

Non-stimulant interventions in ADHD

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UNIVERSITY OF GOTHENBURG

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Ale Tryckteam AB, Bohus

To my parents and my family

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ABSTRACT

Aim: The overall aim of the thesis was to study alternative non-stimulant treatments for Attention Deficit Hyperactivity Disorder (ADHD) in children, adolescents and adults. **Method:** The thesis includes four studies referring to three different treatment trials. Study 1: Randomized double-blind placebo-controlled trial of Omega 3/6 fatty acids (Equazen eyeq) treatment of ADHD in children and adolescents. Study 2: Changes in plasma fatty acid profiles in the Omega 3/6 trial, and comparison with treatment response. Study 3: One-year trial of efficacy and safety of the non-stimulant medication atomoxetine in adults with ADHD. Study 4: Study of the effectiveness of the cognitive-behavioural model “Collaborative Problem Solving” (CPS) in children with ADHD and Oppositional Defiant Disorder (ODD). **Results:** The overall group results of Study 1 were negative, but clinical response was seen in subgroups such as those with ADHD inattentive subtype, Developmental Coordination Disorder (DCD), and reading-writing disorder. Study 2 findings suggested that clinical response to Omega 3/6 was associated with plasma fatty acid changes, especially with reduction of the n-6/n-3 ratio. Study 3 showed a moderate effectiveness of atomoxetine after 10 weeks in adults with ADHD, but the longer-term compliance to treatment was poor. In study 4 CPS showed promise in reducing problem behaviours in children with ADHD and ODD, and children with severe ADHD symptoms may be improved by combining CPS and ADHD medication.

Conclusions: The trials of non-stimulant treatments included in this thesis showed some promising results and suggested directions for future research and study designs.

Keywords: Attention Deficit Hyperactivity Disorder, Omega 3/6, Plasma Fatty Acids, Atomoxetine, Collaborative Problem Solving

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SAMMANFATTNING PÅ SVENSKA

Avhandlingens syfte är att studera alternativa behandlingar (icke-centralstimulantia) för Attention Deficit Hyperactivity Disorder (ADHD). Den består av fyra studier avseende tre olika typer av behandling. Studie 1: Randomiserad dubbel-blind placebo-kontrollerad studie av behandling med Omega 3/6-fettsyror för ADHD hos barn och ungdomar. Studie 2: Studie av förändringar av fettsyror i plasma under Omega 3/6-studien och jämförelse med klinisk behandlingseffekt. Studie 3: Ettårig öppen studie av effekt och säkerhet för atomoxetin hos vuxna med ADHD. Studie 4: Studie av den kognitiva träningsmetoden "Collaborative Problem Solving" för barn med ADHD och trotsyndrom (ODD). I Studie 1 fann vi ingen signifikant effekt för hela gruppen, men kliniskt meningsfull förbättring noterades särskilt i subgruppen med utvecklingsneurologisk problematik, som t.ex. ADHD huvudsakligen uppmärksamhetsstörning, motoriska problem (DCD), och läs- och skrivsvårigheter. Studie 2 tydde på att klinisk förbättring med Omega 3/6 hade samband med förändringar i fettsyror i plasma, särskilt minskning av n-6/n-3 kvoten. Studie 3 visade en måttlig effekt av atomoxetin efter 10 veckor hos vuxna med ADHD, men följsamheten under längre tid i behandlingen var låg. Studie 4 visade resultat talande för att CPS kan förbättra problemskapande beteende hos barn med ADHD och ODD, och att barn med svåra ADHD-symtom kan förbättras med en kombination av CPS och ADHD-medicinering.

Sammanfattningsvis visar studierna med alternativa behandlingar för ADHD en del lovande resultat, och ger ledtrådar för inriktning och design av framtida studier inom området.

LIST OF PAPERS

This thesis is based on the following studies, referred to in the text by their Roman numerals.

