiology of ADHD [2, 1].

The dopamine neurotransmitter system is likely involved in the pathoetiology of ADHD [2, 1]. Medications prescribed in the management of ADHD increase the availability of dopamine in the brain [2, 1]. Several genes related to the dopamine pathway have been linked to ADHD, including the dopamine D4 and D5 receptors, dopamine- β -hydroxylase and dopamine transporter genes [2, 1]. Neuroimaging studies, including functional assessments, have identified differences in dopamine pathways in children and adults with ADHD [2, 1].

1.1.3 Diagnosis of Attention Deficit/Hyperactivity Disorder

The diagnosis of ADHD is based on diagnostic interviews. These interviews are supported by collateral history, psychometric assessment, behaviour rating scales and

direct observation. Diagnosticians apply validated criteria for ADHD from the Diagnostic and Statistical Manual of Mental Disorders: Fourth Edition, Text Revision (DSM-IV TR) [5, 2, 1, 3].

1.1.4 Treatment for Attention Deficit/Hyperactivity Disorder

The recommended treatment for ADHD consists of a combination of pharmacological and non-pharmacological interventions [1, 2, 3, 4]. First-line pharmacological options include stimulant medications, such as methylphenidate and dextroamphetamine, and non-stimulant medications, such as atomoxetine [1, 2, 3, 4]. Non-pharmacological interventions include parent effectiveness training, behaviour management plans and psychological interventions [1, 2, 3, 4]. However, behavioural therapies do not appear to be effective without co-administration of medication [6].

Evidence suggests that stimulant medications are effective in improving inattention and behavioural symptoms [1, 2, 3, 4]. However, this evidence suggests that these medications are less effective in improving achievement and cognition [1, 2, 3, 4]. Benefits associated with medical treatment for ADHD do not persist once they are discontinued [1, 2, 3, 4]. All subtypes of ADHD respond similarly to pharmacological interventions [1, 2, 3, 4].

Many patients receiving maximal stimulant therapy still have considerable disability and dysfunction associated with their illness [1, 2, 3, 4]. As well, up to 30% of children with ADHD do not respond to conventional pharmacotherapies [1, 2, 3, 4].

Numerous side-effects are associated with the medications used in the treatment of ADHD, including weight loss, growth restriction, tics, and insomnia [1, 2]. Many of these stimulant medications have considerable abuse potential [1, 2]. These medications

can worsen comorbid conditions, such as tics [1, 2]. Given the limitations in present treatments for ADHD, some families explore alternate treatments [3, 2].

There is a wide variety of alternate treatments available in the treatment of ADHD [3, 2]. In general, rigorous and objective analysis of these therapies has not been conducted, leading to a lack of empirical support in scientific literature. Parents and guardians nonetheless explore these treatment options, sometimes with but at other times without the knowledge, support or guidance of their health care professionals. There is consequently a need for competent and objective analysis of these alternate treatments.

Of the available alternate treatments for ADHD, omega-3 fatty acid supplementation is widely available, in the forms of dietary supplements and food additives [3]. Omega-3 fatty acid supplementation appears to be the most studied and most promising of the alternative treatments of ADHD [7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24]. Several essential variables are presently unknown [7]. These include clear evidence of therapeutic effect, optimal dosing strategies, the length of time to the onset of any therapeutic action, and the duration of any therapeutic action.

1.2 Omega-3 Fatty Acid Supplementation

Omega-3 fatty acids are essential for human brain development and health [25]. The longer-chain, highly unsaturated fatty acids, particularly eicosapentaenoic acid (EPA) (Figure 1.1) docosahexaenoic acid (DHA) (Figure 1.2), are most important for brain development and function. DHA is the major polyunsaturated fatty acid in the adult brain [26]. EPA and DHA can be synthesized within the body from the essential fatty acid precursor alpha-linolenic acid, although this conversion process is not very efficient in humans, particularly males [27, 28]. By historical standards, dietary intake

of omega-3 fatty acids is very low in many modern developed countries. The key omega 3 fatty acids (EPA and DHA) are found in high quantities only in fish and other seafood [25].

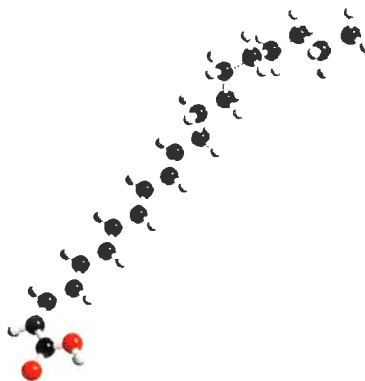


Figure 1.1: Eicosapentaenoic Acid (EPA) Structure. From “Eicosapentaenoic acid structure,” by K. Harrison, 2007, <http://www.3dchem.com/molecules.asp?ID=380>. Copyright 2007 by Karl Harrison.

Several converging lines of evidence suggest a connection between omega-3 fatty acid insufficiency and ADHD, as well as a role for omega-3 fatty acid supplementation in the treatment of ADHD. Several studies have identified clinical and hematologic signs and symptoms of essential fatty acid insufficiency among a high proportion of children and adolescents with ADHD and other disruptive behaviour disorders when compared with controls [29, 30, 22, 31, 32]. Both ADHD and omega 3 fatty acid insufficiency are more prevalent in males [29, 30, 22, 31, 32]. Comparable abnormalities in dopamine metabolism are evident in both ADHD and omega 3 fatty acid insufficiency [33, 34]. This apparent connection between ADHD and omega 3 fatty acid insufficiency suggests that correction of this insufficiency via supplementation might lead to an improvement in ADHD symptomatology.

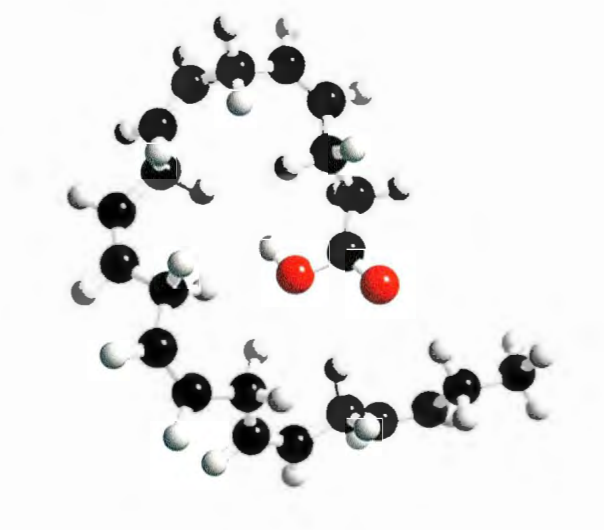


Figure 1.2: Docosahexaenoic Acid (DHA) Structure. From “Docosahexaenoic acid structure,” by K. Harrison, 2006, <http://www.3dchem.com/molecules.asp?ID=238>. Copyright 2006 by Karl Harrison.

It is possible to reliably and non-invasively identify omega-3 fatty acid insufficiency using a symptom questionnaire, as described in subsection 3.10.5 and illustrated in Appendix C [29, 30, 22, 31, 32]. Presently, there is speculation as to the relevance of these signs and symptoms in patients with ADHD in predicting treatment outcome.

1.3 Literature review

There was a recent Cochrane review, conducting a meta-analysis of clinical trials involving the treatment of youth with ADHD with supplements containing polyunsaturated fatty acids, including omega-3 and omega-6 fatty acids, separately or together [7]. Eighteen publications describing 13 clinical trials met inclusion criteria [8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24].

The apparent efficacy of polyunsaturated fatty acid supplementation in youth with ADHD varied among the studies in this meta-analysis [7]. Two trials of parallel

design, involving omega-3/6 polyunsaturated fatty acids compared to placebo suggested improvement (97 participants; risk ratio 2.19, 95% confidence interval (*CI*) 1.04 to 4.62) [17, 22]. Five trials found no statistically significant differences in parent-rated total ADHD symptoms (413 participants; standardized mean difference (*SMD*) -0.17, 95% *CI* -0.38 to 0.03) [14, 18, 21, 20, 35, 22, 23]. Six trials found no statistically significant differences in parent-rated inattention (469 participants; *SMD* -0.04, 95% *CI* -0.29 to 0.21) [14, 18, 19, 20, 35, 22, 24]. Five trials found no statistically significant differences in parent-rated hyperactivity/impulsivity (416 participants; *SMD* -0.04, 95% *CI* -0.25 to 0.16) [14, 18, 19, 21, 20, 35, 22]. Four trials found no statistically significant differences in teacher-rated total ADHD symptoms (324 participants; *SMD* 0.05, 95% *CI* -0.18 to 0.27) [14, 18, 19, 35]. Three trials found no statistically significant differences in teacher-rated inattention (260 participants; *SMD* 0.26, 95% *CI* -0.22 to 0.74) [14, 18, 22]. Three trials found no statistically significant differences in teacher-rated hyperactivity/impulsivity (259 participants; *SMD* 0.10, 95% *CI* -0.16 to 0.35) [14, 18, 22]. These negative study outcomes do not support omega-3 fatty acid supplementation in the treatment of ADHD.

The meta-analysis identified several key limitations among the included studies [7]. These weaknesses included small sample sizes, variability of selection criteria, variability of the type and dosage of supplementation, and short follow-up times (4 to 16 weeks). It is difficult to conclude whether these negative results are indicative of a lack of efficacy (i.e. a true negative) or a failure of these studies to recognize efficacy as a result of their limitations (i.e. a false negative).

Due to the limitations of previous studies and the early stage of this research, no standard has yet been defined regarding a source for omega-3 fatty acid supplementation, dosage or relative proportions of omega-3 fatty acids of interest, including EPA and DHA. Fish oils have been the most common and the most readily available

source [36, 22, 16, 37]. These supplements come in a variety of doses, capsule sizes and alternate preparations, such as soft-chews and syrups. This is an important and practical consideration in clinical practice with children, who may find swallowing large capsules difficult.

Dosages of EPA studied ranged from 80 mg per day [22] to 558 mg per day [37]. Dosages of DHA studied ranged from 174 mg per day [37] to approximately 510 mg per day [15]. The ratios of DHA to EPA studied have ranged from approximately 6:1 [22] to 1:3 [37]. These relative proportions of EPA and DHA seem to be largely determined by the unique characteristics of each supplement used in the studies. Commercially available omega-3 fatty acid fish oil supplements generally have a ratio of EPA:DHA between 2:1 and 1:2.

Omega-3 fatty acids are essential nutrients and are regarded as safe in doses much higher than those used in this and similar studies [38]. No significant difference in rates of adverse effects between polyunsaturated fatty acids and placebo was found in any of the trials included in the previously noted meta-analysis [7]. Side effects of high doses of fish oils can include digestive symptoms such as nausea, belching or loose stools [38].

1.3.1 ADHD Subtypes

The Cochrane Review [7] did not compare the efficacy of omega-3 fatty acid supplementation among ADHD subtypes. There is no evidence to suggest that omega-3 fatty acid supplements are more or less efficacious depending on ADHD subtype [8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24].

1.3.2 Concurrent Treatment

As described in subsection 5.3.1 and Table 5.1, some of the studies included in the Cochrane Review [7] permitted ongoing use of conventional treatments for ADHD, usually stimulants [16, 22, 24]. Participants in these trials continued to receive their existing therapies throughout the trials, both pharmacological and non-pharmacological interventions. Other included studies did not permit concurrent use of such treatments [18, 39, 23, 17].

As outlined in section 3.3, this study permits ongoing prescription of existing pharmacotherapies for ADHD and comorbid illnesses, as well as continued participation in non-pharmacological interventions, such as those described in subsection 1.1.4. This design is compatible with some studies [16, 22, 24] and not others [18, 39, 23, 17]. The primary reason for permitting concurrent therapies is clinical relevance. As explained in subsection 1.1.4, the recommended treatment for ADHD is multimodal [1, 2, 3, 4]. At present, omega-3 fatty acid supplements are of interest as possible complementary therapies to established interventions. This study therefore seeks to assess the efficacy of these supplements in this clinical context.

This choice to permit concurrent therapies does present several potential challenges. A greater treatment effect will likely be required to differentiate a treatment effect of the study supplement from the effect of some other variable, such as concurrent therapies. This challenge will undoubtedly affect this pilot study, with a small sample size. A follow-up study based on this protocol would need to take this challenge into account when calculating sample size.

The heterogeneity of these existing therapies presents a related challenge. Differences in the efficacies of these concurrent therapies could introduce another variable that could mask a treatment effect from this omega-3 fatty acid supplement. While

individual patients may preferentially respond to one intervention over another, on a clinical population level, there are no clinically significant differences in the efficacy of the first-line therapies for ADHD [1, 2, 3, 4]. A follow-up study based on this protocol would need to ensure proper randomization of the study population and adequate sample size to address this challenge.

1.3.3 Outcome Measures

As discussed in section 1.1, ADHD is a complex, multifaceted condition [1, 2, 3, 4, 5]. As a result, researchers and clinicians employ a variety of subjective and objective assessment tools to assess the severity of ADHD symptomatology, the cumulative burden of illness, and response to treatment. The high rates of comorbidity further complicates this challenge, demanding outcome measures that provide a holistic assessment.

The studies included in the recent Cochrane Review [7] employ a combination of subjective and objective measures to quantify baseline ADHD severity and response to treatment [8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24]. They assess both specific ADHD symptomatology, as well as broad measures of patient function. As the primary outcome measure, the meta-analysis assessed the change in ADHD symptoms as measured by validated scales, such as the Conners Rating Scales [40] or Child Behaviour Checklist [41]. The Conners Rating Scales are described in subsection 3.10.2. The Child Behaviour Checklist is a comparable rating scale. These studies include objective measures of ADHD symptomatology among their secondary outcome measures, such as the Conners' Continuous Performance Test II [42], which is described in subsection 3.10.3.

To address the inherent complexities of assessing ADHD, and permit comparison with related research, this study employs these accepted and validated outcome measures. These measures are discussed in section 3.10.

Chapter 2

Purpose

2.1 Rationale

Existing trials of omega-3 fatty acid supplementation in youth with ADHD have been hampered by numerous limitations and have yielded largely negative outcomes [7]. The goal of this trial was to conduct a small clinical trial employing a protocol designed to address many of the limitations identified in other studies. The study population, clinical setting, and length of study were all chosen to reflect clinical practice. Supplementation rather than replacement of existing treatments was chosen to reflect current best practices. In addition to assessing the primary and secondary outcomes, this trial was also intended to serve as a pilot study, to establish feasibility of a future larger potential trial and to optimize the study protocol.

2.2 Scientific Question

In children and adolescents meeting the study's inclusion and exclusion criteria, is the supplementation of existing and stable treatment for ADHD with a fish oil supplement containing omega-3 fatty acids superior to supplementation with a placebo in improving symptoms of ADHD, as measured by the teacher rated version of the Conners Third Edition (Global Index: Total Score subscale)?

2.2.1 Null Hypothesis

The null hypothesis of this study is: there is no change in symptoms of ADHD as measured by the Conners Third Edition: Teacher Report: Global Index: Total Score (C3T-T) after six months of supplementation with a fish oil supplement containing omega-3 fatty acids versus a placebo.

2.3 Alternate Hypothesis

The alternate hypothesis of this study is: there is an improvement in symptoms of ADHD as measured by the C3T-T (a decrease in the mean T-score by at least 12) after six months of supplementation with a fish oil supplement containing omega-3 fatty acids versus a placebo.

Chapter 3

Methods

3.1 Type of Research Design

This was a randomized, double-blind, placebo-controlled augmentation trial involving treatment in parallel groups for six months. Active treatment was an orange flavoured syrup containing omega-3 fatty acids. The placebo was a similar orange flavoured syrup. All primary and secondary outcome measures were obtained at pre-treatment baseline and 6-month follow-up points. This frequency of follow-up was intended to reflect standard clinical practice.

3.1.1 Length of Study

As discussed in subsection 1.1.4, the length of time to the onset of any therapeutic action and the duration of this action are unknown at present [7]. A study length of six months was chosen for several reasons: it was in keeping with the longer of the completed studies at the time [7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24]; it was thought to be sufficiently long to establish whether there are at least

short-term to mid-term therapeutic effects; and it was thought to be long enough to identify short-term and mid-term problems with the protocol, active treatment and placebo.

3.2 Ethics Approval

Approval was sought and granted through the local health research ethics authority. Initially, this was the Human Investigation Committee, Faculty of Medicine, Memorial University of Newfoundland. As of July 1, 2011, The Health Research Ethics Authority Act came into force. Authority thereafter passed to the Health Research Ethics Authority.

3.3 Eligibility Criteria

3.3.1 Inclusion Criteria

Potential participants were eligible with the following inclusion criteria:

1. Age from 6—17 years.
2. Attending the Janeway Hospital Child and Adolescent Outpatient Psychiatry Clinic in St. John's, Newfoundland and Labrador, Canada.
3. A diagnosis of ADHD, made by their treating psychiatrist, using DSM-IV TR criteria [5]. The severity of ADHD symptoms present at the time of enrolment was not used as either an inclusion or an exclusion criterion.
4. Currently receiving medical treatment for ADHD, taking any combination of stimulant or non-stimulant medications at doses that had been stable for at least

12 weeks, other than dosage adjustments to account for growth (many of the treatments for ADHD are dosed according to patient weight). Stimulant medications include any preparations of methylphenidate, dextroamphetamine, and amphetamine salts. Non-stimulant medications included atomoxetine, clonidine, bupropion, venlafaxine, and tricyclic antidepressants if prescribed for the treatment of ADHD. Participants could avail of non-medical treatments for ADHD, such as behaviour management at the time of enrolment and at any time during the study.

Note: The choice to permit concurrent use of existing therapies is discussed in subsection 1.3.2, including potential limitations and challenges.

3.3.2 Exclusion Criteria

Potential participants were ineligible with the following exclusion criteria:

1. Comorbid diagnoses of Oppositional-Defined Disorder, Conduct Disorder. Substance Abuse. Substance Dependence, Learning Disability, Mental Retardation ($IQ \leq 70$), or Pervasive Developmental Disorder, diagnosed by their treating psychiatrist according to DSM-IV TR criteria [5].
2. Changes to medications for the treatment of ADHD within the past 12 weeks, other than dosage adjustments to account for growth.
3. Significant comorbid medical illness, as judged by the patient's treating psychiatrist.
4. Failure to complete all baseline measures prior to the randomization/pre-treatment clinic visit.

Potential participants were not excluded on the basis of comorbid psychiatric conditions not explicitly listed in the above exclusion criteria, including mood and anxiety disorders, or on the basis of any medications or non-medical treatments they were receiving for these conditions. No restrictions on use of such treatments during the trial were made. An exclusion log was recorded.

The diagnoses referred to in the eligibility criteria were based on clinical interview by the participants' treating psychiatrists.

3.3.3 Modification of the Inclusion/Exclusion Criteria

As discussed in section 3.4, study enrolment was slow. The referring psychiatrists identified the exclusion criteria as the greatest barrier to recruitment. They reported high rates of comorbid diagnoses that precluded enrolment among their clinic populations. In consultation with the supervisory committee, an amendment was submitted to and approved by the Human Investigation Committee, changing the inclusion and exclusion criteria. This change permitted the enrolment of patients with Learning Disabilities and comorbid disruptive behaviour disorders, including Oppositional Defiant Disorder and Conduct Disorder. Following this change, no additional patients were excluded based on the revised inclusion/exclusion criteria.

3.4 Study Enrolment

Study enrolment was slow to begin, with 19 weeks passing from the initiation of study enrolment to enrolment of the first patient. Ten participants were enrolled over the next 13 weeks, after which there were no further enrolments until the inclusion and exclusion criteria were changed (section 3.3), 62 weeks after the initiation of study enrolment and 29 weeks following the enrolment of the last preceding study participant. Another

4 participants were then enrolled over the next 10 weeks. Another approximately 7 weeks passed without further patient enrolment, after which the study was closed to further enrolment. Enrolment was closed at that time (April, 2011) due the study design, which precluded further enrolment until September, 2011 because of the need for repeated assessments to be completed by teachers within the same academic year.

As described in section 3.5, all the recruiting physicians were geographically located in the same clinic area. In addition to the planned monthly recruitment reminders, the physical proximity also permitted frequent informal reminders, about once weekly.