- I. Johnson M, Östlund S, Fransson G, Kadesjö B, Gillberg C (2009). Omega-3/Omega-6 Fatty Acids for Attention Deficit Hyperactivity Disorder. A Randomized Placebo-Controlled Trial in Children and Adolescents. *Journal of Attention Disorders* 12, 394–401.
- II. Johnson M, Månsson J-E, Östlund S, Fransson G, Areskoug B, Hjalmarsson K, Landgren M, Kadesjö B, Gillberg C (2012). Fatty acids in ADHD: plasma profiles in a placebo-controlled study of Omega 3/6 fatty acids in children and adolescents. *ADHD Attention Deficit and Hyperactivity Disorders* 4, 199-204.
- III. Johnson M, Cederlund M, Råstam M, Areskoug B, Gillberg C (2010). Open-Label Trial of Atomoxetine Hydrochloride in Adults with ADHD. *Journal of Attention Disorders* 13, 539-545.
- IV. Johnson M, Östlund S, Fransson G, Landgren M, Nasic S, Kadesjö B, Gillberg C, Fernell E (2012). Attention-deficit/hyperactivity disorder with oppositional defiant disorder in Swedish children – an open study of Collaborative Problem Solving. *Acta Paediatrica* 101, 624-630.

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ABBREVIATIONS

AA	Arachidonic Acid
AD	ADHD Inattentive Subtype
ADHD	Attention Deficit Hyperactivity Disorder
ADHD-RS	ADHD Rating Scale
ADORE	ADHD Observational Research in Europe
ALC	Autism-Like Condition
ANOVA	Analysis Of Variance
APA	American Psychiatric Association
ASD	Autism Spectrum Disorder
ASDI	Autism Spectrum Diagnostic Interview
BMI	Body Mass Index
BPT	Behavioural Parent Training
CAARS-S	Conners' Adult ADHD Rating Scale – Self Report
CAMT	Cologne Adaptive Multimodal Treatment
CGI-I	Clinical Global Impression – Improvement
CGI-S	Clinical Global Impression - Severity
CPS	Collaborative Problem Solving (Proactive Solutions)
DCD	Developmental Coordination Disorder
DHA	Docosahexaenoic acid
DMN	Default Mode Network

DSM	Diagnostic and Statistical Manual of Mental Disorders
DSM-IV	DSM, 4 th edition
DSM-5	DSM, 5 th edition
EPA	Eicosapentaenoic acid
ESSENCE	Early Symptomatic Syndromes Eliciting Neurodevelopmental Clinical Examinations
FBIM	Family Burden of Illness Module
FSI	Family Strain Index
GLA	Gamma Linolenic Acid
LD	Learning Difficulties
LOCF	Last Observation Carried Forward
MPH	Methylphenidate
NFPP	New Forest Parenting Programme
PEP	Prevention Programme for Externalizing Problem behaviour
PT	Parent Training
OCD	Obsessive Compulsive Disorder
ODD	Oppositional Defiant Disorder
PUFA	Polyunsaturated Fatty Acids
RCT	Randomized Controlled Trial
RWD	Reading Writing Difficulties
SCID-I	Structured Clinical Interview for DSM-IV axis I disorders
SMD	Standardized Mean Difference

SNAP-IV Swanson, Nolan and Pelham Scale – IV
TAU Treatment As Usual

1 INTRODUCTION

ADHD (*Attention-Deficit/Hyperactivity Disorder*), as defined in the Diagnostic and Statistical Manual of Mental Disorders, 4th edition (DSM-IV; APA 1994) and the text revised version DSM-IV-TR (APA 2000), is characterized by developmentally inappropriate and impairing core symptoms of inattention, hyperactivity and impulsivity. DSM-IV describes three subtypes of ADHD; inattentive, hyperactive-impulsive, and combined.

The recently published DSM-5 includes the same symptom criteria, but uses the term *presentations* rather than *subtypes*, in the light of evidence that the subtypes are unstable in the long term, and the symptom profile often changes with age. Also, the DSM-IV criterion for the first appearance of symptoms before the age of 7 is adjusted to 12 years in the DSM-5 (APA 2013).

1.1 The history of ADHD

The German physician Melchior Adam Weikard may have been first (1775) to describe what we currently consider to be ADHD (Barkley and Peters 2012). The Scottish physician Alexander Crichton in 1798 very accurately defined the typical symptoms of distractibility and “mental restlessness”. A century later, the London paediatrician George Still (1902) described similar symptoms but labelled it “a defect of moral control”. Since then the knowledge about ADHD has grown, slowly at first, then very rapidly worldwide during the last decades. Labels have developed over time, from MBD (Minimal Brain Damage or Minimal Brain Dysfunction), to more well-defined operational diagnoses such as ADD, DAMP (Deficits in Attention, Motor control and Perception, Gillberg et al. 1982), ADHD (DSM-IV, APA 1994, 2000) to the modified ADHD definition in the DSM-5 (APA 2013). The term DAMP highlighted the neurodevelopmental origins of ADHD, combining the focus on ADHD symptoms, motor coordination difficulties, and deficits in perception (e.g. auditory, visual, tactile), dysfunctions which often co-occur in children with ADHD. The perception deficits or hypersensitivities themselves may cause significant distress and functional impairment. The combination of dysfunctions encompassed in the term DAMP also includes the delayed or aberrant language development seen in many children with ADHD (Rasmussen et al. 1983, Hagberg et al. 2010, Gillberg 2014).

1.2 The genetics and neurobiology of ADHD

Family, twin and adoption studies indicate that ADHD is strongly hereditary (Faraone et al. 2005, Burt 2009). Molecular genetic studies suggest that the genetic architecture of ADHD is complex and involves both common and rare genetic variants. Several candidate genes coding for components of neurotransmission have been identified, some involving the catecholaminergic networks (Swanson et al. 2007, Franke et al. 2012, Bralten et al. 2013). Clock gene variants and mutations in genes of the melatonin pathway may play a role in the circadian rhythm disturbances often associated with ADHD (Chaste et al. 2011, Dueck et al. 2012). However, all these gene variants have only relatively small effects, suggesting that multiple genes are involved in the etiology of ADHD (Franke et al. 2012, Gillberg 2014). The inheritance pattern makes a multifactorial polygenic etiology most likely, and there is evidence that environmental factors are also involved (Sonuga-Barke 2010, Franke et al. 2012). Variability in genes involved in dopaminergic signaling (e.g. DRD 4) has been associated with reduced cortical thickness in orbitofrontal and prefrontal regions which gradually normalized when the clinical symptoms improved (Shaw et al. 2007).

Genetic studies also show that loci with genetic risk factors are shared between several neuropsychiatric disorders, for instance ADHD and autism, findings which accord well with the high frequency of comorbidities in clinical samples (Cross-Disorder Group of the Psychiatric Genomics Consortium 2013, Thapar et al. 2013).

Neuroimaging studies suggest that the neurobiology of ADHD is heterogeneous, involving dysfunction of several brain regions and networks. Among the most replicated findings in neuroimaging studies in ADHD are volume reductions and dysfunctions in frontostriatal and frontocerebellar circuits, in the Default Mode Network (DMN), and in regions involved in the processing of reward and motivation (Valera et al. 2007, Bush 2011, Kasperek et al. 2013). DMN are brain areas where activity increases when the person is resting, but is reduced during goal-oriented activity. Several studies have shown impaired connectivity between these areas in ADHD (Sonuga-Barke and Castellanos 2007, Uddin et al. 2008). Animal and human studies suggest that neuroplasticity modulated by the dopaminergic system is important. Both genetic and environmental influences seem to affect neuronal development and function, and increasing catecholamine neurotransmission through treatment with ADHD medication (methylphenidate or atomoxetine) has been shown to improve brain structure, activity and functional connectivity (Cortese and Castellanos 2012, Kasperek et al. 2013).

1.3 The prevalence and comorbidity of ADHD

Analysis of more than one hundred studies in countries all over the world shows a pooled ADHD prevalence of 5.29% in children and adolescents (Polanczyk et al 2007). Symptoms often persist into adult age, and are associated with increased risks of adverse outcomes (Rasmussen and Gillberg 2000, Kessler et al. 2006, Barkley et al. 2006). Estimates of the average prevalence of ADHD in adults in population surveys and follow-up studies lie between 2.5 and 4.9% (Kessler et al. 2006, Fayyad et al. 2007, Simon et al. 2009). It has also been shown that ADHD may continue through the lifespan into old age (Guldborg-Kjär 2013). ADHD seems to be somewhat more common in boys than in girls, but the diagnosis is probably still underestimated in girls due to their less overt symptomatology (Kopp et al. 2010).

In patients with ADHD, comorbidity is the rule rather than the exception (Kadesjö and Gillberg 2001, Kadesjö et al. 2003, Gillberg et al. 2004), for instance motor coordination problems (Developmental Coordination Disorder; DCD), Oppositional Defiant Disorder (ODD), anxiety, depression, tics, Tourette, Autism Spectrum Disorder (ASD), learning difficulties, reading/writing disorders. Comorbidities are very common in child psychiatry and developmental medicine in general, and the term ESSENCE (Early Symptomatic Syndromes Eliciting Neurodevelopmental Clinical Examinations) has been proposed to describe this co-existence of disorders, which can be observed from an early age onwards (Gillberg 2010, 2014; Gillberg et al. 2014).