Slow recruitment was an early concern. Initially, the principal investigator and recruiting physicians believed there were enough eligible patients in their practices and that recruitment would therefore improve given time. It became increasingly clear that time alone would not improve matters. The principal investigator consulted with the other recruiting physicians and the masters supervisory team to explore options. Many options were explored, most of which are discussed in subsection 6.5.2. As noted earlier in this section, the recruiting physicians had cited the restrictive exclusion criteria as the main barrier to recruitment. The process of deciding on a means of addressing the slow recruitment and amending the study protocol took longer than expected. By the time it was clear that this change would not sufficiently hasten recruitment, the window of opportunity to make further changes to the protocol had ended before closing the study to recruitment.

Study response rate, in terms of potentially eligible patients declining participation, was not recorded, nor was it identified as a concern by the recruiting physicians.

3.5 Sampling Methods/Recruitment

Participants were recruited from the Child and Adolescent Outpatient Psychiatry Clinic of the Janeway Children's Health and Rehabilitation Centre, in St. John's, Newfoundland and Labrador, Canada. This site serves as the province's tertiary centre for child and adolescent psychiatry, as well as providing specialist care to the surrounding area. This clinic is affiliated with Memorial University of Newfoundland's Faculty of Medicine and Discipline of Psychiatry. The clinic employs a full-time nurse who functions as an outpatient nurse and research nurse. Each psychiatrist is affiliated with the university and regularly participates in clinical research. Throughout the study, the clinic employed eight child and adolescent psychiatrists, each of whom maintained a large practice. Six of these psychiatrists operated full-time outpatient clinics, while the remaining two divided their time between outpatient and inpatient practice. Each psychiatrist was invited to participate in the study and accepted. Each psychiatrist was responsible for recruiting patients from his/her clinic. He/she made the initial determination of eligibility, which was later confirmed by the research nurse. Monthly reminders were circulated among the psychiatrists regarding the study and recruitment. A poster was placed in the clinic's waiting room to inform patients and their guardians of the study and who was eligible to participate.

This study site was chosen for several reasons. As the province's tertiary centre for child and adolescent psychiatric care, it seemed likely to have access to sufficient numbers of patients to complete the study without requiring a second study site, which would compound the complexity of study administration. Patients attending this clinic generally have high levels of ADHD symptomatology, which was expected to increase the likelihood of identifying a clear response to the supplements used in this study.

Each potential study participant and his/her parent/guardian was initially approached by his/her treating psychiatrist, who outlined the nature and purpose of the study. If the patient and their guardians expressed interest in participating in the study, they were given the opportunity to meet the research nurse during that same clinic visit. The nurse provided them with the informed consent document. The nurse read through the consent document with each patient and his/her guardian(s) and allowed them to take time to consider whether to participate in the trial. If the patient and their guardians were interested in taking part, they were scheduled for the first trial visit. At that visit, the physician investigator discussed the consent and answered any questions. Once the questions had been answered by the physician, the research nurse obtained the signed and witnessed consent of each parent/guardian and the assent of any child/adolescent who was able to understand the nature and purpose of the study. Assent indicates willingness to participate in research by those too young to give informed consent but old enough to understand the proposed research in general.

3.6 Randomization

Upon enrolment and collection of baseline data, participants were randomized to treatment and placebo groups. Randomization of treatment was accomplished by the research nurse blindly choosing a slip of paper from an envelope containing a randomly sorted collection of slips, each of which corresponded to a lot number of supplement bottles containing either placebo or active ingredient.

3.7 Blinding

The treatments were coded so that participants, clinicians and the research nurse were blinded to treatment assignment. A sealed group assignment registry was maintained

and kept in the hospital's emergency department for consultation in the event that a participant required unblinding on an emergency basis. Participants were given the telephone number to this emergency department with instructions to call if necessary. Key emergency room staff were oriented regarding this registry and printed instructions were attached to the sealed envelope.

3.8 Sample Size Determination

Previous studies involving omega-3 supplementation in patients with ADHD and closely related diagnoses using the C3T-T showed a reduction of 6 points in their T-scores [37, 36], which is considered clinically significant [40] (the raw scores of the C3T-T are converted to T-scores with a mean of 50 and a standard deviation of 10). Power calculations indicate that group sizes of 42 would detect a 6-point reduction in the T-score with $> 80\%$ power at the $p < .05$ level. The target sample size of 50 subjects per group was therefore chosen as the optimal number for a follow-up study, once the feasibility of such a study was established, and the protocol optimized.

As a pilot study, the target sample size of 10 subjects per group was chosen, for a total of 20 subjects. A study of this size is statistically powered to detect a reduction of the T-score by 12 (T-score $\Delta = 12$), that is a treatment effect of 1.2 standard deviations, with $> 80\%$ at a $p < .05$ level.

3.9 Intervention

A survey of commercially available omega-3 fatty acid supplements was conducted, involving telephone and in-person contact with several pharmacists and alternative medicine retailers. Each supplement was evaluated based on omega-3 fatty acid content, the ratio of EPA to DHA, preparation (e.g. capsule, soft-chew, gummy candy, syrup),

palatability and cost. The majority of available candidates were rejected because they were large capsules and swallowing was expected to be a problem for some of the younger study participants. The soft-chews and gummy candies were rejected because the omega-3 content was so low that the amount required per day would be impractical. The other syrups were rejected because of poor taste that was noted by several adults and children. The chosen supplement was Nutripur Genius Liquid: Kids and Teens (Appendix D) [43].

The supplement used in this study was chosen based on its commercial availability, which is important for replication and clinical use, liquid preparation for ease of swallowing, and a once daily dose of 5 mL of syrup. The dosage of 4,000 mg fish oil daily, consisting of 5 mL in the active treatment group was chosen as it provides 450 mg of EPA, close to the highest used in other studies [37] and 730 mg of DHA, which was well within the range of dosages used in other studies [36, 22, 15, 37]. The palatability of this supplement was informally assessed, involving taste tests by several children, adolescents and adults. No concerns were identified through this process.

The supplement manufacturer was contacted regarding obtaining bulk quantities of their supplement and possibly a placebo. The manufacturer offered to supply both at no cost. A placebo was developed using the same packaging and supplement ingredients without the omega-3 fatty acids. Bottles were coded according to lot numbers, which aided in randomization and blinding. Each participant was randomized to one of two lot numbers, one of which was the active supplement and the other the placebo. It was impossible to tell from the numerically coded lot number which lot was active versus placebo.

The active treatment was an orange flavoured syrup containing 4,000 mg of fish oil, including oils from anchovy, mackerel, sardine and tuna. Each 5 mL dosage

contained 450 mg of EPA and 730 mg of DHA. The placebo treatment was a syrup which matched the active treatment in appearance and flavour.

Participants were instructed to take 5 mL of syrup once daily. Participants were provided with a supply of syrup at each clinic visit by the research nurse. This supply was sufficient for the eight weeks between clinic visits with at least an additional 2-week supply to account for delays and cancelations. Participants were instructed to bring unused syrup to each clinic visit. Compliance was determined by measuring amounts of remaining syrup and using pill counts of other prescribed medications.

3.10 Measurements

The primary outcome measure was the change observed during six months of treatment, in parallel groups, of the C3T-T [40]. Secondary outcome measures were the Conners Third Edition: Parent's Report (C3P) [40], the Conners' Continuous Performance Test II (CCPT-II) [42], the Clinical Global Impression (CGI) (Appendix A) [44], and the Thirst/Skin Questionnaire (TSQ) (Appendix C) [29, 30, 22]. The Conners Third Edition: Teacher Report (C3T), the C3P and the CCPT-II are commercial products, protected by copyright and could not be reproduced as appendices. Descriptions of each of these measures are presented in the following paragraphs.

A subjective outcome measure, the C3T, was chosen as the primary outcome variable rather than an objective outcome measure, the CCPT-II, to maintain consistency with several of the key existing studies [36, 37]. As well, the CCPT-II is dependant on the state of the participant and the time of the test [42], whereas the C3T reports on a wide variety of behavioural characteristics over several months [40].

3.10.1 Study Schedule

As outlined in Table 3.1, the C3T and C3P were completed immediately prior to initiating treatment (Visit 2, Week 2) and immediately prior to completing the trial (Visit 5, Week 26). The CCPT-II and TSQ were completed at each clinic visit (Visits 2 - 5, Weeks 2, 10, 18 and 26). As the CGI measures the change from baseline, it was completed at each clinic visit except the initial visit (Visits 3 - 5, Weeks 10, 18 and 26).

3.10.2 Conners' Rating Scales

The Conners' Rating Scales (Parent and Teacher Versions) are self-report scales [40]. Clinically, they are widely used for screening, as diagnostic aides, and for monitoring treatment effectiveness. In research, they are also widely used as a surrogate for clinical diagnosis, to establish the severity of disease, and for monitoring treatment effectiveness. A large normative database supports the instruments' reliability and validity. The scales take 15–20 minutes to complete. The C3T contains 59 items, while the C3P contains 80 items. Both scales include the following subscales: Oppositional, Cognitive Problems/Inattention, Hyperactivity, Anxious-Shy, Perfectionism, Social Problems, Psychosomatic, Conners' Global Index, DSM-IV Symptom Subscales, and ADHD Index. The Conners' Global Index is the single best subscale to use as an overall indicator of severity of illness and level of impairment [40]. Higher scores reflect worse symptomatology. Scores less than 65 reflect non-clinical levels of symptomatology, between 65 and 69 reflect elevated (clinical) symptomatology, and greater than or equal to 70 reflect severe symptomatology.

The Conners' assessments were given to the parents/guardians of study participants during their first and last appointment (Weeks 0 and 26) (see Table 3.1). Parents

Table 3.1: Study Schedule

Visit	Week	Purpose	C3T	C3P	CGI	CCPT-II	TSQ	AEI	Nurse	MD	Pill Count
1	0	Recruitment							X	X	
2	2	Initiation of Treatment	X	X		X	X		X	X	
3	10	Follow-up Visit			X	X		X	X	X	X
4	18	Follow-up Visit			X	X		X	X	X	X
5	26	Final Study Visit	X	X	X	X	X	X	X	X	X

Note. C3T = Conners Third Edition: Teacher's Report. C3P = Conners Third Edition: Parent's Report.
 CGI = Clinical Global Impression. CCPT-II = Conners' Continuous Performance Test II.
 TSQ = ThirstSkin Questionnaire. AEI = Adverse Effect Inquiry. MD = Psychiatrist visit.

were asked to complete the C3T and ask the participants' teachers to complete the C3P. Parents and teachers were directed to follow the standard instructions included with the C3P and C3T.

3.10.3 Conners' Continuous Performance Test II

The CCPT-II is an automated, objective, computer-based test widely used clinically and in research with ADHD [42]. Respondents are required to press the space bar when any letter except the letter "X" appears. The results are considered a reflection of sustained attention, or vigilance, which is the essential deficit in ADHD. The computer-generated report provides numerous indices, with the Confidence Index (CCPT-CI), reported as a percentage likelihood of having ADHD, being the best and most widely used single measure of severity of illness and level of impairment. CCPT-CI scores above 50% are suggestive of ADHD.

The CCPT-II was administered by the research nurse. The C3T, the C3P and the CCPT-II were each scored and analyzed by a psychologist.

3.10.4 Clinical Global Impression

The CGI is an investigator-rated scale consisting of 3 subscales: severity, clinical improvement and efficacy (Appendix A) [44]. The CGI severity subscale consists of a 7-item scale, with scores ranging from 0 (not evaluated) to 7 (extremely ill). The CGI clinical improvement subscale is also a 7-item scale, with scores ranging from 0 (not evaluated) to 7 (much worse). The CGI efficacy subscale combines a measure of adverse events with a measure of clinical improvement, with scores ranging from 1 (no adverse effect/notable clinical improvement) to 16 (adverse effect is higher than beneficial effects/no clinical improvement/clinically worse). A group training session was conducted with the participating psychiatrists on the use of the CGI scale.

3.10.5 Thirst/Skin Questionnaire

The TSQ was developed by Stevens et al. [29, 30, 22] and was used with permission (Appendix C). This scale identifies participants with signs and symptoms of omega-3 fatty acid insufficiency. Stevens et al. [29, 30, 22] demonstrated that this questionnaire is an effective, economical and rapid means of identifying participants with signs and symptoms of omega-3 fatty acid insufficiency, comparable to more elaborate and involved tests, including assays based on blood and breath. The scores of the individual questions were summed for a total score. Scores of four or greater are considered indicative of clinically significant omega-3 fatty acid insufficiency. This questionnaire was administered both at the beginning and at the end of the study (Table 3.1).

3.10.6 Adverse Effect Inquiry

Adverse effect inquiry forms (AEI) (Appendix B) were completed at each follow-up visit, recording the presence or absence of 8 commonly cited side-effects of omega-3 fatty acid supplementation.

3.10.7 Baseline Characteristics

The following baseline characteristics were collected prior to randomization: age (years), gender, height (cm), weight (kg), blood pressure and pulse, ADHD subtype (inattentive, hyperactive/impulsive, or combined), medications and dosages, TSQ score, C3T (t-scores), C3P (t-scores), CCPT-CI (percentage), comorbid psychiatric diagnoses (DSM-IV TR Code). Medications were recorded at baseline and throughout the study using medication tracking sheets.

3.11 Study Schedule

Once patients and their parent(s) or guardian(s) agreed to participate in the study and informed consent was obtained, they met with the research nurse (Table 3.1). The research nurse then oriented the parent(s) or guardian(s) to the C3P and the C3T, instructing them to complete the C3P themselves and have the participants' primary teacher complete the C3T and return both the C3P and the C3T to the appointment with the research nurse in two weeks or later. Failure to complete these forms or attend this follow-up appointment resulted in exclusion from the study prior to randomization.

At the follow-up visit with the research nurse (week 2), the baseline data noted in subsection 3.10.7 were recorded. In addition, the CCPT-II was administered at this follow-up visit to establish a baseline score [42]. The CGI was not completed at this follow-up appointment. The participant's psychiatrist also completed an enrolment form, including the baseline characteristics with as much redundancy as possible to ensure maximum accuracy of the data. The study did not require that the patients and their parent(s) or guardian(s) meet with the psychiatrist during their first follow-up visit. The research nurse conducted all subsequent measures of height, weight, blood pressure and pulse for consistency. The research nurse determined treatment assignment according to the method outlined in section 3.6. The research nurse reviewed the schedule of survey administration with each participant and their parent(s) or guardian(s) and provided them with four 114 mL bottles of the syrup (4×114 mL bottles @ 5 mL/day = an 88-day supply) and a follow-up appointment with their psychiatrist in eight weeks (week 10).

At each follow-up appointment following treatment initiation (weeks 10, 18 and 26), the research nurse measured the participant's height, weight, blood pressure

and pulse. At each follow-up visit, the nurse also measured the remaining syrup and conducted pill counts of other prescribed medications to estimate compliance. The psychiatrist completed a CGI scale at each visit. The participants completed the CCPT-II and a side-effects monitoring survey at each clinic visit.

On weeks 10 and 18, the participants and their parent(s) or guardian(s) were provided with another four 114 mL bottles of the coded syrup and a follow-up appointment with their psychiatrist in eight weeks. At the week 18 clinic visit, the research nurse gave the participants and their parent(s) or guardian(s) another C3T and C3P, with instructions to complete them prior to their last clinic visit at week 26. The research nurse also phoned the participants and their parent(s) or guardian(s) during week 24 to remind them to complete the survey. The TSQ was repeated at the final clinic visit. Participants and their parent(s) or guardian(s) had the opportunity to ask questions with any team member during these clinic visits. They were also instructed to contact the research nurse between visits with any questions.

Perfect attendance at follow-up appointments was not compulsory to remain in the study. Study participants were contacted following missed appointments by the research nurse. They were offered another appointment and arrangements would have been made for a another supply of their assigned supplement. Unfortunately, all study participants that missed appointments chose to withdraw from the study when they were contacted by the research nurse. This is discussed further in section 4.3 and section 5.3.

3.12 Statistical Analysis

3.12.1 Baseline Data

Baseline data were compared using t tests for continuous variables, χ^2 and Fisher's exact tests for categorical and nominal variables, and Mann-Whitney U tests for rank and ordinal variables.

3.12.2 Planned Analyses

Planned group comparisons were performed on the primary and secondary outcome measures where possible. Data distributions were normal for the C3T [40], the C3P [40], CCPT-II [42] and CGI; therefore 2-tailed t tests ($p < .05$) were used for these analyses. The TSQ produces non-parametric data requiring analysis using the Mann-Whitney U , 2-tailed tests ($p < .05$). An *a priori* decision was made to use the last observation carried forward (LOCF) for missing data.

The original intent was to use multivariate analysis to assess the effect of group assignment on the primary and secondary outcomes, controlling for potential covariates. These covariates were to include the degree of omega-3 fatty acid insufficiency, as measured by the TSQ, number of comorbid diagnoses, age, gender, ADHD subtype, and baseline ADHD severity, as measured by the C3T, C3P and CCPT-II. It was not possible to conduct this analysis due to insufficient data. One patient per group completed the study, resulting in one completed pair of C3T and C3P per group. The C3T and C3P were each completed prior to the first and last clinic visits. This is discussed further in section 4.3 and section 5.3.

All study data were collected in a password protected Microsoft Excel Spreadsheet. Statistical analysis of study data was conducted in SPSS version 20.

Chapter 4

Results

This was a pilot study intended to assess the feasibility of augmenting the treatment of ADHD in children and adolescents with an omega-3 fatty acid supplement. Due to a high number of dropouts the study was not sufficiently powered to detect group differences. All values of the primary and secondary outcomes yielded p values greater than .05. The values are not reported on a scale as this would imply meaning where none exists. Reporting specific values might lead the reader to make inferences about the strength of associations, which are not appropriate.

4.1 Demographics

4.1.1 Age

As displayed in Table 4.1 and Figure 4.1, the mean ages of the active, placebo and combined groups were 13.3 ($SD = 3.7$), 12 ($SD = 3.6$) and 12.7 ($SD = 4.0$) respectively. An independent-samples t test was conducted to compare the mean age of active and placebo group participants. There was no significant difference in the mean age of

active and placebo group participants; $p > .05$. This suggests the active and placebo groups were comparable in their mean ages.

Table 4.1: Age

	M^a	SD	Min.	Max.	Mdn
Active ^b	13.3	3.7	8.1	16.8	15.4
Placebo ^b	12.0	3.6	6.7	16.9	12.8
Total	13.0	4.0	6.7	16.9	13.5

Note. M = Mean. SD = Standard Deviation. Min. = Minimum.
 Max. = Maximum. Mdn = Median.
^aActive vs. Placebo: $p > .05$. ^b $n = 7$

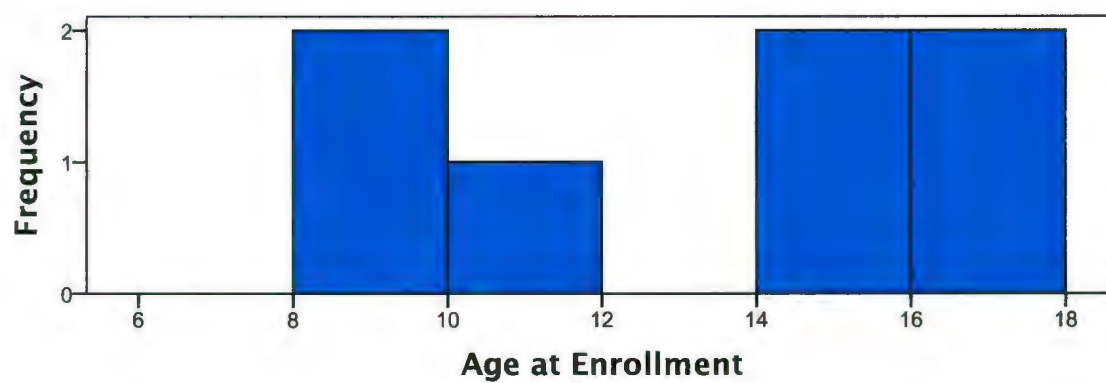
4.1.2 Gender

There was a nearly even distribution of males to females in the study groups, with 43%, 57% and 50% males in the active, control and combined groups respectively. A Pearson Chi-Square test was conducted to compare the proportions of male and female participants in the active and placebo groups. There was no significant difference in these proportions; $p > .05$. This suggests the active and placebo groups were comparable in their gender distributions.