1.4 Stimulant treatment for ADHD

In the last decades the effects of medication with stimulants (amphetamine, methylphenidate) have been examined in numerous placebo-controlled trials, which have demonstrated robust efficacy on core ADHD symptoms (Banaschewski et al. 2006, Faraone & Buitelaar 2010), and the side effects are well documented and usually mild (Graham et al. 2011, Hamilton et al. 2012, Cortese et al. 2013). However, stimulant treatment does not work well for all, and it may be associated with unwanted side effects. There have also been some concerns that the safety of the treatment is not fully known (Graham et al. 2011). This indicates the need for alternative treatments. The possibility that other treatments may improve symptoms and function through other mechanisms is also appealing, and they could thus serve as alternative, complementary or even augmenting treatments if the stimulant

effect is insufficient. For various reasons some families may prefer other interventions than medication, and the public interest in alternative treatments is growing.

1.5 Alternative non-stimulant treatments

The parents of children with neurodevelopmental/neuropsychiatric disorders such as ADHD are often met by claims and advertising in media about the effectiveness of alternative treatments. Common examples of treatments are Omega 3 fatty acids, diets without sugar and colorings, hypoallergenic diet, acupuncture, neurofeedback. However, the claims for effects have rarely been solidly supported by research, since studies of alternative treatments have been few, small, and of varying quality. It is important for clinical researchers to contribute to knowledge about different treatments, based on research of high quality, to be able to give families well informed advice about the efficacy and safety of the treatments.

With this in mind we planned studies of non-stimulant treatments which were relatively new and encountered by many families looking for the most effective treatments available. Our choice fell on treatments that had shown at least some promising results in studies, but for which more research was needed to substantiate both effectiveness and safety.

Study 1 and 2 are from a randomized placebo-controlled double-blind trial of treatment with Omega 3/6 fatty acids for children and adolescents, and included blood tests for following the changes in plasma fatty acid profiles during the trial (Paper I and II). The trial was planned since the public interest in this kind of treatment has been considerable for many years now, and two previous studies in England (Richardson & Montgomery 2005) and Australia (Sinn & Bryan 2007) showed promising results in children and adolescents with attention deficits/ADHD and/or DCD. We wanted to examine if the results could be replicated in a sample with clinically diagnosed ADHD and well characterized comorbidities, intellectual levels, and difficulties with reading/writing and learning.

Earlier research has suggested neurological mechanisms for the action of polyunsaturated fatty acids (PUFA) such as Omega 3/6. Neuronal cell membranes are rich in phospholipids containing these fatty acids and experimental studies indicate that PUFA play a role in neurochemical and cell membrane functions including the dopaminergic system (Chalon 2006, Innis 2007, Raz and Gabis 2009). Lower levels of Omega 3 (n-3) fatty acids and higher Omega 6/3 (n-6/n-3) ratios in erythrocytes or plasma have been reported in children and adolescents with ADHD compared to controls, but

generally with small sample sizes (Stevens et al. 1995, 2003, Burgess et al. 2000, Chen et al. 2004, Germano et al. 2007, Colter et al. 2008).

Previous treatment studies in children with ADHD symptoms suggest that the ratio of the Omega 3 fatty acids EPA and DHA is important. More positive results have been reported from trials with EPA, or a combination of EPA and DHA (Bloch and Qawasmi 2011), than with supplements containing mainly DHA (Voigt 2001, Hirayama, Hamazaki, & Terasawa 2004).

Study 3 was planned to examine the long-term effects and safety of the noradrenaline reuptake inhibitor atomoxetine for adults with ADHD (Paper III). It was a one-year open-label trial. This medication has been examined in a large number of studies with children and adolescents during the last two decades (Banaschewski et al. 2006; Bushe and Savill 2014). Long-term trials in adults, however, were few at the time when we planned our study, and treatment of adults with ADHD in Sweden was still rare in those years.

Study 4 is a pilot study (Paper IV) with the cognitive-behavioural model "Collaborative Problem Solving" (CPS), developed by Dr. Ross Greene at Harvard University (Greene 1998, 2009, 2010, Greene and Ablon 2005).¹ The method is based on the theory that children (or adults for that matter), who display challenging behaviour, do so because they have not yet developed the cognitive skills needed to meet the expectations in a certain situation. Thus these behaviours are thought to emanate from lagging cognitive skills, commonly in the domains of executive function, emotion regulation (frustration tolerance), cognitive flexibility, language-processing skills or social skills. Especially the lagging skills in emotion regulation and cognitive flexibility are common factors behind explosive behaviours.

CPS treatment is based on a systematic assessment of the child's lagging cognitive skills and of situations where behaviour problems arise (i.e. unsolved problems). A specific emphasis is placed on analysing the problems in detail from the child's perspective, in a discussion facilitated by using empathy, to find a core factor causing the problem. Thereafter the adults' perspective of the problem is discussed, and the adult and child exchange ideas of how to reach a mutually satisfactory solution to the problem. The solutions are then practiced in everyday life to see how well they work.

¹ "Dr. Greene is the originator of the **Collaborative Problem Solving** approach - and referred to his model by that name in his articles, chapters, research papers, and books prior to 2013 - but now calls his model **Collaborative & Proactive Solutions (CPS)**" (<http://www.livesinthebalance.org>, August 7, 2014).

The CPS model has been studied by Ross Greene et al. in the US for families, in schools, and in psychiatric institutions for children with severe behaviour problems, with promising results (Greene et al. 2004; 2006; Greene and Ablon 2005, Martin et al. 2008). One of these studies was a randomized controlled trial which examined CPS compared to Barkley's (1997) behavioural parent training (BPT) program in 50 children with ODD and affective dysregulation (subthreshold features of bipolar disorder or major depression), aged 4-12 years. The trial showed equivalent to superior outcome for CPS compared to BPT on ODD symptoms and other measures of functioning at post-treatment and 4-month follow-up (Greene et al. 2004). Our small open pilot study was the first in Sweden.

Methods of BPT for behaviour problems in children have been developed since many years and several programs are available (Cunningham et al. 1995, Barkley 1997, Webster-Stratton and Hammond 1997, Sonuga-Barke et al. 2001, Thompson et al. 2009, Hanisch et al. 2010, Hautmann et al. 2008, 2013). The BPT methods focus on behaviour modification techniques for improving child behaviour and reducing maladaptive parent strategies. CPS differs from these in focusing on the cognitive/neurodevelopmental functions of the child, and on the compatibility with the adult. Other problem solving training programs are also available and studied in ongoing research (Kazdin 2005, Görtz-Dorten and Döpfner 2010, Görtz-Dorten 2012).

In a joint effort to systematize research findings, the American Psychiatric Association (APA), Division 12 (for adults) and Division 53 (for children) have developed a system of categories describing the level of research support for psychological treatments.

Level 1 (*Well established*) treatments have the strongest research support, for instance efficacy demonstrated in at least two large-scale randomized trials, conducted by two independent research teams. Level 2 (*Probably efficacious*) treatments meet Level 1 criteria, with the exception of the independent investigator criterion, or have one study showing that the treatment is at least equivalent to a Level 1 treatment. Level 3 (*Possibly efficacious*) treatments may have one study showing superiority to no treatment, or a number of smaller studies lacking methodological controls (Chambless et al. 1998, Silverman and Hinshaw 2008, Southam-Gerow and Prinstein 2014).

According to this system BPT is rated as a well-established treatment for disruptive behaviour and ADHD in children and adolescents, whereas CPS is rated as probably/possibly efficacious (Eyberg, Nelson and Boggs 2008, Pelham and Fabiano 2008, Ollendick 2011, Evans et al. 2013). Thus the CPS

model can be considered as promising, and further research is warranted. New positive results have just been reported from a study of 134 children aged 7-14 years with ODD at the Child Study Center, Virginia Polytechnic Institute, comparing CPS to Barkley's (1997) BPT program and waitlist controls (Ollendick 2011, Ollendick et al. submitted). The focus of the CPS method on cognitive training to improve lagging skills seems especially well suited to the children with neuropsychiatric impairments.

2 AIM

The overall aim of the thesis was to study alternative (non-stimulant) treatments for ADHD in children and adolescents. The specific aims were to;

1. Assess treatment with omega 3/6 fatty acids (Equazen eyeq) for ADHD in children and adolescents in a randomized double-blind placebo-controlled trial (RCT).
2. Assess changes in plasma fatty acid profiles in the children and adolescents participating in the RCT, and relate these to treatment response.
3. Assess long-term efficacy and safety of the non-stimulant medication atomoxetine in adults with ADHD.
4. Evaluate the cognitive-behavioural model “Collaborative Problem Solving” in children with ADHD and oppositional defiant disorder (ODD).