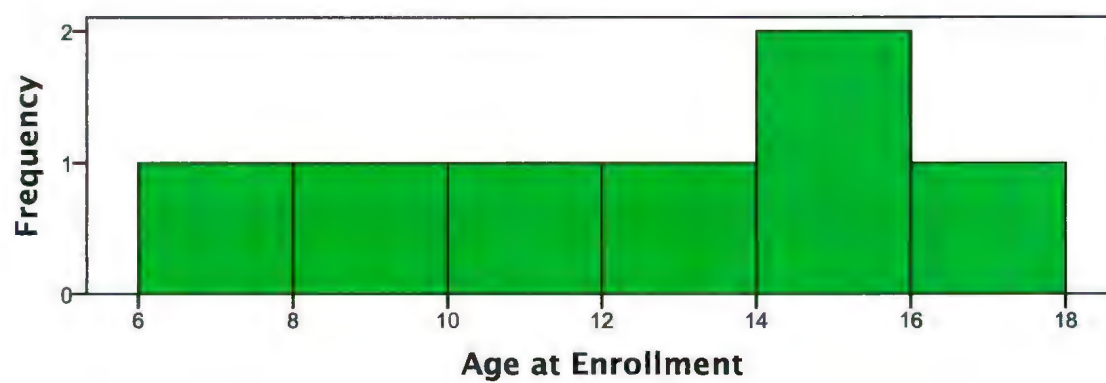
4.1.3 ADHD Subtype

Eighty-six percent of the active group and 71% of the control group were diagnosed with the combined subtype of ADHD (Table 4.2). Fourteen percent of each group were diagnosed with the inattentive subtype, while none of the active group and 14% of the control group were diagnosed with the hyperactive/impulsive subtype.

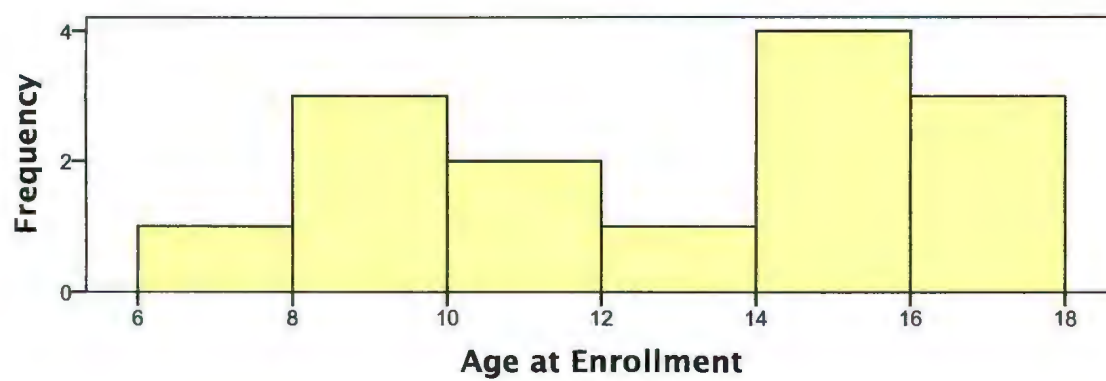
As noted in Table 4.2, the numbers and proportions of participants with inattentive, hyperactive/impulsive and combined subtypes of ADHD in the active and



(a) Active Group



(b) Placebo Group



(c) Total

Figure 4.1: Histograms of Age

placebo groups were compared. A Pearson Chi-Square test was conducted to compare the proportions of participants in active and placebo groups with each subtype of ADHD. There was no significant difference in these proportions; $p > .05$. This suggests the active and placebo groups were comparable in their distribution of ADHD subtypes.

Table 4.2: Attention Deficit Hyperactivity Disorder Subtypes

Sub-type	Active		Placebo		Total	
	<i>n</i>	%	<i>n</i>	%	<i>N</i>	%
Inattentive Type	1	14	1	14	2	14
Hyperactive/Impulsive Type	0	0	1	7	1	7
Combined Type	6	86	5	71	11	79
<i>Note.</i> Pearson Chi-Square test: $p > .05$.						

4.1.4 Comorbidities

As noted in Table 4.3 and Figure 4.2, the numbers and types of comorbidities in the active and placebo groups were compared. Pearson Chi-Square tests were conducted to compare the proportions of participants in active and placebo groups with these comorbid diagnoses. There were no significant differences in these proportions; $p > .05$. This suggests the active and placebo groups were comparable in the rates of these comorbid diagnoses.

A visual inspection of the distribution of the total number of comorbid diagnoses among study participants (Figure 4.2) suggested this variable may not be normally distributed. A Shapiro-Wilk Test of normality indicated this variable significantly deviates from a normal distribution; $p < .05$. This suggests that non-parametric analysis is necessary.

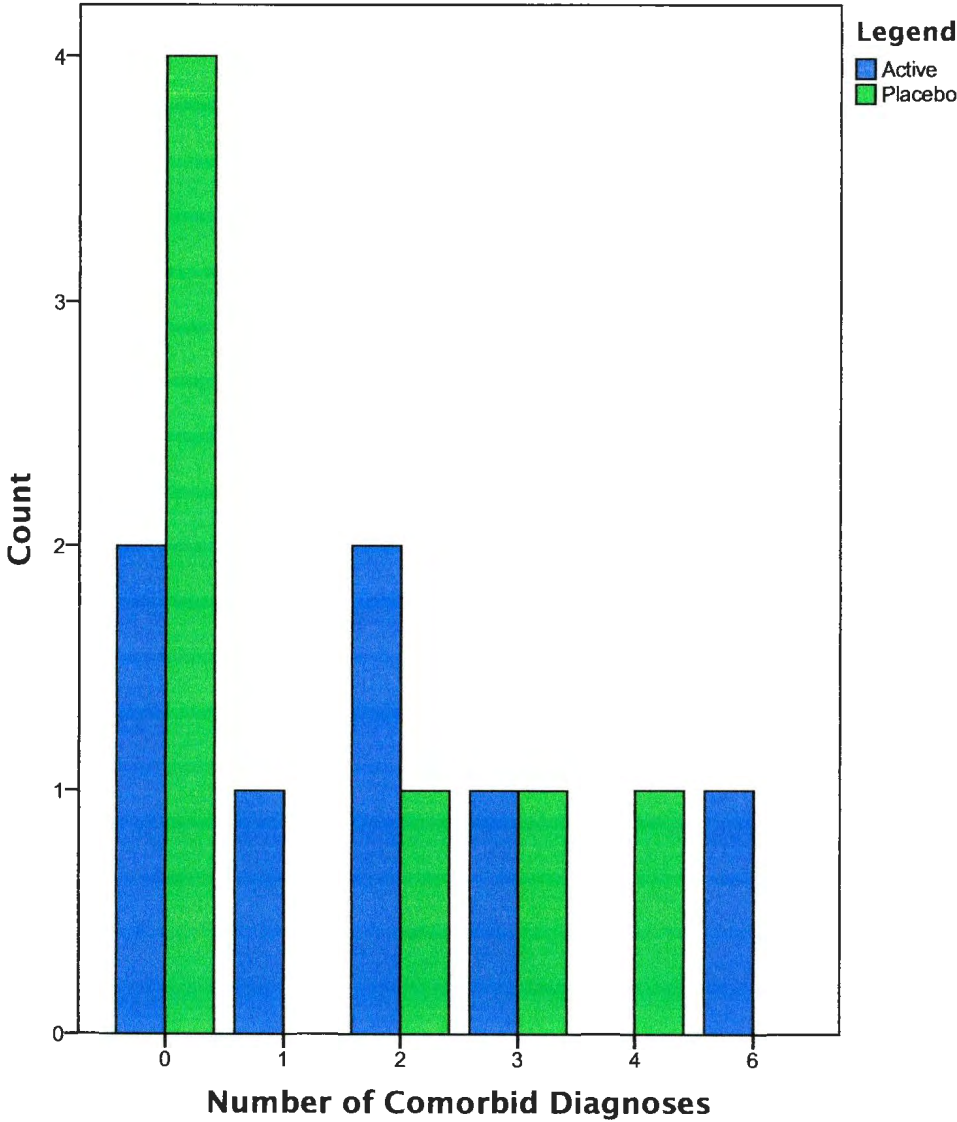


Figure 4.2: Bar Chart of the Number of Comorbid Diagnoses Among Treatment Groups

Table 4.3: Comorbidities

Sub-type	Active		Placebo		Total	
	<i>n</i>	%	<i>n</i>	%	<i>N</i>	%
Conduct Disorder	1	14	0	0	1	7
Generalized Anxiety Disorder	3	43	3	43	6	43
Learning Disability	1	14	0	0	1	7
Obsessive Compulsive Disorder	2	29	2	29	4	29
Oppositional Defiant Disorder	1	14	2	29	3	21
Social Anxiety Disorder	1	14	1	14	2	14
Tourette Syndrome	0	0	1	14	1	7

Note. Pearson Chi-Square tests: $p > .05$.

Participants had a median of 2.0 ($M = 2.0$, $SD = 2.1$) and 0.0 ($M = 1.3$, $SD = 1.7$) comorbidities in the active and placebo groups respectively, with a combined median of 1.5 ($M = 1.6$, $SD = 1.9$) comorbidities. A Mann-Whitney U test was conducted to compare the median number of comorbid diagnoses among active and placebo group participants. There was no significant difference in the mean number of comorbid diagnoses between active and placebo group participants; $p > .05$. This suggests the active and placebo groups were comparable in their mean rates of comorbidity.

In total, 8 (57%) of the study participants had at least one comorbid diagnosis, while 6 (43%) did not. A single-sample Chi-Square test did not identify any significant difference in the proportions of study participants with and without at least one comorbid diagnosis; $p > .05$. This suggests that the presence or absence of a comorbid diagnosis was approximately equally likely among study participants.

To determine whether study participants had a median number of comorbid diagnoses greater than 1, a one-sample Wilcoxon Signed Rank Test was conducted to compare the median number of comorbid diagnoses to 1. The combined group's median number of comorbid diagnoses ($Mdn = 1.5$, $M = 1.6$, $SD = 1.9$) was not

significantly different than 1; $p > .05$. This analysis was repeated, including only study participants with at least one comorbid diagnosis, to determine if the median number of comorbid diagnoses was greater than 1 in this subset. This subset's median number of comorbid diagnoses ($Mdn = 2.5$, $M = 2.9$, $SD = 1.6$) was significantly different than 1; $p < .05$. This suggests a bimodal distribution of this variable, with a nearly equal likelihood of study participants having either no comorbidities or multiple comorbidities. Participants with a single comorbidity appear to be relatively underrepresented. The study population seemed to be heterogeneous in this regard, with approximately half the study participants having no additional diagnoses, while the remainder had multiple additional diagnoses, adding to their cumulative burden of illnesses.

4.1.5 Number of Medications

A visual inspection of the distribution of the total number of medications prescribed per study participant (Figure 4.3) suggested this variable may not be normally distributed. A Shapiro-Wilk Test of normality indicated this variable significantly deviates from a normal distribution; $p < .05$. This suggests that non-parametric analysis is necessary.

Participants enrolled in the active group were prescribed a median of 1.0 ($M = 1.4$, $SD = 0.5$) medications while those in the control group were prescribed a median of 2.0 ($M = 1.9$, $SD = 0.9$) medications. A Mann-Whitney U test was conducted to compare the median number of medications prescribed to participants in active and placebo groups. There was no significant difference in the mean number of medications prescribed to active and placebo group participants; $p > .05$. This suggests the active and placebo groups were comparable in the median number of medications prescribed.

To determine whether study participants had a median number of prescribed medications greater than 1, which would otherwise be expected for uncomplicated ADHD [3, 4, 2], a one-sample Wilcoxon Signed Rank Test was conducted to compare the

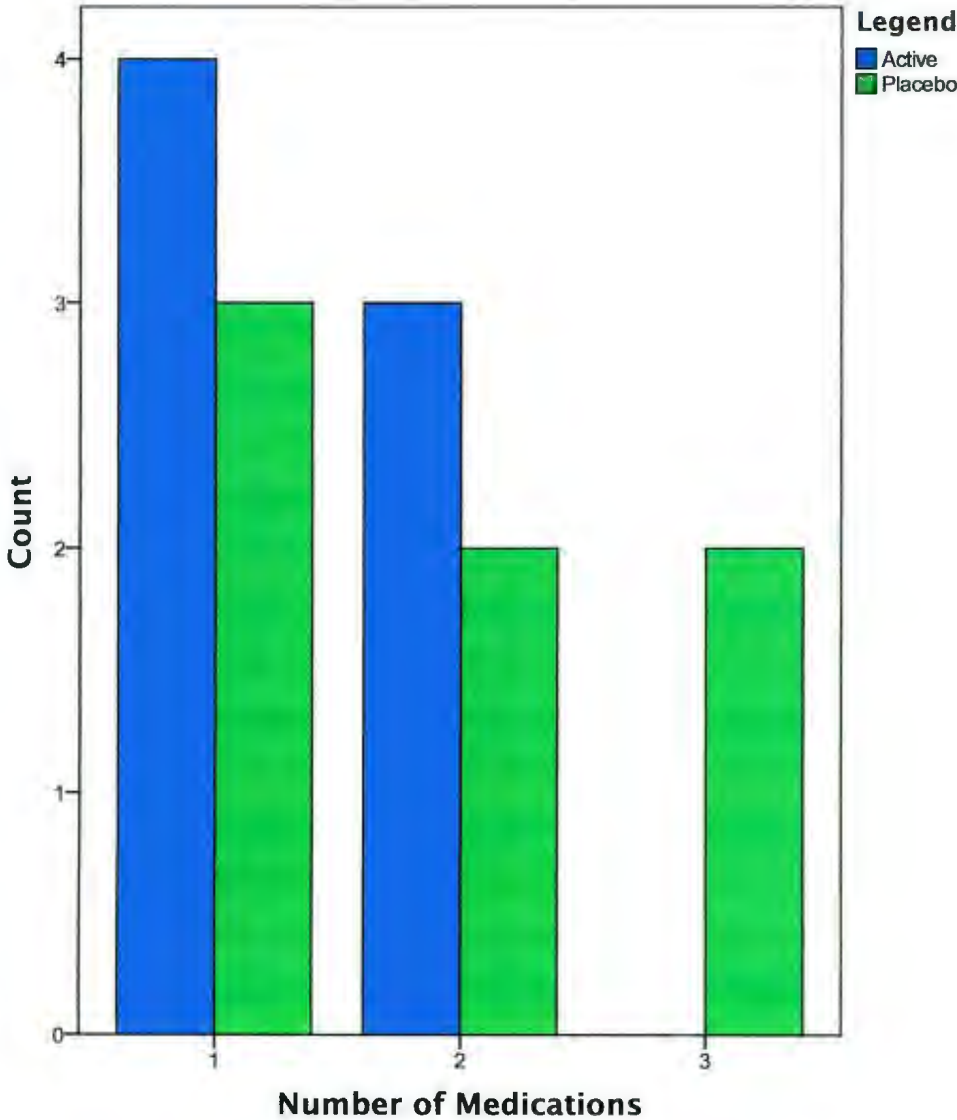


Figure 4.3: Bar Chart of the Number of Medications Prescribed Per Patient Among Treatment Groups

median number of prescribed medications to 1. Combined, participants were prescribed a median of 1.5 ($M = 1.6$, $SD = 0.7$) medications. This median number of medications prescribed was significantly greater than 1; $p < .05$. Study participants were therefore more likely to be prescribed additional medications. This finding could suggest a high level of ADHD severity among participants, or a high likelihood of comorbid diagnoses requiring additional medications. In either case, the prescription of additional medications suggests an additional burden of illness beyond uncomplicated ADHD, which would usually be treated with a single medication [3, 4, 2].

4.2 Baseline Characteristics

4.2.1 ADHD Severity Measures

There were 3 composite measures of ADHD severity derived from the data: the CCPT-CI, the C3T-T, and the C3P-T. Each measure was generated automatically as part of each standardized tool's schedule of analysis, as discussed in the methods. Parents, guardians and teachers completed the C3P and C3T in every case that a participant returned for a follow-up appointment. No problems in completing these assessments were evident.

4.2.1.1 Conners Continuous Performance Test II

Four study participants did not complete their baseline CCPT-II prior to receiving their supplements. These baseline assessments were not completed because of an inability or unwillingness to complete the entire assessment process. Incomplete assessments resulted in no data. These 4 participants had each been assigned to the active group but had not begun taking their supplement at the time of this initial assessment.

As displayed in Figure 4.4, the mean baseline CCPT-CI was 61.9 ($SD = 24.1$), 52.3 ($SD = 16.7$), and 55.2 ($SD = 18.4$) in the active, placebo and combined groups respectively, with Confidence Index scores above 50% suggesting clinically significant symptoms of ADHD. An independent-samples t test was conducted to compare the mean CCPT-CI scores by participants in active and placebo groups. There was no significant difference in the mean scores for active and placebo group participants; $p > .05$. This suggests the active and placebo groups were comparable in their baseline ADHD symptom severity, as measured by the CCPT-CI.

A single-sample two-sided t test was conducted to compare the mean CCPT-CI score by participants in the combined group to the “Clinically Significant” cut-off score of 50%. The combined group’s mean score ($M = 55.2$, $SD = 18.4$) was not significantly different than the “Clinically Significant” cut-off score of 50%; $p > .05$. This suggests the average severity of ADHD symptoms among study participants, as measured by the CCPT-CI, were clinically significant but not markedly so.

4.2.1.2 Conners 3: Teacher Report

As noted in Figure 4.5 and Table 4.4, the mean baseline C3T-T scores were 76.1 ($SD = 13.4$), 74.6 ($SD = 13.8$), and 75.4 ($SD = 13.1$) in the active, placebo and combined groups respectively. An independent-samples t test was conducted to compare the mean C3T-T scores by participants in active and placebo groups. There was no significant difference in the mean scores for active and placebo group participants; $p > .05$. The remaining mean subtest scores in the C3T did not differ significantly between the active and placebo groups. This suggests the active and placebo groups were comparable in their mean baseline symptom severity, as reported by their teachers and measured by the C3T, including symptoms of ADHD and commonly associated Disruptive Behaviour Disorders.