3 PATIENTS AND METHODS

A total of 92 (75 + 17) children and adolescents (76 boys, 16 girls) participated in Study 1, 2 and 4. Twenty adults (12 men, 8 women) participated in Study 3. The author took part as a clinician (investigator) in Study 1, 2 and 4 (in which he examined all patients himself) and as the monitor in Study 3.

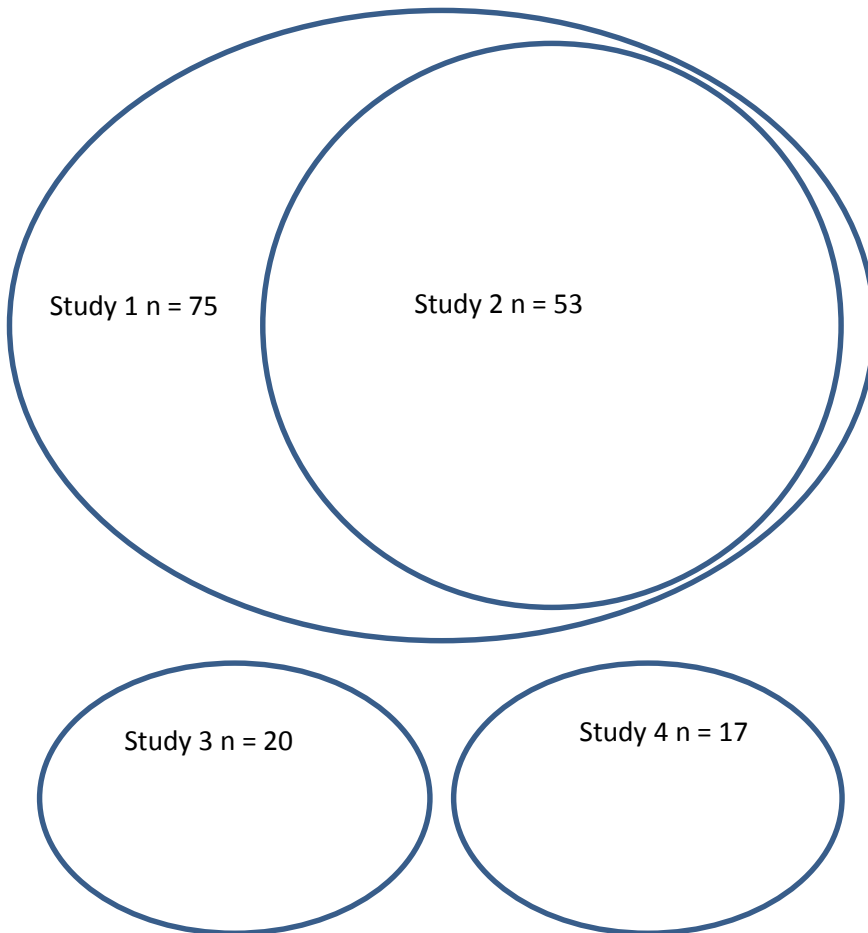


Figure 1. Groups of participants in all studies.

3.1 Study 1

This was a randomized parallel-group placebo-controlled trial comprising two three-month periods. *Study period 1* was double-blind, and *Study period 2* was an open-label continuation phase. The participants were randomized to receive identical capsules with Omega 3/6 or placebo (olive oil). The capsules were provided in consecutively numbered identical bottles, 50% of which contained Omega 3/6 and 50% placebo, in random order according to a code list that was not accessible to the investigators. The dosage of Omega 3/6 (and of placebo) was 3 capsules twice daily (the Omega 3/6 capsules contained a daily dose of 558 mg EPA, 174 mg DHA (Omega 3 fatty acids), 60 mg GLA (gamma linolenic acid, an Omega 6 fatty acid), and 10.8 mg Vitamin E. In *Study period 2* all patients received Omega 3/6 in the same dosage. The one-way crossover study design was chosen because of the slow turnover of fatty acids in neuronal membranes (Bourre et al. 1993), which might possibly confound results in a two-way crossover design (i.e. active group switching to placebo after *Study period 1*).

The study was performed at three sites in south-west Sweden; the Child Neuropsychiatry Unit at Queen Silvia's Hospital for Children in Göteborg, the General Child Psychiatry Clinic in Göteborg, and the Unit of Neurodevelopmental Disorders in Mariestad. The subjects were recruited among patients who had been clinically diagnosed at these clinics after comprehensive neuropsychiatric assessment. Inclusion criteria were children and adolescents aged 8-18 years meeting DSM-IV criteria for a diagnosis of ADHD of any subtype, scoring at least 1.5 standard deviations above the age norm for their diagnostic subtype according to US norms for the ADHD Rating Scale-IV – Parent Version (ADHD-RS-IV) (Du Paul et al. 1998).