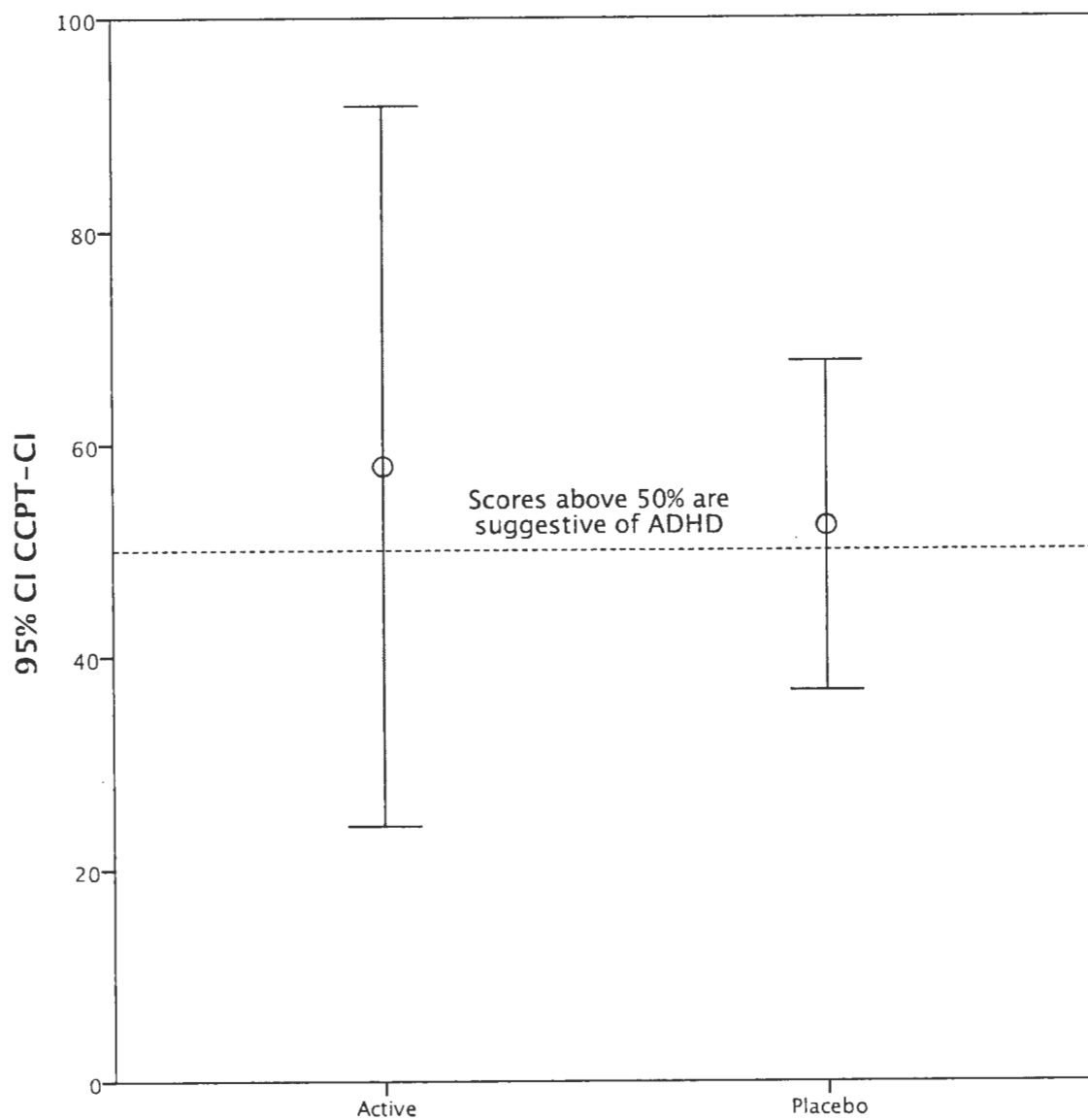


Figure 4.4: Mean Initial Conners Continuous Performance Test II: Confidence Index (CCPT-CI) Results (95% Confidence Intervals)

Table 4.4: Conners 3: Teachers Report (Baseline)

Sub-test ^{a,b}	Active ^c		Placebo ^c		Total ^{d,e}	
	<i>M</i>	<i>SD</i>	<i>M</i>	<i>SD</i>	<i>M</i>	<i>SD</i>
Inattention	72.9	15.4	67.6	10.7	70.2	1.5
Hyperactivity/Impulsivity	72.3	19.2	69.6	15.6	70.9	1.3
Learning Problems	63.4	13.4	62.6	9.8	63.0	-1.8
Executive Functioning	63.1	13.9	66.1	10.1	64.6	-0.1
Defiance/Aggression	80.0	15.7	60.3	29.0	70.1	0.8
Peer Relations	70.9	18.4	56.0	14.3	63.4	-0.3
ADHD (Inattentive Type)	69.3	17.3	66.7	11.1	68.0	0.8
ADHD (Hyperactive-Impulsive Type)	72.6	19.4	68.6	16.7	70.6	1.2
Conduct Disorder	69.0	13.5	56.6	9.8	62.8	-0.6
Oppositional Defiant Disorder	81.6	15.2	70.6	16.4	76.1*	2.6
Global Index: Restless-Impulsive	74.9	13.6	71.7	15.0	73.3*	2.2
Global Index: Emotional Lability	71.7	16.0	71.1	17.2	71.4	1.5
Global Index: Total	76.1	13.4	74.6	13.8	75.4*	3.0

Note. *M* = Mean. *SD* = Standard Deviation. ^aScores < 65 are Average or Below; 65 - 69 are Elevated; ≥ 70 are Very Elevated.

^bIndependent-samples *t* test comparing mean group scores: all $p > .05$.

^c $n = 7$. ^d $N = 14$. ^eSingle-sample *t* test of combined group scores versus 65 cutoff score. * $M > 65$; $p < .05$.

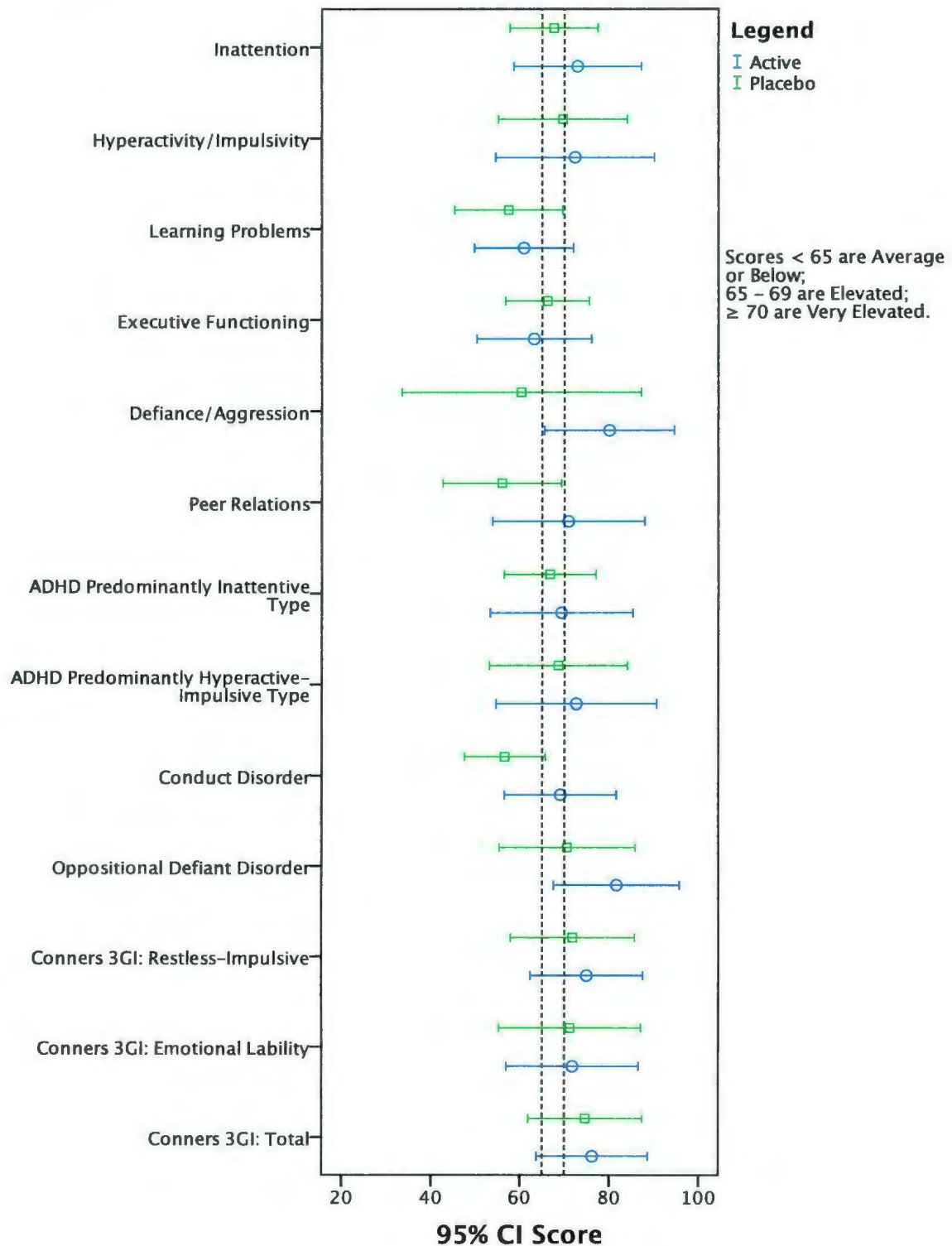


Figure 4.5: Mean Conners 3: Teachers Reports Subtest Scores (95% Confidence Intervals)

A single-sample two-sided t test was conducted to compare the mean C3T-T score by participants in the combined group to the “Elevated” cut-off score of 65. The combined group’s mean total score ($M = 75.4$, $SD = 13.1$) was significantly greater than the “Elevated” cut-off score of 65; $p < .05$. This suggests the average severity of ADHD symptoms among study participants, as reported by their teachers and measured by the C3T-T, was elevated and likely clinically significant.

A single-sample two-sided t test was conducted to compare the mean C3T-T score by participants in the combined group to the “Very Elevated” cut-off score of 70. The combined group’s mean total score ($M = 75.4$, $SD = 13.1$) was not significantly greater than the “Very Elevated” cut-off score of 70; $p > .05$. This suggests the average severity of ADHD symptoms among study participants, as reported by their teachers and measured by the C3T-T, was elevated but not markedly so.

Single-sample two-sided t tests were conducted to compare the mean C3T subtest scores by participants in the combined group to the “Elevated” cut-off score of 65. The mean scores in the Oppositional Defiant Disorder ($M = 76.1$, $SD = 16.2$) and Global Index: Restless-Impulsive ($M = 73.3$, $SD = 13.8$) sub-tests were each significantly greater than 65; $p < .05$. The remaining subtests were not significantly different from the “Elevated” cut-off score of 65; $p > .05$. This suggests the average symptom severity of ADHD and commonly associated Disruptive Behaviour Disorders among study participants, as reported by their teachers and measured by the C3T subtests, were elevated and likely clinically significant in several cases and did not exceed this threshold in other cases.

4.2.1.3 Conners 3: Parent Report

As noted in Table 4.5 and Figure 4.6, the mean C3P-T scores were 79.9 ($SD = 8.9$), 89.6 ($SD = 0.8$), and 84.7 ($SD = 7.9$) in the active, placebo and combined groups

respectively. An independent-samples t test was conducted to compare the mean C3P-T scores by participants in active and placebo groups. There was a significant difference in the mean scores for active and placebo group participants; $p < .05$. This suggests that placebo group participants experienced significantly greater mean baseline ADHD symptom severity, as reported by their parent(s) and/or guardians and measured by the C3P-T, than did active group participants. The remaining mean subtest scores in the C3P did not differ significantly between the active and placebo groups. This suggests that active and placebo group participants were otherwise comparable in their mean baseline symptom severity, as reported by their parent(s) and/or guardians and measured by the C3P subtests, including symptoms of ADHD and commonly associated Disruptive Behaviour Disorders.

A single-sample two-sided t test was conducted to compare the mean C3P-T score by participants in the combined group to the "Very Elevated" cut-off score of 70. The combined group's mean total score ($M = 84.7$, $SD = 7.9$) was significantly greater than the "Very Elevated" cut-off score of 70; $p < .05$. This suggests the average severity of ADHD symptoms among study participants, as reported by their parent(s) and/or guardians and measured by the C3P-T, was markedly elevated and clinically significant.

Single-sample two-sided t tests were conducted to compare the mean C3P subtest scores by participants in the combined group to the "Very Elevated" cut-off score of 70. The mean scores in 7 of the 12 remaining sub-tests (Inattention, Hyperactivity/Impulsivity, Defiance/Aggression, ADHD (Inattentive Type), ADHD (Hyperactive-Impulsive Type), Oppositional Defiant Disorder and Global Index: Emotional Lability) were significantly greater than 70; $p < .05$. The mean scores of an additional 2 sub-tests (Executive Functioning and Global Index: Restless-Impulsive)

Table 4.5: Conners 3: Parent Report (Baseline)

Sub-test ^{a,b}	Active ^c		Placebo ^c		Total ^{d,e}	
	<i>M</i>	<i>SD</i>	<i>M</i>	<i>SD</i>	<i>M</i>	<i>SD</i>
Inattention	76.6	9.6	81.1	8.7	78.9 ^{***}	9.1
Hyperactivity/Impulsivity	78.1	10.7	87.0	7.5	82.6 ^{***}	10.0
Learning Problems	67.0	15.2	62.9	13.9	64.9	14.2
Executive Functioning	74.3	11.3	75.4	11.8	74.9 ^{**}	11.1
Defiance/Aggression	73.6	18.0	85.9	8.6	79.7 ^{***}	15.0
Peer Relations	66.7	17.8	73.1	18.5	69.9	17.8
ADHD (Inattentive Type)	78.6	11.0	77.6	10.2	78.1 ^{***}	10.2
ADHD (Hyperactive-Impulsive Type)	76.7	11.0	87.0	7.5	81.9 ^{***}	10.5
Conduct Disorder	68.1	17.0	76.6	13.5	72.4	15.3
Oppositional Defiant Disorder	74.3	14.4	81.9	8.9	78.1 ^{***}	12.1
Global Index: Restless-Impulsive	80.1	10.7	86.6	5.2	83.4 ^{**}	8.7
Global Index: Emotional Lability	71.6	6.9	81.9	11.7	76.7 ^{***}	10.7
Global Index: Total [*]	79.9	8.9	89.6	0.8	84.7 ^{***}	7.9

Note. *M* = Mean. *SD* = Standard Deviation. ^aScores < 65 are Average or Below; 65 - 69 are Elevated; ≥ 70 are Very Elevated.

^bIndependent-samples *t* test comparing mean group scores. ^c*n* = 7.

^d*N* = 14. ^eSingle-sample *t* test of combined group scores versus 65 and 70 cutoff scores. ^{*}Active \neq Placebo; $p < .05$. ^{**} $M > 65$; $p < .05$.

^{***} $M > 70$; $p < .05$.

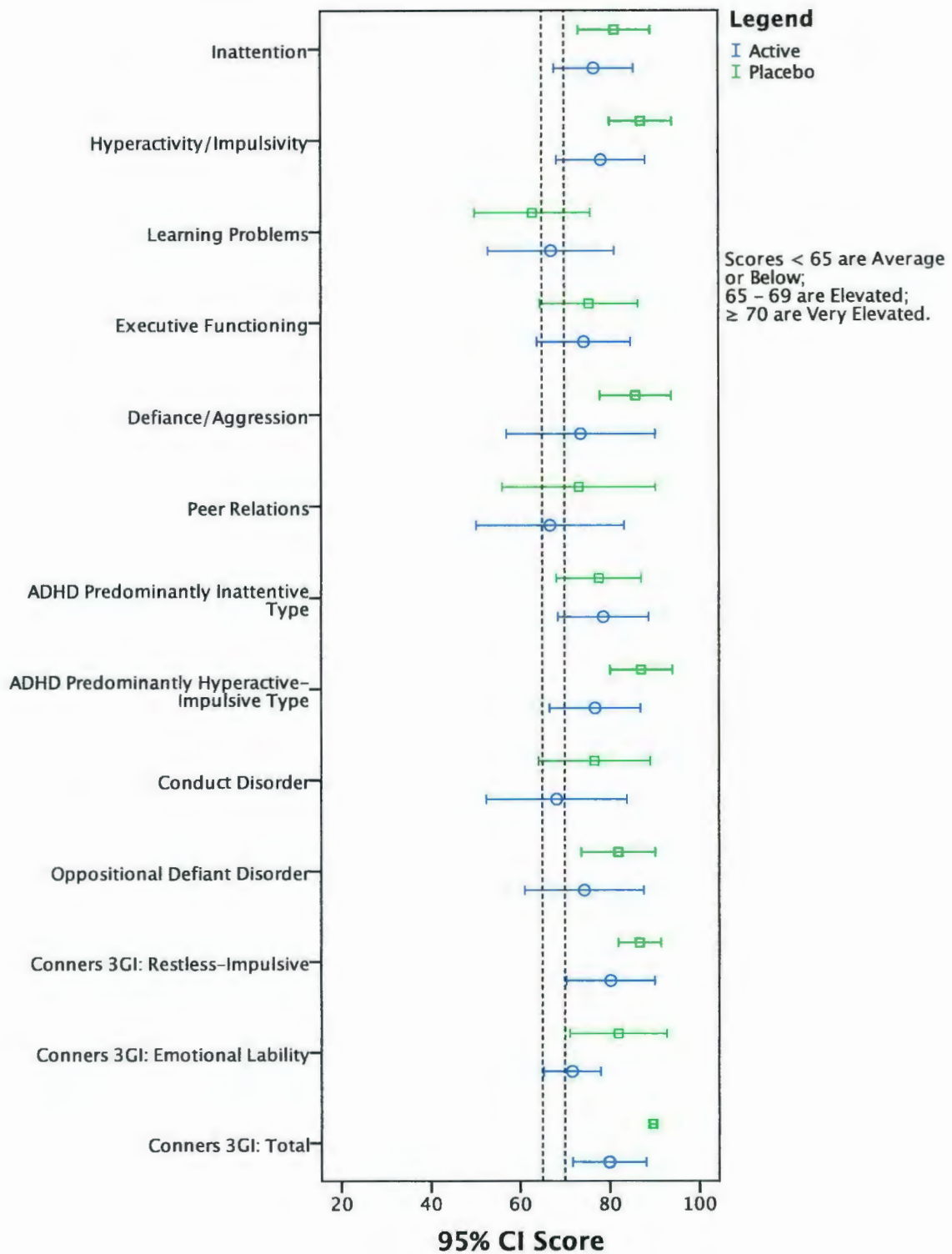


Figure 4.6: Mean Conners 3: Parent Reports Subtest Scores (95% Confidence Intervals)

were significantly greater than the “Elevated” cut-off score of 65; $p < .05$. The remaining subtests (Learning Problems, Peer Relations and Conduct Disorder) were not significantly different from the “Elevated” cut-off score of 65; $p > .05$. This suggests the average symptom severity of ADHD and commonly associated Disruptive Behaviour Disorders among study participants, as reported by their parent(s) and/or guardians and measured by the C3T subtests, were elevated and likely clinically significant in several cases and did not exceed this threshold in other cases.

4.2.1.4 Conners 3: Teacher and Parent Reports Compared

The C3T and C3P include the same sub-tests and the same standardized scoring system. The teacher and parent mean baseline sub-test scores were compared using two-sided paired t tests. The active and placebo groups were combined for these baseline comparisons.

The Parent report scores were consistently higher in each subtest, with differences ranging from 1.9 to 11.6 (t-score) (Table 4.6 & Figure 4.7). Seven of the 13 sub-tests (Inattention, Hyperactivity/Impulsivity, Executive Functioning, ADHD (Inattentive Type), ADHD (Hyperactive-Impulsive Type), Global Index: Restless-Impulsive, Global Index: Total) were significantly different; $p < .05$. This suggests that, in some cases, study participant parent(s) and/or guardians reported significantly higher symptom severity of ADHD and commonly associated Disruptive Behaviour Disorders than did their teachers, while in other cases, their reporting of symptom severity was comparable.

4.2.2 Signs of Omega-3 Fatty Acid Deficiency

Approximately half of each group were omega-3 deficient according to the initial TSQ (Appendix C), with total scores greater than or equal to 4. A Pearson Chi-Square

Table 4.6: Baseline Conners 3: Teacher and Parent Reports Compared

Sub-test ^a	Teacher ^b		Parent ^b		D^c
	M	SD	M	SD	
Inattention	70.2	13.0	78.9	9.1	8.7*
Hyperactivity/Impulsivity	70.9	16.9	82.6	10.0	11.6*
Learning Problems	63.0	11.3	64.9	14.2	1.9
Executive Functioning	64.6	11.8	74.9	11.1	10.2*
Defiance/Aggression	70.1	24.6	79.7	15.0	9.6
Peer Relations	63.4	17.6	69.9	17.8	6.5
ADHD (Inattentive Type)	68.0	14.0	78.1	10.2	10.1*
ADHD (Hyperactive-Impulsive Type)	70.6	17.5	81.9	10.5	11.3*
Conduct Disorder	62.8	13.1	72.4	15.3	9.6
Oppositional Defiant Disorder	76.1	16.2	78.1	12.1	2.0
Global Index: Restless-Impulsive	73.3	13.8	83.4	8.7	10.1*
Global Index: Emotional Lability	71.4	15.9	76.7	10.7	5.3
Global Index: Total	75.4	13.1	84.7	7.9	9.3*

Note. M = Mean. SD = Standard Deviation.

D = Mean Parent - Teacher sub-test scores.

^aScores < 65 are Average or Below; 65 - 69 are Elevated;

≥ 70 are Very Elevated. ^bActive and Placebo groups combined.

^cIndependent-samples t test comparing mean group scores.

* $p < .05$.