Comorbidities were assessed by DSM-IV interview. Reading/writing ability was determined by standardized tests and RWD (Reading Writing Difficulties) was diagnosed according to DSM-IV criteria for Reading Disorder and/or Disorder of Written Expression (APA 2000). The term Learning Difficulties (LD) was used for subjects who met criteria for DSM-IV Borderline Intellectual Functioning. Exclusion criteria were autism (although subjects not meeting full symptom criteria for autistic disorder or Asperger syndrome were eligible for the study), psychosis, bipolar disorder, intellectual disability, uncontrolled seizure disorder, hyper- or hypothyroidism, significant other medical conditions, weight below 20 kg, alcohol or drug abuse, or use of psychoactive drugs or Omega 3 supplements in the past three months.

3.1.1 Study 1 Participants

Of the 89 patients who were pre-screened for the trial, seven met exclusion criteria; mild mental retardation/intellectual disability (n=4), autism (n=1), sertraline treatment (n=1) or meeting too few ADHD criteria (n=1). Another 7 patients were excluded from this analysis due to missing outcome data from post-baseline visits. Thus 75 patients (64 boys, 11 girls) remained for analysis in this study, of which 35 had ADHD combined subtype and 40 ADHD inattentive subtype (here abbreviated "AD"). Most patients (78%, 59/75) had at least one comorbid diagnosis (Table 1). All but one patient were medication-naïve (one subject previously treated with methylphenidate).

3.1.2 Study 1 visits

The trial comprised 3 clinical visits at the sites; Visit 1 at screening/baseline, Visit 2 after 3 months (before switching to open treatment with Omega 3/6) and Visit 3 after 6 months. Visit 1 included signing of informed consent, review of inclusion and exclusion criteria, physical examination and medical/psychiatric history, assessment of diagnosis and comorbidity through DSM-IV interview, and of ADHD symptom severity by investigator-rated ADHD-RS-IV and CGI-S. Neuropsychological tests were performed by a psychologist and reading/writing tests by a special education teacher. At visits 1-3 a blood sample was collected from all patients who consented to this, for analysis of the plasma fatty acid profile. Visit 2 and 3 included the same measures as visit 1 with the exception of the baseline assessments, and also the parents and child were asked about any adverse events/side effects (open-ended questions).

Compliance was assessed by telephone contacts with parents, bi-weekly in study period 1, monthly in study period 2. Compliance was defined as taking the prescribed dosage on more than 70% of the days in the interval.

3.1.3 Study 1 outcome measures

The primary outcome measures were the investigator-rated ADHD-RS-IV - Parent Version and the CGI-S scale. The raters of the ADHD-RS and CGI scales in the present study were paediatricians or child psychiatrists who had received training in using the scales. The ADHD-RS-IV scores each of the 18 ADHD criteria/symptoms in the DSM-IV diagnosis on a 0-3 point scale, giving a maximum total of 54 points. For *clinically meaningful response*, we used a definition often used in clinical ADHD trials (e.g. Michelson et al. 2004, Young et al. 2011), i.e. a reduction of at least 25% of the symptom score on the ADHD-RS scale. A subject who reached that degree of improvement is

thus a “responder”. A definition of clinical response is of course a subjective measure, but still an important one because it represents an effort to describe a degree of improvement which is meaningful for the patients, and which really makes a noticeable difference in everyday life. Definitions vary between studies, but common cut-off values are 25%, 30% or 40% improvement.

The global impression of symptom severity and functional impairment was measured with the CGI-S scale, which is a clinician rating of the patient’s symptom severity related to the clinician’s total experience with ADHD patients, scored from 1 (normal, not ill) to 7 (among the most extremely ill patients).