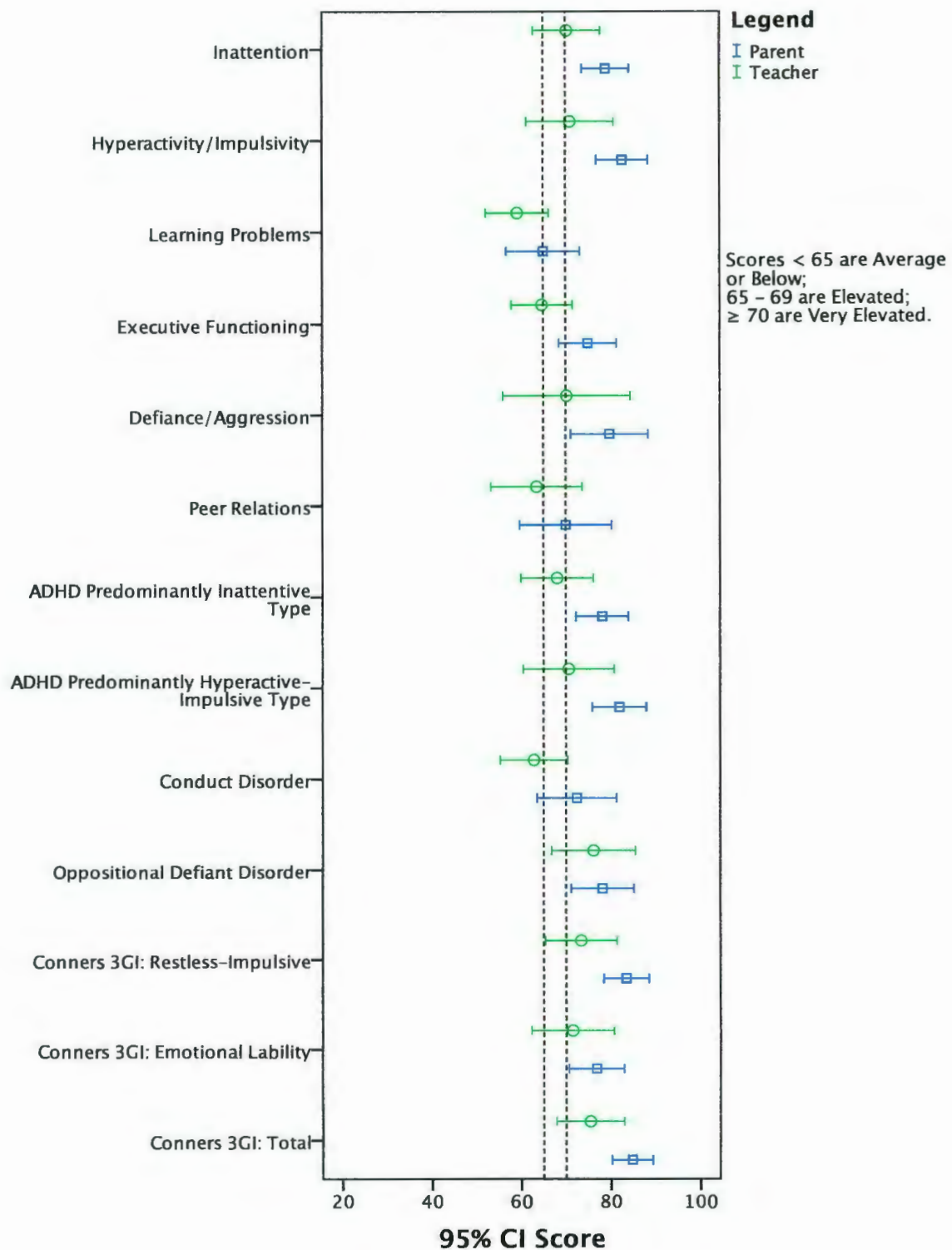


Figure 4.7: Mean Conners 3: Teacher and Parent Reports Subtest Scores (95% Confidence Intervals)

test was conducted to compare the proportions of participants in active and placebo groups with initial TSQ total scores ≥ 4 . There was no significant difference in the proportions of active group participants ($n = 4$, 57%) and placebo group participants with total scores greater than or equal to 4 ($n = 3$, 43%); $p > .05$. This suggests the active and placebo groups were comparable in the prevalence of baseline omega-3 fatty acid deficiency, as measured by the TSQ.

A Mann-Whitney U test was conducted to compare the median initial TSQ scores among active and placebo group participants (Table 4.7). There was no significant difference in the median initial TSQ scores in the active group participants ($Mdn = 6.0$, $M = 5.6$, $SD = 4.4$) and the placebo group participants ($Mdn = 3.0$, $M = 3.7$, $SD = 3.5$), $p > .05$. This suggests the active and placebo groups were comparable in median degree of baseline omega-3 fatty acid deficiency, as measured by the TSQ.

Table 4.7: Thirst-Skin Questionnaire Initial Responses

Specific Symptoms ^a	Active ^b			Placebo ^b			Total ^c		
	M	Mdn	SD	M	Mdn	SD	M	Mdn	SD
Brittle Nails	0.6	0.0	1.0	0.6	0.0	1.0	0.6	0.0	0.9
Bumps	1.0	0.0	1.4	1.1	1.0	1.3	1.1	0.5	1.3
Dandruff	0.3	0.0	0.5	0.1	0.0	0.4	0.2	0.0	0.4
Dry Hair	0.3	0.0	0.5	0.1	0.0	0.4	0.2	0.0	0.4
Dry Skin	0.9	0.0	1.2	0.1	0.0	0.4	0.5	0.0	0.9
Excessive Thirst	2.1	3.0	1.2	1.3	1.0	1.4	1.7	2.0	1.3
Frequently Urinates	1.0	0.0	1.3	0.9	0.0	1.5	0.9	0.0	1.3
Total Score ^d	5.6	6.0	4.4	3.7	3.0	3.5	4.6	3.5	3.9

Note. M = Mean. Mdn = Median. SD = Standard Deviation.

^aMann-Whitney U tests comparing group median TSQ scores; all $p > .05$. ^b $n = 7$. ^c $N = 14$.

^dScores ≥ 4 indicate Omega-3 fatty acid deficiency.

Mann-Whitney U tests were conducted to compare the median scores for each symptom on the initial TSQ symptoms among active and placebo group participants. There were no significant differences in these median initial scores for each symptom among the active group participants and the placebo group participants; $p > .05$. This suggests the active and placebo groups were comparable in the baseline prevalence of specific symptoms suggestive of omega-3 fatty acid deficiency, as measured by the TSQ.

A single-sample two-sided Wilcoxon signed rank test was conducted to evaluate whether the median initial TSQ total score for the total study population was significantly different than 4. The median of the initial TSQ total score for the total study population was 3.5 ($M = 4.6$, $SD = 3.9$). The results did not indicate a significant difference, $p > .05$. This suggests the median baseline degree of omega-3 fatty acid deficiency did not exceed the clinically significant threshold, with a TSQ total score greater than 4.

4.3 Study Completion

Five (71%) of the active group participants and 3 (43%) of the placebo group participants did not return for the first check-in following treatment assignment at 10 weeks (Table 4.8). Another 1 (14%) of the active group participants and 3 (43%) of the placebo group participants did not return for the second check-in at 18 weeks. One study participant per group returned for the 18 and 26 week visits, completing the study (14%). Active group participants remained in the study for a mean of 6.4 weeks ($SD = 9.2$) while placebo group participants withdrew after an average of 8.8 weeks ($SD = 8.4$).

Table 4.8: Study Completion

Week	Description	Active		Placebo	
		<i>n</i>	%	<i>n</i>	%
0	Study introduction visit	7	100	7	100
2	Treatment initiation	7	100	7	100
10	Follow-up visit 1	2	29	4	57
18	Follow-up visit 2	1	14	1	14
26	Study Completion	1	14	1	14

Note. *n* = Number of participants returning.
 %= Percentage of group.

A Kaplan–Meier survival analysis (log–rank test) was conducted to compare study withdrawal by participants in active and placebo groups. There was no significant difference in the survival curves between active and placebo group participants; $p > .05$. This suggests the active and placebo groups were comparable in regard to study completion.

A Kaplan–Meier survival analysis (log–rank test) was conducted to compare study withdrawal by participants with and without comorbid diagnoses. There was a significant difference in the survival curves between participants with and without comorbid diagnoses; $p < .05$. This suggests that study participants with comorbid diagnoses were significantly more likely to prematurely withdraw from the study.

4.3.1 Reasons for Withdrawal

Two participants (33%) in each treatment group cited the taste/aftertaste of the supplement as the reason for study withdrawal (Table 4.9). One (17%) participant in the active group and 2 (33%) in the placebo group listed gastrointestinal complaints, including heartburn, cramps and stomach upset, as their reasons for study withdrawal. One active group participant (17%) developed a fish allergy and had to withdraw. 1

participant from each group (17%) withdrew for undisclosed reasons, cited as unrelated to the study. One placebo group participant (17%) withdrew complaining of lack of efficacy of the supplement. An active group participant (17%) withdrew fearing side-effects, noting they had not actually experienced any adverse-effects.

Table 4.9: Reasons for withdrawal from study

Reason ^{a,b}	Active		Placebo	
	<i>n</i>	%	<i>n</i>	%
Taste/Aftertaste	2	33	2	33
Gastrointestinal Complaints	1	17	2	33
Developed Fish Allergy	1	17	0	0
Factors Unrelated to Study	1	17	1	17
Lack of Efficacy	0	0	1	17
Fear of side effects	1	17	0	0

Note. *n* = Number of participants.

% = Percentage of group. ^aFisher's exact test comparing frequency of reasons for study withdrawal. ^bAll $p > .05$.

Fisher's Exact Tests were conducted to compare the frequency of reasons for study withdrawal recorded by participants in active and placebo groups. There were no significant differences in the frequency of reasons for study withdrawal between active and placebo group participants, $p > .05$. This suggests the active and placebo group participants were comparable in their reasons for withdrawal.

4.3.2 Cox Proportional Hazards Regression

A Cox Proportional Hazards Regression was conducted on several variables to assess their effect on study withdrawal (Table 4.10). The variables included in the regression model were: the treatment assignment group, the number of comorbidities, the number of medications prescribed, and 3 baseline measures of ADHD severity (the CCPT-CI, the C3T-T and the C3P-T). The variables were entered in a single block, using the

“Enter” method in SPSS. None of the variables yielded an $Exp(B)$ with a $p < .05$. The regression was repeated using a variety of permutations of removing various variables and using multiple blocks and methods of variable entry, with no meaningful change from the initial outcome. The process was repeated using the presence/absence of comorbidities rather than the number of comorbidities in light of the significant result in the Kaplan–Meier survival analysis (section 4.3). There was no meaningful change to the Cox Proportional Hazards Regression analysis as a result. Linear Regression analysis similarly yielded no significant relationships between these variables and time in study; $p > .05$. This suggests these baseline measures of ADHD symptom severity, treatment group assignment, and the number of comorbidities and medications prescribed did not have a significant effect on study withdrawal.

Table 4.10: Cox Proportional Hazards Regression Analysis of Factors Affecting Study Withdrawal

Variable	$Exp(B)^a$
Number of Cormorbidities	0.612
Conners Continuous Performance Test II Confidence Index	0.948
Conners 3: Teachers Report Global Index: Total	1.130
Conners 3: Parent Report Global Index: Total	1.294
Number of Medications Prescribed	2.557
Active Group Assignment	39.465
<i>Note.</i> ^a All $p > .05$	

4.3.3 Tolerability/Adverse Effects

Two study participants in the active group and 4 in the placebo group completed at least one AEI (Appendix B, Table 4.11).

A Shapiro-Wilk Test of normality indicated the number of adverse effects experienced by participants does not significantly deviate from a normal distribution; $p > .05$. This suggests that parametric methods can be employed. An independent-samples

Table 4.11: Adverse Effects

Adverse Effect	Active ^a		Placebo ^b	
	<i>n</i>	%	<i>n</i>	%
Belching	0	0	3	75
Nausea	0	0	3	75
Diarrhoea	0	0	3	75
Bloating	0	0	2	50
Gas	0	0	2	50
Fishy Body Odour	0	0	1	25
Fish Breath	2	100	0	0
Fishy Aftertaste	1	50	2	50

Note. *n* = Number of respondents experiencing adverse effects.

% = Percentage of respondents experiencing adverse effects.

^a*n* = 2. ^b*n* = 4.

t test was conducted to compare the mean number of adverse effects experienced by active and placebo group participants. There was no significant difference in the mean number of adverse effects experienced by active group participants ($M = 1.5$, $SD = 0.7$) and placebo group participants ($M = 4.3$, $SD = 2.1$); $p > .05$. This suggests the active and placebo groups were comparable in their mean number of adverse effects reported.

Fisher's Exact Tests were conducted to compare the occurrence of specific adverse effects experienced by participants in active and placebo groups. There were no significant differences in the occurrence of specific adverse effects between active and placebo group participants; $p > .05$. This suggests the active and placebo groups were comparable in the rates of specific adverse effects.

4.3.4 Compliance

Although the number of study participants returning for follow-up visits was too small to permit statistical analysis of the data, compliance with omega-3 supplements and prescribed medications was comparable between the active and placebo supplements, and between the omega-3 supplements and prescribed medications.

4.4 Outcomes

Several of the planned analyses could not be conducted as only one study participant per treatment group completed the trial, including the Conners 3 Parent and Teacher Reports, which were only administered at the beginning and end of the trial. The remaining measures were repeated at each clinic visit throughout the trial. Analysis of single values per treatment group would not be meaningful, so study outcomes were analyzed using an LOCF approach. The use of before and after measurements in the analysis meant that only observations from participants with at least one post-treatment assessment could be included in the analysis.

An LOCF analysis was conducted rather than other approaches for handling missing data for several reasons. Analysis of only subjects that completed the trial would be of limited value. Other means of imputation, including regression-based statistical models were not possible with the limited sample size.

4.4.1 ADHD Severity Measures

4.4.1.1 Conners Continuous Performance Test II

As noted in subsection 4.2.1.1, 1 of the 4 study participants that did not complete their baseline CCPT-II prior to receiving their supplements was able to complete these

assessments later in the course of his/her participation. This data was included in the comparison of initial and final scores, with the last observation carried forward. This data was included to permit analysis of this variable. Without inclusion of these observations, comparison of the change in ADHD symptom severity, as measured by the CCPT-II, would not have been possible. This analysis is included for the purposes of generating hypotheses and assessing the data analysis process as part of the larger goal of establishing the feasibility of and refining the protocol for a larger study. No inferences regarding the efficacy of the supplement being studied are intended.

Two participants from the active treatment group and 4 from the control group were included in this analysis of CCPT-CI [42] (Table 4.12 and Figure 4.8).

Table 4.12: Conners Continuous Performance Test II Confidence Index

	Active			Placebo		
	<i>n</i>	<i>M</i>	<i>SD</i>	<i>n</i>	<i>M</i>	<i>SD</i>
First Recorded ^a	3	58.0	21.2	7	52.3	16.7
First Recorded (Censored) ^{a,b}	2	40.3	8.1	4	48.7	21.1
Last Recorded ^a	2	31.4	26.3	4	56.5	24.7
Delta ^a	2	-8.9	18.2	4	7.8	17.0

Note. *M* = Mean Confidence Index (%). Scores above 50% are suggestive of ADHD. *SD* = Standard Deviation.

^aIndependent-samples *t* test comparing mean group scores; all $p > .05$. ^bSubjects with only initial observations removed.

An independent-samples *t* test was conducted to compare the change in scores on the CCPT-CI in active and placebo groups. There was no significant difference in the change in scores for active group participants ($M = -8.9$, $SD = 18.2$) and placebo group participants ($M = 7.8$, $SD = 17.0$); $p > .05$. This suggests the active and placebo groups were comparable in the change in ADHD symptom severity, as measured by the CCPT-CI.

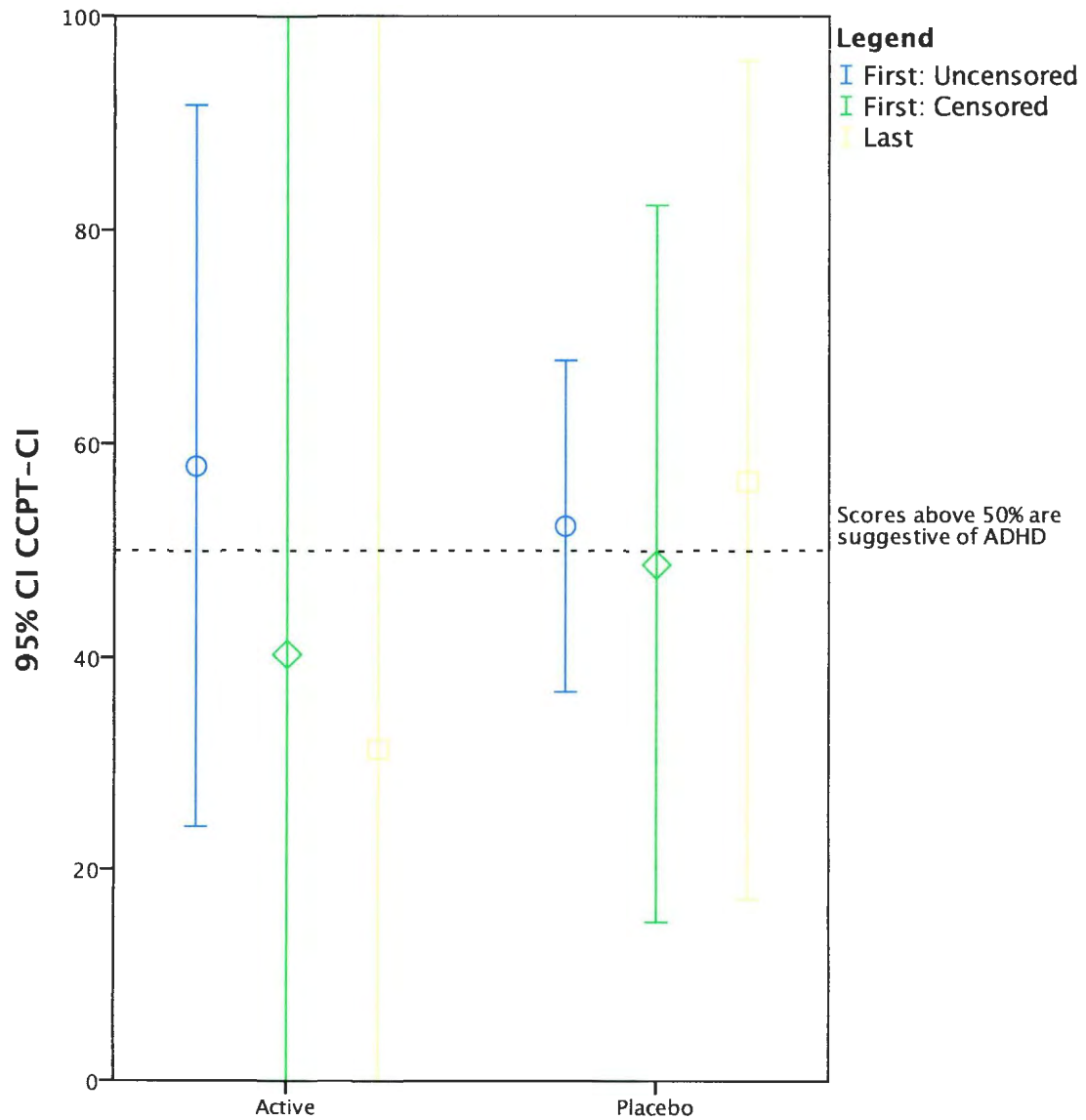


Figure 4.8: Mean Connors Continuous Performance Test II: Confidence Index (CCPT-CI) Results (95% Confidence Intervals): First and Last Observations

The initial and final scores in each group were not significantly different from the cut-off score of 50% using single-sample two-sided t tests; $p > .05$. This suggests that both the initial and final scores were not markedly greater than the 50% cut-off score, indicating clinically significant ADHD symptom severity.

4.4.1.2 Conners 3: Teachers and Parent Reports

As noted in section 4.4 and section 5.4, 1 participant in each group completed the trial and Conners 3: Teachers and Parent Reports. Statistical comparison was therefore not possible.

4.4.2 Clinical Global Impression Scale

Two active group participants and 4 placebo group participants were assessed by their psychiatrist via the CGI Scale at least once (Table 4.13, Figure 4.9 and Appendix A). The last available CGI scores were used for each participant in the planned LOCF comparisons.

Table 4.13: Clinical Global Impression Scale (Last Observation Carried Forward)

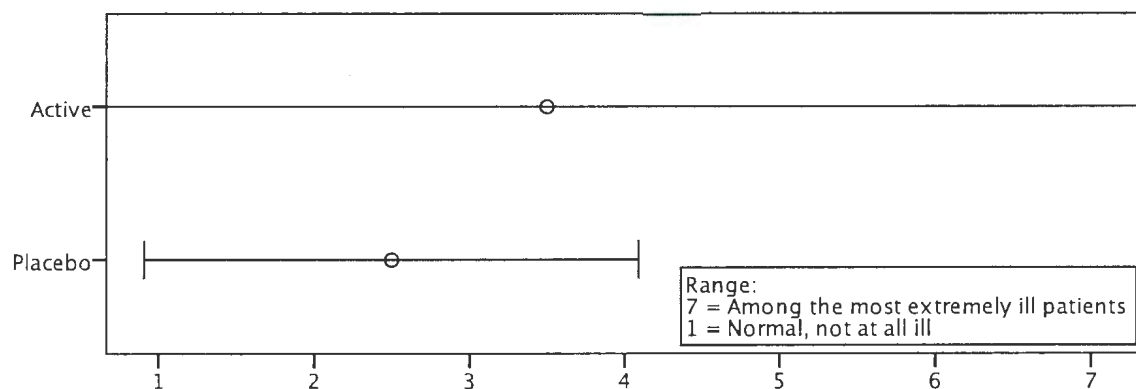
Scale ^a	Active ^b		Placebo ^c	
	<i>M</i>	<i>SD</i>	<i>M</i>	<i>SD</i>
Severity of Illness ^d	3.5	0.7	2.5	1.0
Global Improvement ^e	3.0	0.0	3.3	1.0
Efficacy ^f	9.5	0.7	9.5	5.2

Note. *M* = Mean. *SD* = Standard Deviation.

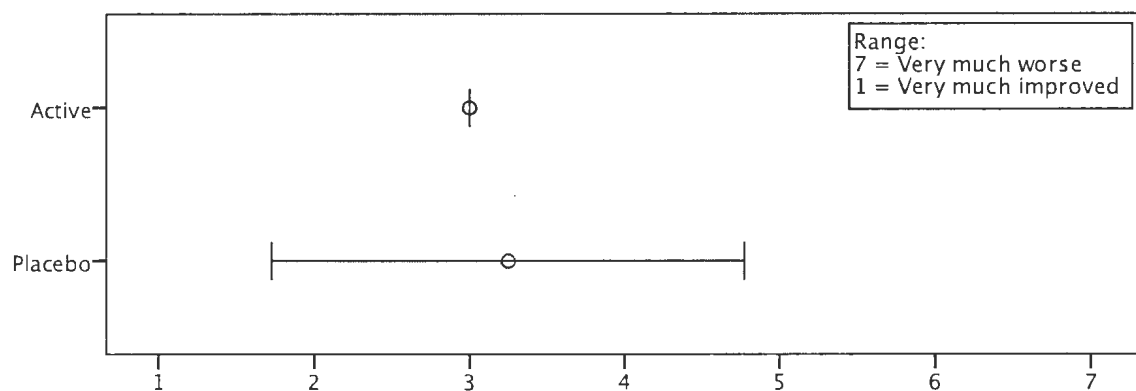
^aIndependent-samples t test comparing mean group scores; all $p > .05$. ^b $n = 2$. ^c $n = 4$.

^d1, Not at all ill – 7, Extremely ill. ^e1, Very much improved – 7, Very much worse.

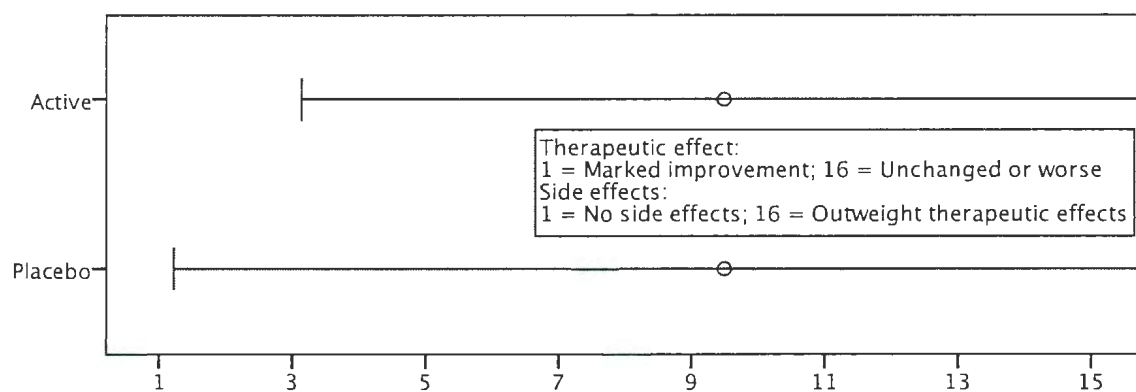
^f1, Marked improvement, No side effects – 16, Unchanged or worse, Side effects outweigh therapeutic effects.



(a) Severity of Illness



(b) Global Improvement



(c) Efficacy

Figure 4.9: Mean Clinical Global Impression Scale Scores (Last Observation Carried Forward) (95% Confidence Intervals)

An independent-samples t test was conducted to compare scores on the Severity of Illness scale in the active and placebo groups. There was no significant difference in the scores for active group participants ($M = 3.5$, $SD = 0.7$) and placebo group participants ($M = 2.5$, $SD = 1.0$); $p > .05$. A score of 3.5 on this scale is between “mildly and moderately ill”, while a score of 2.5 is between “borderline mentally ill” and “mildly mentally ill”. This suggests the active and placebo groups were comparable in their last observed severity of illness, as measured by the CGI.

An independent-samples t test was conducted to compare scores on the Global Improvement scale in the active and placebo groups. There was no significant difference in the scores for active group participants ($M = 3.0$, $SD = 0.0$) and placebo group participants ($M = 3.3$, $SD = 1.0$); $p > .05$. A score of 3.0 on this scale is “minimally improved”, while a score of 3.3 is between this and “no change”. This suggests the active and placebo groups were comparable in their overall improvement, as measured by the CGI.

An independent-samples t test was conducted to compare scores on the Efficacy scale in the active and placebo groups. There was no significant difference in the scores for active group participants ($M = 9.5$, $SD = 0.7$) and placebo group participants ($M = 9.5$, $SD = 5.2$); $p > .05$. A score of 9 corresponds to “Minimal” therapeutic effect and no side effects, while a score of 10 corresponds to the same “Minimal” therapeutic effect and side effects that “do not interfere with patient’s functioning”. This suggests the active and placebo supplements were comparable in their last observed efficacy, with minimal therapeutic and adverse effects, as measured by the CGI.

4.4.3 Signs of Omega-3 Fatty Acid Deficiency

One active group participant and 2 placebo group participants completed a second TSQ (Figure 4.10 and Appendix C).

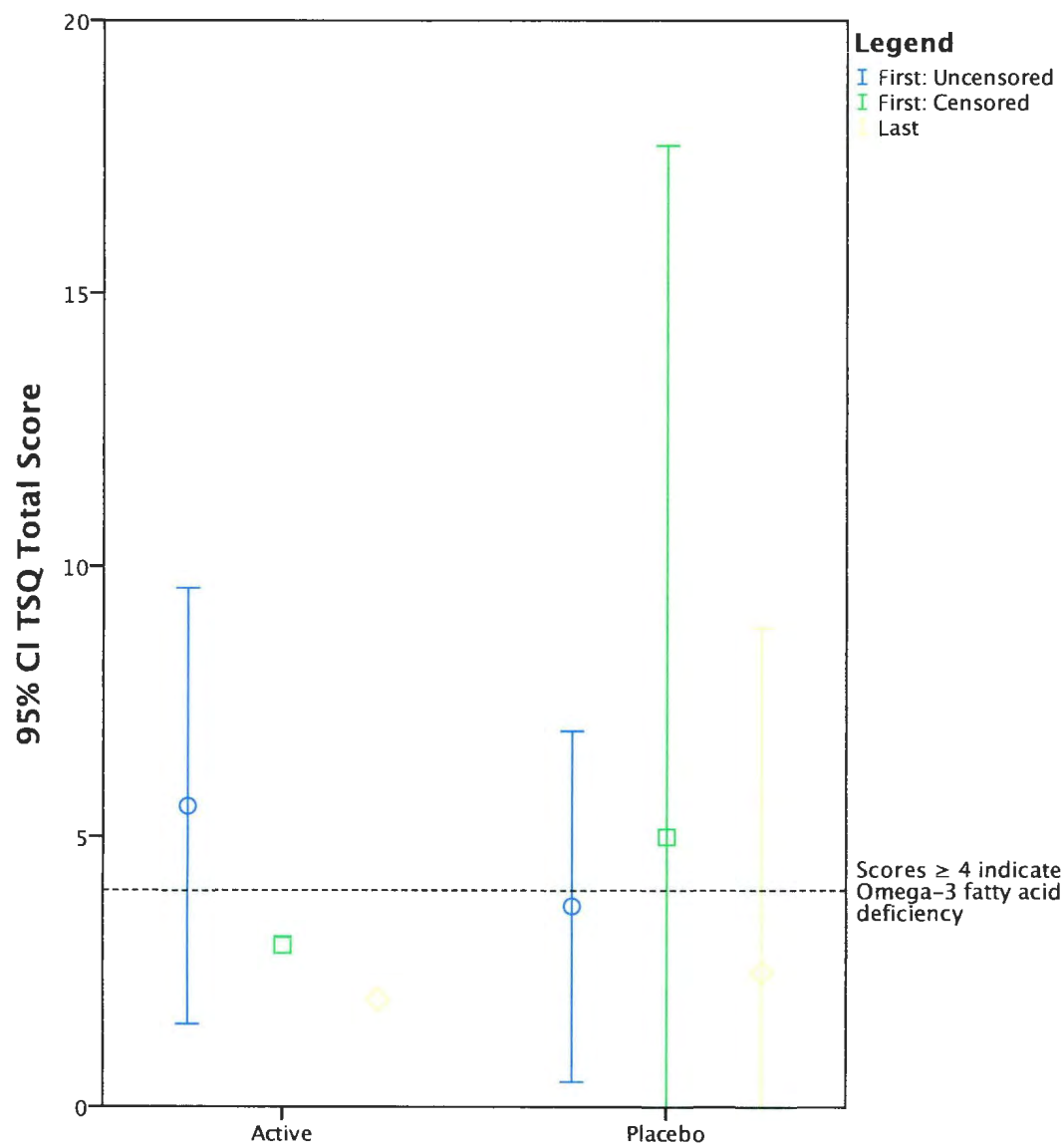


Figure 4.10: Mean Thirst Skin Questionnaire (TSQ) Scores: First and Last Observations (95% Confidence Intervals)

A Mann-Whitney U test was conducted to evaluate the hypothesis that participants in the active group would experience a greater decrease in Total Score, on average, than placebo group participants on the TSQ. There was no significant difference in the median changes in the TSQ scores for the active and placebo groups, $p > .05$. The active group participant had a decrease in total score of 1.0, while the placebo group participants had a median decrease in total score of 2.5 ($M = 2.5$, $SD = 2.1$). This suggests the active and placebo supplements were comparable in their effect on the degree of omega-3 fatty acid deficiency, as measured by the TSQ.

Chapter 5

Discussion

5.1 Demographics

5.1.1 Age

As discussed in subsection 4.1.1, the mean age, age range and median ages were typical of this clinical population, both locally and abroad [1, 2, 4].

5.1.2 Gender

As described in subsection 4.1.2, the nearly 1:1 gender ratio is unusual as reported gender ratios typically range from 3:1 to 5:1 [1, 2, 4]. This difference could be due to the small sample size. It is possibly attributable to the referral source for this study; as a tertiary sub-specialty clinic, the clinic population would not necessarily be identical to that in the general population. Also, the inclusion and exclusion criteria may have resulted in a study population not reflecting the gender ratio found in the general population. This is particularly likely as comorbid disruptive behaviour disorders,

which are highly comorbid with ADHD and also overrepresented in males [1, 2, 4], were initially excluded from the study. This difference could also suggest a referral bias towards females or an unknown factor making it more likely for females than males in this population to participate in this study, although there is nothing to support either possibility.

5.1.3 ADHD Subtype

The distribution of ADHD subtypes among the groups and study population as a whole was similar, with the minor variation being most likely attributable to random variation and small sample size (subsection 4.1.3). There is little information available regarding the proportions of ADHD subtypes within non-clinical and clinical populations [1, 2, 4]. Anecdotally, this distribution of the majority of cases being of the combined subtype, with a roughly equal number of inattentive and hyperactive/impulsive subtypes, seems reflective of the distribution in general clinical practice. As discussed in subsection 1.3.1, there is no evidence that omega-3 fatty acid supplements are more or less efficacious depending on ADHD subtype.

5.1.4 Comorbidities

The frequency and types of comorbidities in each group were comparable (Table 4.3, subsection 4.1.4). These comorbid diagnoses and the percentage of participants with these diagnoses are comparable to reported rates [1, 2, 4]. Anecdotally, this is in keeping with this clinic's general population, which served as the referral base for this study.

Comorbidity is common among patients with ADHD from clinical populations [1, 2, 4]. However, there is a paucity of published information concerning the total number of comorbidities typical per patient with ADHD from clinical populations,

or in general. Additional comorbidities likely confer a greater burden of illness, resulting in greater cumulative dysfunction with more comorbidities. It is unclear whether this cumulative effect of comorbid illnesses is additive or multiplicative, synergistically resulting in additional dysfunction.

The proportions of study participants with and without comorbid diagnoses were not significantly different; these proportions are comparable to reported rates [1, 2, 4].

The median number of comorbidities per study participant ($Mdn = 1.5$, $M = 1.6$, $SD = 1.9$) was not significantly different than 1. This suggests the level of comorbidity in this study population is at least as great as that seen in typical clinical populations. The median was trending towards an average of more than one comorbidity per participant. It is unclear whether this lack of a significant difference represents the true nature of this population, or if it is due to the small sample size. This study population was therefore likely experiencing considerable challenges, living with ADHD and most often one or more comorbidities.

In a separate analysis of study participants with at least one comorbid diagnosis, the median total number of comorbidities per study participant ($Mdn = 2.5$, $M = 2.9$, $SD = 1.6$) was significantly greater than 1. This suggests a bimodal distribution of comorbidity, whereby these study participants were equally likely to have comorbid diagnoses or not, but if they were diagnosed with comorbid illnesses, they were significantly more likely than not to have more than one comorbid diagnosis (Figure 4.2).

5.1.5 Number of Medications

Both treatment groups were prescribed a comparable median number of medications, with no significant difference between these medians (subsection 4.1.5). The median

number of medications prescribed to the entire study population ($Mdn = 1.5$, $M = 1.6$, $SD = 0.9$) is significantly greater than 1. This is anecdotally comparable to the clinic population from which the study population is derived. There is little published on the subject of the number of medications which patients with ADHD are typically prescribed in clinical or general populations. Treatment guidelines generally advocate for monotherapy for uncomplicated ADHD [45, 2, 3].

The prescription of more than one medication to the majority study participants seems compatible with the earlier finding that many study participants were diagnosed with one or more comorbid illnesses, with these additional medications possibly prescribed for these comorbid illnesses. This prescribing practice could also suggest suboptimal response to monotherapy in the treatment of their ADHD, which is sometimes the case with complex, treatment refractory cases of ADHD [45, 2, 3].

An analysis of the number of medications prescribed for ADHD versus comorbidities was not conducted because many medications that are prescribed for patients with one or more comorbidities often are effective in the treatment of more than one condition. Clonidine is a common example of this. It is prescribed to treat both ADHD and tic disorders, which are common comorbidities [45, 2, 3].

5.2 Baseline Characteristics

5.2.1 ADHD Severity Measures

5.2.1.1 Conners Continuous Performance Test II Confidence Index

The mean CCPT-CI scores were not significantly different between groups (subsubsection 4.2.1.1). The mean scores were all above the cutoff score of 50% but not

significantly so (Figure 4.4). In a treatment naive patient or group, this would suggest a modest elevation in symptoms and relatively mild severity of impairment with ADHD. In the study participants, which were all prescribed stable treatment for their ADHD, these average scores likely indicate clinically significant residual symptomatology. Another factor to consider is that the CCPT-CI is a composite score, meaning it can be affected by sub-test scores that markedly differ from the remaining scores, affecting the resulting composite scores accordingly. However, the CCPT-II is a robust, well validated assessment and research tool with sub-tests that account for these circumstances and provide measures of overall test validity that can help guide clinicians and researchers in the interpretation of these results [42]. The CCPT-II, including the CCPT-CI was considered valid in the results that were included for analysis. The small sample size could also have played a part, resulting in a non-representative sample, or a masked trend.

5.2.1.2 Conners 3: Teacher and Parent Reports

While the mean CCPT-CI scores [42] were mildly elevated, the mean C3T-T and C3P-T scores were in the “Very Elevated” range (Table 4.4, Table 4.5, Figure 4.5, Table 4.6, Figure 4.6, & Figure 4.7), which is the highest severity level assigned by this instrument, and is assigned to T-scores ≥ 70 (subsubsection 4.2.1.2, subsubsection 4.2.1.3 and subsubsection 4.2.1.4) [40]. The guidelines for interpretation describe this group as having, “many more concerns than are typically reported” [40]. The mean C3P-T score was significantly above the “very elevated” cutoff score of 70, while the mean C3T-T was significantly above the “elevated” cutoff score of 65 but not 70. Nine of the 12 remaining C3P subtests were significantly greater than the “elevated” cutoff, with 2 significantly greater than the “very elevated” cutoff, while 2 of the 12 remaining C3T subtests were significantly greater than the “elevated” cutoff.

It is unlikely these mean scores are artificially elevated and represent bias on the part of the raters for several reasons. The C3T and C3P are robust, well constructed and validated tools that are designed to detect exaggeration and over-endorsement [40]. The assessment reports did not detect any invalid response patterns. The assessments were completed by different parents and teachers, which would lessen the likelihood of this pattern of elevating these scores out of keeping with the objective CCPT-II [42], unless this suggests a consistent bias in the population.

While it is possible the CCPT-II and the C3T and C3P rate ADHD severity differently, this is unlikely as these tools are constructed and marketed by the same group, use the same language and categories, and are intended to complement each other [40, 42].

These results suggest the CCPT-II and the C3T and C3P, while valid and complementary, are sensitive to different aspects of ADHD symptomatology. The symptoms that improve the most readily and noticeably seem to be preferentially captured by the CCPT-II. The C3T and C3P are known to be better measures of executive function, particularly in real-world, longitudinal settings [40].

The mean scores on the C3T and C3P suggest the study participants (both active and placebo groups) were experiencing considerable residual symptomatology in association with their ADHD in spite of stable treatment. In most cases, patients with ADHD achieve stable treatment when they have reached their maximum tolerable medication dosage or have achieved satisfactory relief of symptoms [3, 2]. This discrepancy may be accounted for by a possible difference in sensitivity to aspects of ADHD symptomatology between the parents, teachers and clinicians, similar to the proposed difference between the C3P and C3T, and the CCPT-II.

Mean C3T scores were consistently greater than C3P scores, including the Global Index: Total and all subtests (Table 4.6 & Figure 4.7). Seven of these 13

differences were statistically significant, including the Global Index: Total score. This finding suggests that parents generally rate their children's symptomatology higher than do teachers. Parents may be more sensitive to their children's difficulties. Parents are more likely to see their children without the benefit of stimulant medications, both in the morning and the evening, prior to stimulant administration and following withdrawal from these stimulants. Conversely, teachers may have a broader perspective with which to rate a child's symptomatology. Children may perform differently in different contexts and environments, which could also account for these differences.

5.2.1.3 Comparison to Related Research

The severity of ADHD among study participants is comparable to that among similar studies [8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24]. As discussed in subsection 1.1.4, these symptom levels are also comparable to clinical populations, in keeping with the considerable residual ADHD symptomatology in spite of maximal therapies [1, 2, 3, 4].

5.2.2 Signs of Omega-3 Fatty Acid Deficiency

As discussed in subsection 4.2.2, the median TSQ scores for the active and placebo groups were not significantly different, nor were the proportion of each group with scores greater than or equal to 4.

The median TSQ scores and the proportion of each group with total scores greater than or equal to 4, indicating omega-3 fatty acid deficiency (Table 4.7) are consistent with other studies using this scale in similar populations [29, 31, 32, 22, 30].

The combined group's median TSQ score was not significantly different than 4, although the mean score was greater than 4 ($M = 4.6$, $SD = 3.9$). This may be due to the nonparametric distribution, small sample size and large standard deviation.

This could also be attributed to a high degree of variability of omega-3 status in the study and clinical population. The study and clinic population may have a mild to moderate degree of omega-3 deficiency. This could be connected to a higher than expected intake of foods rich in omega-3 fatty acids, including the growing number of foods that are enriched with these supplements without parents or children necessarily recognizing this. The clinic population is also derived from a culture with a traditional diet that is rich in fish, although it is unclear whether this reflects the current typical diet of this population.

5.3 Study Completion

The dropout rate among both treatment groups was high (section 4.3). There is no single obvious explanation for this outcome but many factors, including study design and participant characteristics may have contributed to it. Some possible study design related factors include the length of the study, the inter-visit duration, inter-visit follow-up, and the tolerability of the supplement/placebo. Possible participant characteristics contributing to the high dropout rate include the severity of participant ADHD, the burden of comorbid diagnoses, and caregiver factors. These possible factors are explored in this section. Study protocol refinements to address these problems with study completion in addition to other deficits are outlined in section 6.5.

5.3.1 Comparison to Similar Studies

A recent Cochrane review of randomized clinical trials of polyunsaturated fatty acids (PUFAs) for ADHD in children and adolescents [7] assessed loss to follow-up among its outcomes (Table 5.1). This analysis included 7 clinical trials [16, 18, 23, 24, 17, 39, 22] with a total of 589 participants, 347 receiving PUFAs and 242 receiving placebo.

Seventy-seven participants receiving PUFAs (22%) and 52 receiving placebo (21%) were lost to follow-up. The percentage of participants lost to follow-up did not differ by treatment assignment; $\chi^2(1, N = 589) = 2.77, p = .100$. The percentage of participants lost to follow-up among these studies ranged from 0% [16] to 34% [22], with a mean loss to follow-up of 22%.

Table 5.1: Comparison of Loss to Follow-up Among Polyunsaturated Fatty Acids versus Placebo Clinical Trials

Study	Active			Placebo			Total			Med.	Suppl.	LOS
	<i>n</i>	<i>N</i>	%	<i>n</i>	<i>N</i>	%	<i>n</i>	<i>N</i>	%			
Hirayama 2004	0	20	0	0	20	0	0	40	0	Y	EF	8
Johnson 2009	3	37	8	8	38	21	11	75	15	N	C	24
Manor 2011	37	137	27	16	63	25	53	200	27	N	C	15
Raz 2009	7	39	18	8	39	21	15	78	19	N	C	7
Stevens 2003	7	25	28	10	25	40	17	50	34	Y	C	16
Vaisman 2008	18	57	32	5	26	19	23	83	28	N	EF	12
Voigt 2001	5	32	16	5	31	16	10	63	16	Y	C	16
Total	77	347	22	52	242	21	129	589	22			

Note. Adapted from “Polyunsaturated fatty acids (PUFA) for attention deficit hyperactivity disorder (ADHD) in children and adolescents,” by Gillies et al., 2012, *The Cochrane Library*, 2012 (7), p. 59. Copyright 2012 by the Cochrane Collaboration. *n* = Number of participants lost to follow-up. *N* = Number of participants. % = Percentage of participants lost to follow-up. Med. = Concurrent pharmacological treatment of ADHD permitted? Y = Yes. N = No. Suppl. = Supplement Preparation. EF = Enriched Foods. C = Capsule. LOS = Length of Study in Weeks.

There are several noteworthy differences between the present study and this group of studies. None of these studies used a syrup preparation of PUFA supplements. Five of these studies used capsules [18, 39, 22, 24, 17], while 2 used foods enriched with PUFAs [23, 16]. Four studies did not permit the concurrent use of conventional pharmacotherapy for ADHD, including stimulants [18, 39, 23, 17]. These studies varied in length, from 7–8 weeks [39, 16], to 12 [23], 15–16 [18, 22, 24], and 24 weeks [17]. Three

of these studies made note of inter-visit telephone follow-up by a research assistant, with a weekly [23], or biweekly frequency [17, 18]. The remaining studies did not make note of their follow-up procedures beyond the frequency of in-person visits.

5.3.2 Frequency of Follow-up

This study was designed to reflect regular clinical practice, which in the case of youth with ADHD and stable treatment would not be intensive. The frequency of follow-up varies from clinician to clinician, but visits every 2 months in this circumstance would be typical [4]. Follow-up of greater frequency may have improved study retention but may not have reflected typical clinical conditions, limiting the generalizability of the study results. However, the addition of a new treatment, even a dietary supplement, would warrant an increased frequency of follow-up, thus reflecting routine clinical care. Both study groups would have been treated in the same manner, negating the effect of this increased visit frequency as a confounding variable.

The studies reviewed in the Cochrane review [7] conducted in-person clinician follow-up at similar frequencies to the present study, ranging from approximately 6 to 8 weeks. Given the similar frequency of in-person follow-up but markedly different rates of study withdrawal, it is unlikely that the frequency of follow-up significantly contributed to the study's high proportion of non-completion.

5.3.3 Inter-visit Telephone Contact

There was no scheduled inter-visit telephone contact in the study protocol. Study participants and their guardians were able to call with questions and concerns. Regularly scheduled telephone contact with a research nurse may have addressed participant and guardian concerns and questions prior to study drop-out. It may be that the addition of this dietary supplement may have resulted in greater concern than the

use of prescribed medications. Study participants were required to be taking stable doses of their medications, implying a level of familiarity and possibly of comfort with their medication(s). This dietary supplement may have been perceived as unknown and untested, particularly with the added question of whether they were receiving the active supplement or the placebo.

The intent of this design was to reflect clinical practice and to enhance generalizability, as in the case of follow-up visit frequency. Scheduled inter-visit telephone contact, particularly with a nurse or other health professional affiliated with the treating physician is used in some settings but not in others [4]. Thus, scheduled inter-visit telephone contact by a research nurse would likely have improved study retention and completion; such telephone contact should be included as part of the protocol of any future similar study.

5.3.4 Length of Study

The study was designed for 6 months in length to assess for both short-term and longer-term outcomes of adding omega-3 fatty acid supplements to stably treated patients with ADHD, reflecting the goals of generalizability and clinical applicability. A shorter clinical trial, particularly with more frequent in-clinic follow-up and inter-visit telephone contact may have improved study retention and completion, but may have compromised the study's generalizability and clinical applicability.

5.3.5 Participant Characteristics

The study population was derived from a sub-speciality clinic in a tertiary hospital (section 3.5). As a result of this aspect of study design, there may be some participant characteristics that made them poor candidates to participate in this clinical trial. An

example of this is a high rate (approximately one-third) of missed appointments in this clinic population (anecdotal).

While a review of randomized clinical trials of PUFAs for ADHD in children and adolescents [7] was conducted, participant characteristics were not consistently reported among these studies, preventing any meaningful or coherent comparison with participant characteristics in this study.

5.3.5.1 Severity of ADHD

Study participants had considerable residual ADHD-related symptomatology at baseline in spite of stable and often maximal treatment (subsection 4.2.1, subsection 5.2.1, Figure 4.4, Figure 4.5, Table 4.4, Table 4.5 and Figure 4.6). This may reflect the nature of ADHD in general or may reflect the nature of this clinic population [2, 1]. Inherent to the diagnosis, these study participants would struggle with impulsivity, making compliance with a study protocol challenging. Such a group might be quick to give up on a new treatment if they were to encounter challenges, such as adjusting to a new treatment routine, particularly if they disliked some aspect of it, such as the taste or method of delivery (syrup).

5.3.5.2 Oppositionality

As described in subsection 4.2.1, many study participants had problems with oppositionality, as indicated by elevated baseline parent and teacher Conners-3 Oppositional Defiant Disorder sub-test scores (Figure 4.5, Table 4.4, Table 4.5 and Figure 4.6). This is noteworthy for several reasons. Initially, a comorbid diagnosis of Disruptive Behaviour Disorder meant exclusion from study participation. As discussed in section 3.3, this restraint was later lifted to promote study recruitment. Five of the 14 study participants had a comorbid diagnosis involving disruptive disorders, including Disruptive

Behaviour Disorder: Not Otherwise Specified (2), Oppositional Defiant Disorder (1), Conduct Disorder (1), and Adjustment Disorder with Disturbance of Conduct (1). This suggests that many of the study participants had clinically significant problems with disruptive behaviours in spite of stable and often maximal medical management, several of whom were not diagnosed with a comorbid disruptive behaviour disorder even though both teacher and parent reports indicated elevated concerns. It is possible these behavioural concerns were not apparent in the clinical setting or that the clinicians did not consider these symptoms to be of sufficient severity to warrant an additional diagnosis.

Similar to the considerable residual ADHD symptomatology, oppositionality may have influenced study completion. Study participants with greater degrees of oppositionality may have been more likely to refuse their study supplement, particularly if they were having any other issues, such as disliking the supplement or having adverse effects. Further, parents and guardians, already struggling with oppositional behaviour in the home may have been more likely to abandon the supplement in the face of increased oppositionality, particularly if they were facing other issues, as noted above.

5.3.5.3 Comorbidities

Study participants were diagnosed with a median of 1.5 comorbid diagnoses (subsection 4.1.4, subsection 5.1.4, Table 4.3). While the number and types of comorbidities were comparable within groups and comparable to this clinical population, this is still a large number. It is possible that the burden of living and dealing with these other diagnoses in addition to their ADHD and participating in this trial may have predisposed these participants to withdraw from the study early. These participants could have a reduced capacity to tolerate additional demands on their time and attention, such as taking a supplement in addition to their existing medications.

Study participants were prescribed a median of 1.5 medications per day, corresponding with the median of 1.5 comorbid diagnoses. As noted in subsection 4.1.5, there was a significant difference between this median of 1.5 medications per day and 1 medication per day, which would be their ADHD-specific treatment. This prescription of additional medications for comorbid illnesses suggests that these participants and their caregivers were already taking and administering multiple medications per day, likely several times per day. The administration times of each medication were not consistently recorded with sufficient precision to permit comment on the number of times per day participants were taking medications (daily medications were often recorded as “OD” or “daily”, instead of specifying the time of day of administration). It is possible that the addition of the study supplement to already complex medication administration schedules may have contributed to premature study withdrawal.

A Cox Proportional Hazards Regression model of the number of medications, comorbidities, the severity of participant ADHD, and treatment assignment yielded no significant relationships with time in study (i.e. survival time) (subsection 4.3.2). The absence of a statistically significant correlation could reflect the absence of a relationship, or could be the effect of small sample size.

5.3.6 Caregiver Characteristics

No demographic information was collected concerning the caregivers of study participants. There may have been caregiver characteristics which predisposed this study population to early study withdrawal.

There is a high prevalence of Adult ADHD among biological parents of children with ADHD because of the inheritable nature of the illness [1]. Parents struggling with ADHD would have the same issues with inattention and impulsivity that could increase the likelihood of poor study compliance and possibly early study termination.

Inattention could result in problems such as missed or inconsistently administered medications and supplements, and an aversion to the routine of administering treatments, particularly a liquid supplement requiring careful measurement, cleanup and refrigerated storage. All of these individually minor impediments could cumulatively result in suboptimal protocol compliance. Study participants could also be sensitive to this possible caregiver resistance, which in turn could shape their attitudes towards study participation.

No direct measures of caregiver burden were made. Caregiver stress may have affected patient outcomes and could have impacted study retention and compliance. As discussed in subsubsection 5.2.1.2, parent ratings on the Conners 3 reports were significantly higher than teacher ratings in most cases (7 of 13 subtests, including the Global Index: Total) (Table 4.4, Table 4.5, Figure 4.5, Table 4.6, Figure 4.6, & Figure 4.7). This elevation could represent heightened caregiver stress, with greater apparent difficulties and symptomatology in the home, or an increased sensitivity to these problems due to stress. This stress in turn may have affected study retention.

5.3.7 Implications as a Pilot Study

As a pilot study, the high rate of study withdrawal and low rate of study completion highlight problems with the feasibility of this design. The study protocol could be redesigned to address some or all of the identified concerns and a new pilot study run. This is explored further in section 6.5.

5.3.8 Survival Curves

Though there was no significant difference in time to study withdrawal between the two treatment groups, there was a trend towards earlier dropout by active group participants (section 4.3). This may reflect a real difference in survival between these

two groups that was unable to be detected due to small sample size, or it may be an anomaly, the result of a small change having a large effect on a small sample size.

5.3.9 Reasons for Withdrawal

As described in subsection 4.3.1, the high proportion of study participants withdrawing with complaints of taste/aftertaste or miscellaneous gastrointestinal complaints suggests a problem with the tolerability of both the active and placebo supplements (Table 4.9). This is discussed further in subsection 5.3.10.

The development of a fish allergy is a known adverse effect that occurs in other studies involving fish-products.

It is difficult to interpret the study withdrawals for “unrelated reasons” and a “fear of side-effects”. These withdrawals account for 25% of the total. These withdrawals could be interpreted as actually unrelated, or they could suggest other, unidentified reasons for withdrawal that were not adequately addressed or queried.

5.3.10 Tolerability/Adverse Effects

It is difficult to meaningfully compare the tolerability of the supplements used in this trial to those in published trials, as the form of these supplements have differed, with most studies using capsules or gummies. The liquid supplement may be a poor choice for children and teens because of these problems with tolerability (subsection 4.3.3). The Cochrane review [7] did not identify any differences in the rates of adverse effects between groups.

There was no space on the AEI form to solicit or record adverse effects not specifically recorded on the form. It is possible that participants experienced other adverse effects that were not captured and analyzed.

5.3.11 Supplement Formulation

There were no clinical trials assessed by the Cochrane review [7] that employed a syrup preparation of an omega-3 fatty acid supplement (Table 5.1). It is therefore difficult to gauge the effect of supplement preparation on study completion in comparison to other studies and other supplement formulations.

Two participants in each treatment group (33%) cited taste/aftertaste as their reason for study withdrawal (Table 4.9, subsection 4.3.1). An additional 1 participant in the active group and 2 in the placebo group (25%) cited gastrointestinal complaints as their reason for withdrawal. A total of 7 participants (58%) cited taste, aftertaste or gastrointestinal complaints as their reasons for withdrawal. This is likely noteworthy and suggests the tolerability of the supplement and placebo was a major contributing factor to high rates of study withdrawal.

All study participants who returned for the first follow-up clinic visit completed an AEI (Appendix B) and endorsed adverse effects at some point during the trial. Many of these adverse effects were gastrointestinal in nature and may be more problematic in a syrup preparation of an omega-3 fatty acid supplement. However, adverse effects were reported more often by participants in the placebo group, though not to a statistically significant extent. This may suggest the supplement formulation, independent of omega-3 fatty acid content, may have been difficult to tolerate, particularly in comparison to other omega-3 fatty acid supplement preparations, and may have therefore contributed to study withdrawal, independent of omega-3 fatty acid content.

5.4 Outcomes

As noted in section 4.4, several of the planned outcome measure analyses were not performed because only one study participant per group completed the trial and two

of these measures, the Conners 3: Parent and Teacher Reports were only performed at the beginning and end of the trial, precluding even an LOCF analysis of this data. The remaining measures were analyzed using an LOCF approach.

5.4.1 ADHD Severity Measures

5.4.1.1 Conners Continuous Performance Test II

While there was no significant difference in the change in CCPT-CI scores between treatment groups, the trend in the data was towards an improvement (decrease) in CCPT-CI scores in the active group and a worsening (increase) in CCPT-CI scores in the placebo group (subsubsection 4.4.1.1). It is possible that these trends are artifacts of these small data sets with high variability, as evidenced by the 95% confidence intervals which extend past the range of possible values in some cases (Table 4.12 and Figure 4.8).

5.4.1.2 Conners 3: Teacher & Parent Reports

As noted in section 4.4 and section 5.4, analysis of Conners 3: Teacher and Parent Report data was not possible because these measures were conducted at the beginning and end of the study protocol, meaning only those participants completing the study would be included in these measures, and only one participant per group completed the protocol.

5.4.2 Clinical Global Impression Scale

Using an LOCF approach, there was no identifiable difference between the mean CGI scale scores of the active and placebo groups (subsection 4.4.2, Table 4.13 and Figure 4.9). There are several possible interpretations of this finding beyond the

literal interpretation that there was no difference in these outcomes. As the majority of subject data included in this analysis was carried forward due to study dropout, any change which might have occurred later in the study period would have been missed. The missing data due to loss to followup might be substantially different from that analyzed. This difference could favour either treatment group. A change in this outcome might have been observable even at an early stage of study outcome but may have been undetected due to the small sample size.

5.4.3 Signs of Omega–3 Fatty Acid Deficiency

With one measurement from the active group and two from the placebo group, it is impossible to draw any meaningful conclusions from the analysis of the TSQ data (subsection 4.4.3 and Figure 4.10).

Chapter 6

Conclusions

6.1 Outcomes

6.1.1 Primary Outcomes

Due to the high rate of dropout, it was not feasible to draw conclusions regarding the effects of omega-3 fatty acid supplementation on youth with ADHD, as measured by the C3T-T. In a meta-analysis, similar studies have not reported a statistically significant difference between placebo and active supplementation [7].

6.1.2 Secondary Outcomes

Similarly, due to the high rate of dropout, it was not feasible to draw conclusions regarding the effects of omega-3 fatty acid supplementation on youth with ADHD, as measured by the C3P-T, the CCPT-CI, or the CGI clinical improvement scale.

6.1.3 Survival Analysis

A post hoc survival analysis, discussed in section 4.3 and subsection 5.3.8 did not identify any difference between study groups in the time to study withdrawal. It appears study withdrawal was not related to the omega-3 content of the supplement; this suggests that neither the presence nor the absence of omega-3 appeared to confer any benefit in terms of remaining in the study. It is possible that a difference was not detected due to small sample sizes. This finding is compatible with similar studies finding no difference in study withdrawal based on treatment assignment [7].

6.2 Patient Characteristics

6.2.1 ADHD Symptomatology

Based on the initial assessments, this clinical population had considerable residual ADHD symptomatology, as measured by the Conners-3 Teacher and Parent reports. This is noteworthy as all patients in this study were on stable and likely maximal pharmacotherapy for their ADHD. Also noteworthy is the discrepancy between these subjective reports and the objective results of the CCPT-II, which did not detect the same levels of clinically significant residual symptomatology. This suggests these assessment tools measure different aspects of this complex condition and that current pharmacotherapies preferentially target and improve these objectively measurable symptoms, while leaving these other clinical challenges largely unmet. The severity of ADHD in this study population was generally greater than that of subjects in similar studies [7].

Though both teachers and parents reported clinically significant levels of ADHD symptomatology on the Conners-3 assessments, parent ratings were significantly

greater than teachers'. This suggests several possible conclusions, including different perceptions of the same signs and symptoms by these two groups; different observable behaviour by the youth in these different contexts; different challenges and therefore different signs and symptoms evident in different environments; and diminished tolerance among caregivers for the same difficulties, possibly due to caregiver fatigue. This difference was not observed in similar studies [7]. Given the high level of ADHD severity in the study population and the difference between this study population and those in similar studies, this difference in rating between teachers and caregivers may be a function of this heightened severity and thus may not have been seen in other studies working with less impaired populations.

6.2.2 Comorbidities

The study participants had high rates of comorbidity as indicated by recorded comorbid diagnoses as well as polypharmacy, suggesting a high burden of illness for these patients as well as a high caregiver burden.

6.2.3 Signs of Omega-3 Fatty Acid Deficiency

On average, the clinic and study population had mild to moderate signs and symptoms of omega-3 fatty acid deficiency, as measured by the TSQ. This finding was less than expected, possibly due to a higher than average dietary intake of omega-3 fatty acids from fish or dietary supplementation. Anecdotally, Newfoundlanders have historically had diets which were high in omega-3 fatty acids from seafood. Also anecdotally, many foods are now fortified with omega-3 fatty acids. Concerned parents of youth with ADHD might be likely to give these foods to their children, much as they might enrol them in this study. Baseline omega-3 dietary intake and supplementation was not screened or adjusted for. A dietary log could be added to a revised protocol.

6.3 Study Protocol

The high rate of participant dropout suggests several possible limitations in this study and opportunities for refining the protocol. As a clinical trial, this outcome resulted in an inability to evaluate the study's hypothesis. As a pilot study, this is part of an iterative cycle of protocol refinement. Important limitations are outlined in section 6.5, which discusses their implications as a pilot study and potential changes to the protocol.

6.4 Limitations

6.4.1 Dropout

The high rate of participant dropout was a limitation of this study. Numerous possible explanations were explored in the discussion section. Due to the high dropout rate it is not feasible to draw conclusions regarding the effects of omega-3 fatty acid supplementation in the treatment of ADHD. It also suggests there may be problems with the study design, protocol, recruitment and retention strategies, choice of study population and choice of supplement. Study protocol refinements to address these problems with participant retention in addition to other deficits are outlined in section 6.5.

6.4.2 Inability to Conduct Planned Analyses of Data

This high rate of participant dropout prevented several planned analyses, including the analyses of the primary outcome measures.

6.4.3 Change in Protocol

The change in study protocol, expanding the inclusion criteria highlights a limitation of the original protocol. The original inclusion/exclusion criteria was evidently too restrictive and less clinically relevant in an attempt to recruit a relatively homogeneous study population with few confounding factors.

6.4.4 Study Site

The choice of a single study site, particularly a subspecialty clinic, while convenient, was a limitation. It resulted in a relatively small base of patients from whom to recruit. This limitation was compounded by the initially restrictive inclusion/exclusion criteria. This may have excluded many potential participants with high levels of symptom severity and high rates of comorbidity that were likely present in this subspecialty clinic population.

6.4.5 Failure to Recruit Full Complement for Study

The failure to recruit the planned number of study participants was a limitation. This was unforeseen and highlights the importance of this research as a pilot study. Inadequate sample size compounded the unexpectedly high dropout rates to prevent detection of the differences in outcomes that it was powered to detect. The choice of study site and to a lesser extent, the inclusion/exclusion criteria were likely contributing factors. Recruitment strategies, including advertisement of the study to patients and physicians seemed adequate, but may also warrant optimization. Recruitment strategies are discussed in subsection 6.5.2.

6.4.6 Last Observation Carried Forward

As noted in subsection 3.12.2, section 4.4 and section 5.4, an *a priori* decision was made to use an LOCF approach for missing data. This means of analysis can introduce bias [46]. This bias includes a tendency to favour interventions that may be efficacious but difficult to tolerate. This method treats dropouts from each treatment group identically. However, it is possible that study participants may have dropped out for different reasons and ultimately fared differently in terms of outcomes. In the case of this study, the reasons for study withdrawal were captured in an unstructured manner. There did not appear to be a marked difference between the groups in terms of reasons for withdrawal. However, this does not imply the groups would have fared similarly in terms of outcomes.

6.5 Role as a Pilot Study

While this study was unable to meet its primary goal of assessing the efficacy of supplementing children and adolescents with ADHD with omega-3 fatty acids, it did serve its other role as a pilot study very well, assessing feasibility and practicality while suggesting refinements and modifications to future studies.

6.5.1 Study Site

Future studies will require a larger referral base, preferably from primary care, including family doctors and nurse practitioners, as well as specialist care, including paediatricians and community psychiatrists. These patient populations will ensure a high degree of clinical applicability. The use of multiple study sites will help minimize the influence of site-specific effects on study outcomes. The use of multiple sites does

introduce additional logistical challenges, which could have unforeseen consequences that cannot be planned for based on this study. A study coordinator or full-time research nurse would need to be employed to monitor this sort of study.

The benefits associated with the inclusion of sub-speciality services, such as child and adolescent psychiatry and developmental paediatrics is debatable. The referral base should not be restricted to these last groups. These last groups could serve as a valuable source of study participants with higher levels of symptomatology and more challenging comorbidities, which would enhance the generalizability of study results. For the same reasons, these patients may be more difficult to maintain in this sort of study, resulting in high dropout rates.

6.5.2 Recruitment

In addition to expanding the referral base by adding additional study sites, as discussed in subsection 6.5.1, patient recruitment could also be enhanced by increasing awareness among both recruiting physicians and eligible patients.

Additional study sites could be arranged by contacting physicians already familiar to the study team. These physicians could be asked to suggest other physicians that might be willing to establish a study site. Letters and/or emails of introduction could be used to initiate this process. In addition, the Newfoundland and Labrador Medical Association (NLMA) or Medical Care Plan (MCP) mailing lists could be used to distribute such a letter of introduction, outlining the study and inviting interested parties to contact the principal investigator.

Eligible patients could be made aware of the study by distributing a similar letter of introduction through mailing lists that would include the parents and guardians of these youths, including The Newfoundland and Labrador Tourette's Foundation, and The Newfoundland and Labrador Learning Disabilities Association. If necessary,

a wider audience could be reached with study advertisements in the media, including newspapers and radio.

6.5.3 Inclusion/Exclusion Criteria

This study's modified inclusion/exclusion criteria could serve as a reasonable basis for future studies. It includes compromises to help ensure a sufficiently homogeneous study population to permit treatment effects to be detected without being overwhelmed by confounders. It represents a population that is clinically relevant to both primary and specialist care. A proposed study's sample size will need to be increased to account for this increase in sample heterogeneity.

6.5.4 Sample Size

Were the study protocol to remain the same, sample size estimates would have to account for a high dropout rate. However, with the proposed changes to this study protocol, estimates of study dropout rates could be based on the trials reviewed in the Cochrane review, with a mean dropout rate of 22% (Table 5.1) [7].

6.5.5 Study Length

The study length of 6 months could remain unchanged in a future trial. As discussed in subsection 1.1.4 and subsection 3.1.1, the length of time to the onset of any therapeutic action and the duration of this action are unknown at present [7]. Therefore, the study length should remain as long as is practical. Otherwise, failure to identify a therapeutic effect could be due to a brief study duration. Also, identifying a therapeutic effect during a brief trial would not necessarily imply a long-lasting therapeutic effect.

One trial in the Cochrane review [7] was 6 months in length [17]. As discussed in subsection 5.3.1 and Table 5.1, the dropout rate of this trial was comparable with the shorter studies in the review (15% vs. 22%). Once the other protocol changes discussed in this section have been incorporated, it is likely the dropout rate for a future trial would be comparable to published rates and not negatively affected by a study length of 6 months.

6.5.6 Choice of Supplement

In spite of informal assessment of palatability of the supplement and placebo, this appears to have been a barrier to study completion. A short list of potential supplements could be gathered from the clinical trials in the Cochrane review [7]. Any recently introduced supplements that might be appropriate could also be considered. More extensive tests of palatability could then be conducted to ensure potential supplements are acceptable to local children and adolescents. The final choice of supplement could then be based on a combination of palatability and other factors, such as omega-3 composition and supplement preparation (e.g. capsule vs. liquid).

6.5.7 Frequency of Follow-Up

The present study's frequency of clinic follow-up (every 8 weeks) was similar to other studies [7] and could remain unchanged in a future trial. The lack of regular inter-visit telephone follow-up by a research nurse likely contributed to the high rate of dropout and should be corrected in future protocols. Based on other studies, telephone contact every 2 to 4 weeks seems to be the optimal frequency [7].

6.5.8 Outcome Measures

The choice of primary and secondary outcome measures in this protocol are compatible with similar studies [7]. The combination of objective measures, including, the CCPT-II and CGI, and subjective measures, the Conners-3 reports provided a multidimensional perspective on treatment effects. These outcome measures were administered without notable difficulty. They could be reused in a future protocol.

The TSQ was consistently administered, although the results were not entirely as expected or in keeping with other studies [7]. This is likely not a limitation of this validated and widely used tool. This discrepancy is more likely attributable to the small sample size and possible cultural and dietary factors discussed in subsection 6.2.3.

The AEI was effective in assessing tolerability. A useful addition to this tool would be the addition of an “Other” option, with space to elaborate on the adverse effect and make comments.

A study withdrawal form would be useful in a revised protocol. A process whereby a research assistant or nurse routinely calls participants that have withdrawn from the study could be added to the study protocol and consent process. The reasons for withdrawal collected during this study could be used as the basis for such a form, including: Taste/Aftertaste, Gastrointestinal Complaints, Developed Fish Allergy, Factors Unrelated to Study, and Lack of Efficacy. Like the AEI, an additional option of “Other” could be added, with additional space for notes and comments.

6.6 Summary

This study had several limitations, including problems with recruitment, initially restrictive inclusion criteria, early study withdrawal, and a supplement and placebo with low tolerability. Several of the planned analyses could not be performed due to

small sample size. The analyses that were conducted relied heavily on LOCF data. Conclusions specific to the null hypothesis cannot be drawn from the results of the planned analyses that were able to be conducted. There was no statistically significant differences between the groups. No conclusions can be made regarding the efficacy of this omega-3 supplement in the treatment of ADHD based on this study.

As a pilot study, these limitations highlight some of the necessary changes to the study protocol. Some of the key changes include finding and using a more tolerable supplement and placebo, using multiple, non-sub-specialty sites for patient recruitment, broader inclusion criteria, and between visit telephone contact.

Appendix A

Clinical Global Impression Scale

Clinical Global Impression (CGI)

1. Severity of illness

Considering your total clinical experience with this particular population, how mentally ill is the patient at this time?

- | | |
|-----------------------------|---|
| 0 = Not assessed | 4 = Moderately ill |
| 1 = Normal, not at all ill | 5 = Markedly ill |
| 2 = Borderline mentally ill | 6 = Severely ill |
| 3 = Mildly ill | 7 = Among the most extremely ill patients |

2. Global improvement: Rate total improvement whether or not, in your judgement, it is due entirely to drug treatment.

Compared to his condition at admission to the project, how much has he changed?

- | | |
|------------------------|---------------------|
| 0 = Not assessed | 4 = No change |
| 1 = Very much improved | 5 = Minimally worse |
| 2 = Much improved | 6 = Much worse |
| 3 = Minimally improved | 7 = Very much worse |

3. Efficacy index: Rate this item on the basis of drug effect only.

Select the terms which best describe the degrees of therapeutic effect and side effects and record the number in the box where the two items intersect.

EXAMPLE: Therapeutic effect is rated as 'Moderate' and side effects are judged 'Do not significantly interfere with patient's functioning'.

Therapeutic effect		Side effects			
		None	Do not significantly interfere with patient's functioning	Significantly interferes with patient's functioning	Outweighs therapeutic effect
Marked	Vast improvement. Complete or nearly complete remission of all symptoms	01	02	03	04
Moderate	Decided improvement. Partial remission of symptoms	05	06	07	08
Minimal	Slight improvement which doesn't alter status of care of patient	09	10	11	12
Unchanged or worse		13	14	15	16
Not assessed = 00					

Reproduced from Guy W, editor. ECDEU Assessment Manual for Psychopharmacology. 1976. Rockville, MD, U.S. Department of Health, Education, and Welfare

Appendix B

Adverse Effect Inquiry Form

Patient Number:		
Side Effect:	Yes	No
Belching	<input type="checkbox"/>	<input type="checkbox"/>
Nausea	<input type="checkbox"/>	<input type="checkbox"/>
Diarrhea	<input type="checkbox"/>	<input type="checkbox"/>
Bloating	<input type="checkbox"/>	<input type="checkbox"/>
Intestinal Gas	<input type="checkbox"/>	<input type="checkbox"/>
Fishy Body Odour	<input type="checkbox"/>	<input type="checkbox"/>
Fish Breath	<input type="checkbox"/>	<input type="checkbox"/>
Fishy aftertaste	<input type="checkbox"/>	<input type="checkbox"/>

Appendix D

Omega-3 Fatty Acid Supplement

Table D.1: Genius Liquid Kids And Teens - Omega-3: Formulation Per 5 mL Serving

Ingredient	mg
Wild tuna fish oil	1000
Wild fish oil blend (mackerel, anchovy, sardine)	1000
Certified Organic Flax seed oil, (<i>Linum usitatissimum</i>) Cold Pressed	320
Borage oil (<i>Borago officinalis</i>) (20% GLA)	150
Soy lecithin (<i>Glycine max.</i> bean) rich in Phosphatidyl choline (4.5 mg)	15
Vitamin E (d-alpha-tocopherol)	9
Antioxidant blend	
Rosemary extract	
Natural Orange Flavour	
<i>Note.</i> Adapted from <i>Genius Liquid Kids And Teens - Omega-3</i> , by Nutripur, 2013. Retrieved from http://www.nutripur.com/	

Table D.2: Genius Liquid Kids And Teens - Omega-3: Polyunsaturated Fatty Acid Content Per 5 mL Serving

Polyunsaturated Fatty Acid	mg
Omega-3	
Docosahexaenoic acid (DHA)	365
Eicosapentaenoic acid (EPA)	225
Alpha-Linolenic acid (ALA))	160
Omega-6	
Gamma-Linolenic acid (GLA)	30
Linoleic Acid (LA)	90
Arachidonic acid (AA)	15
<i>Note.</i> Adapted from <i>Genius Liquid Kids And Teens - Omega-3</i> , by Nutripur, 2013. Retrieved from http://www.nutripur.com/	

Bibliography

- [1] Benjamin J Sadock, Virginia Alcott Sadock, and Pedro Ruiz, (ed.) (2012) Kaplan and Sadock's Comprehensive Textbook of Psychiatry (2 Volume Set), Lippincott Williams & Wilkins, 9th edition.
- [2] Andres Martin and Fred R Volkmar, (ed.) (2012) Lewis's Child and Adolescent Psychiatry: A Comprehensive Textbook, Lippincott Williams & Wilkins, 4th edition.
- [3] Canadian Attention Deficit Hyperactivity Disorder Resource Alliance (CADDRA) (2012) *Canadian ADHD Practice Guidelines*.
- [4] Pliszka, S. and onQuality Issues, A. W. G. (2012) *Journal of the American Academy of Child and Adolescent Psychiatry* **46(7)**, 894–921.
- [5] Association, A. P. (2012) Diagnostic and Statistical Manual of Mental Disorders DSM-IV-TR Fourth Edition (Text Revision), Amer Psychiatric Pub, 4th edition.
- [6] Group, T. M. C. (2012) *Archives of general psychiatry* **56(12)**, 1073–1086.
- [7] Gillies, D., Sinn, J. K., Lad, S. S., Leach, M. J., and Ross, M. J. (2012) *Cochrane database of systematic reviews (Online)* **7**, CD007986.
- [8] Aman, M. G., Mitchell, E. A., and Turbott, S. H. (2012) *Journal of abnormal child psychology* **15(1)**, 75–90.

- [9] Arnold, L., Pinkham, S. M., and Votolato, N. (2012) *Journal of child and adolescent psychopharmacology* **10(2)**, 111–117.
- [10] Arnold, L., Kleykamp, D., Votolato, N., Gibson, R. A., and Horrocks, L. (2012) *Journal of child and adolescent psychopharmacology* **4(3)**, 171–182.
- [11] Arnold, L., Kleykamp, D., Votolato, N. A., Taylor, W. A., Kontras, S. B., and Tobin, K. (2012) *Biological psychiatry* **25(2)**, 222–228.
- [12] Bélanger, S. A., Vanasse, M., Spahis, S., Sylvestre, M.-P., Lippé, S., L'heureux, F., Ghadirian, P., Vanasse, C.-M., and Levy, E. (2012) *Paediatrics & child health* **14(2)**, 89–98.
- [13] Brue, A. W. and Oakland, T. D. (2012) *Alternative Therapies in Health and Medicine* **8(1)**, 68.
- [14] Gustafsson, P. A., Birberg-Thornberg, U., Duchén, K., Landgren, M., Malmberg, K., Pelling, H., Strandvik, B., and Karlsson, T. (2012) *Acta Paediatrica* **99(10)**, 1540–1549.
- [15] Hamazaki, T. and Hirayama, S. (2012) *European Journal of Clinical Nutrition* **58(5)**, 838.
- [16] Hirayama, S., Hamazaki, T., and Terasawa, K. (2012) *European Journal of Clinical Nutrition* **58(3)**, 467–473.
- [17] Johnson, M., Ostlund, S., Fransson, G., Kadesjo, B., and Gillberg, C. (2012) *Journal of Attention Disorders* **12(5)**, 394–401.
- [18] Manor, I., Magen, A., Keidar, D., Rosen, S., Tasker, H., Cohen, T., Richter, Y., Zaaroor-Regev, D., Manor, Y., and Weizman, A. (2012) *European psychiatry : the journal of the Association of European Psychiatrists* **27(5)**, 335–342.

- [19] Raz, R., Carasso, R. L., and Yehuda, S. (2012) *Journal of child and adolescent psychopharmacology* **19(2)**, 167–177.
- [20] Sinn, N. (2012) *Journal of developmental and behavioral pediatrics : JDBP* **28(3)**, 262–263.
- [21] Sinn, N., Bryan, J., and Wilson, C. (2012) *Prostaglandins, leukotrienes, and essential fatty acids* **78(4-5)**, 311–326.
- [22] Stevens, L., Zhang, W., Peck, L., Kuczek, T., Grevstad, N., Mahon, A., Zentall, S. S., Arnold, L. E., and Burgess, J. R. (2012) *Lipids* **38(10)**, 1007–1021.
- [23] Vaisman, N., Kaysar, N., Zaruk-Adasha, Y., Pelled, D., Brichon, G., Zwingelstein, G., and Bodennec, J. (2012) *The American journal of clinical nutrition* **87(5)**, 1170–1180.
- [24] Voigt, R. G., Llorente, A. M., Jensen, C. L., Fraley, J. K., Berretta, M. C., and Heird, W. C. (2012) *The Journal of Pediatrics* **139(2)**, 189–196.
- [25] Richardson, A. J. (2012) *International review of psychiatry (Abingdon, England)* **18(2)**, 155–172.
- [26] Innis, S. M. (2012) *Developmental neuroscience* **22(5-6)**, 474–480.
- [27] Pawlosky, R. J., Hibbeln, J. R., Novotny, J. A., and Salem, N. (2012) *Journal of lipid research* **42(8)**, 1257–1265.
- [28] Salem, N., Pawlosky, R., Wegher, B., and Hibbeln, J. (2012) *Prostaglandins, leukotrienes, and essential fatty acids* **60(5-6)**, 407–410.
- [29] Stevens, L. J., Zentall, S. S., Deck, J. L., Abate, M. L., Watkins, B. A., Lipp, S. R., and Burgess, J. R. (2012) *The American journal of clinical nutrition* **62(4)**, 761–768.

- [30] Stevens, L. J., Zentall, S. S., Abate, M. L., Kuczek, T., and Burges, J. (2012) *Physiology and Behaviour* **59(4)**, 915–920.
- [31] Stevens, L. J., Kuczek, T., Burgess, J. R., Hurt, E., and Arnold, L. (2012) *Clinical Pediatrics* **50(4)**, 279–293.
- [32] Stevens, L. J., Kuczek, T., and Arnold, L. E. (2012) *Nutrition reviews* **69(7)**, 383–384.
- [33] Takeuchi, T., Fukumoto, Y., and Harada, E. (2012) *Behavioural brain research* **131(1-2)**, 193–203.
- [34] Zimmer, L., Vancassel, S., Cantagrel, S., Breton, P., Delamanche, S., Guilloteau, D., Durand, G., and Chalon, S. (2012) *The American journal of clinical nutrition* **75(4)**, 662–667.
- [35] Sinn, N. and Bryan, J. (2012) *Journal of developmental and behavioral pediatrics : JDBP* **28(2)**, 82–91.
- [36] Richardson, A. J. and Puri, B. K. (2012) *Progress in neuro-psychopharmacology & biological psychiatry* **26(2)**, 233–239.
- [37] Richardson, A. J. and Montgomery, P. (2012) *Pediatrics* **115(5)**, 1360–1366.
- [38] United States Food and Drug Administration Letter Regarding Dietary Supplement Health Claim for Omega-3 Fatty Acids and Coronary Heart Disease United States Food and Drug Administration (2012).
- [39] Raz, R. and Gabis, L. (2012) *Developmental Medicine & Child Neurology* **51(8)**, 580–592.
- [40] Conners, C. (2012) Conners 3rd edition manual, Toronto, Ontario, Canada: Multi-Health Systems, toronto, ontario, canada: multi-health systems edition.

- [41] Achenbach, T. and Ruffle, T. (2012) *Pediatrics in Review* **21(8)**, 265–271.
- [42] Conners, C. and Staff, M. (2012) Conners' Continuous Performance Test II (CPT II V. 5), Multi-Health Systems Inc., North Tonawanda, NY, multi-health systems inc., north tonawanda, ny edition.
- [43] Nutripur <http://www.nutripur.com/> (2012).
- [44] Guy, W. (2012) *ECDEU assessment manual for psychopharmacology* **76**, 218–220.
- [45] Volkmar, F., Pomeroy, J., Realmuto, G., and Tanguay, P. (2012) *Journal of the American Academy of Child and Adolescent Psychiatry* **38(12 Suppl)**, 32S–54S.
- [46] Horton, N. J. and Kleinman, K. P. (2012) *The American Statistician* **61(1)**, 79–90.