Table 1. Study 1. Demographics of sample

Patient characteristics	Treatment group		
	Active (n=37)	Placebo (n=38)	Total (n=75)
Age, years, mean (SD)	11,8 (2,14)	12,2 (2,19)	12 (2,16)
Age groups, n (%)			
8-12 years	27 (56%)	21 (44%)	48 (64%)
13-18 years	10 (37%)	17 (63%)	27 (36%)
Gender, n (%)			
Male	33 (44%)	31 (41%)	64 (85%)
Female	4 (5%)	7 (9%)	11 (15%)
ADHD subtype, n (%)			
Combined	19 (25%)	16 (21%)	35 (47%)
Hyperactive/impulsive (HD)	0	0	0
Inattentive (AD)	18 (24%)	22 (29%)	40 (53%)

Associated conditions, n (%)				
Reading/writing difficulties (RWD)	12 (16%)	20 (27%)	32 (43%)	
Oppositional Defiant Disorder (ODD)	8 (11%)	10 (13%)	18 (24%)	
Developmental Coordination Disorder (DCD)	10 (13%)	13 (17%)	23 (31%)	
Learning Difficulties (LD)	3 (4%)	6 (8%)	9 (12%)	
Autistic traits	6 (8%)	2 (3%)	8 (11%)	
Autism-like condition (ALC)	7 (9%)	4 (5%)	11 (15%)	
Tourette syndrome	0	2 (3%)	2 (3%)	
Depression/anxiety	2 (3%)	4 (5%)	6 (8%)	
Obsessive Compulsive Disorder (OCD)	1 (1%)	0	1 (1%)	

3.1.4 Study 1 statistical analyses

Treatment differences in mean changes of symptom scores from baseline to endpoint were assessed using the Wilcoxon test. All randomized patients with at least one post-baseline measurement were included in the analysis. Baseline was defined as the last measurement obtained at or before randomization (the screening/baseline visit could be divided into 2 visits if needed). Endpoint was defined as the last measurement obtained after the randomization. Differences in responder rates were assessed using the Chi² test.

3.2 Study 2

Blood samples for analysis of fatty acid profiles in plasma phospholipids were collected from all Study 1 subjects who consented to this (n=53; active n=22, placebo n=31). Samples were obtained at baseline, 3 months and 6 months. All subjects with a baseline sample and at least one post-baseline sample were included in this analysis. The samples (fasted) were stored at -80 °C until analysis. Each set of samples was assayed at the same time. Pooled plasma samples from healthy blood donors, stored and analysed in the same way, were used as quality control and assayed simultaneously. The fatty acid compositions are given as molar percentage (mol %).

Primary outcome measures in the plasma fatty acid analysis were baseline levels of EPA, DHA, n-3, n-6 and n-6/n-3 ratio and changes in these parameters at 3 months and at 6 months.

3.2.1 Study 2 statistical analyses

Comparisons of baseline demographics between the original group (n=75) and the group who had blood samples taken (n=53) were made with chi-square test, active to active and placebo to placebo. Correlation analysis of changes in ADHD-RS-IV symptom scores and plasma fatty acid levels were made by Pearson correlations. Changes in plasma fatty acids were compared between treatment groups by means of 2-sample Wilcoxon tests applied to differences from baseline to 3 and 6 months, respectively. Changes were also compared between responders and non-responders in the same way.

3.3 Study 3

This was a one-year open-label study of atomoxetine for ADHD in adults, consisting of three phases. *Phase 1* was an assessment/washout phase of two weeks. *Phase 2* was a 10-week dose optimization and treatment phase of 8 clinical visits, where a morning dose of atomoxetine was titrated from 40-80-100 mg based on efficacy and tolerability, and could be lowered back to 40 mg if needed for tolerability. *Phase 3* was a continuation therapy period with monthly visits for patients who met the primary response criteria (reduction of CGI-S score by ≥ 2) from baseline to the last two visits of *Phase 2*. During this phase, all patients whose symptoms relapsed to a predefined severity level were discontinued from the study.

The trial was single-centre, performed in connection with the Adult Project (Anckarsäter et al. 2006), at the Child Neuropsychiatry Clinic, Sahlgrenska University Hospital, Göteborg, Sweden, and approved by the local ethics committee and the Medical Products Agency.

3.3.1 Study 3 participants

At *pre-screening*, all patients were diagnosed by detailed assessments that were part of the standard procedure of the Adult Project. Clinical diagnosis of ADHD and comorbidities were established using the DSM-IV Structured Clinical Interview for Diagnosis (SCID-I) (First et al. 2002), the ADHD-RS-IV, and the Autism Spectrum Diagnostic Interview (ASDI) (Gillberg et al 2001). Patients were then invited to the *screening phase* through written informed consent. At screening inclusion and exclusion criteria were

reviewed, and laboratory tests and other measures were collected (see Outcome measures below).

Inclusion criteria were adults aged 18-50 years, meeting DSM-IV criteria for ADHD of any subtype. Exclusion criteria were mental retardation, bipolar disorder, psychosis, psychoactive medication, substance use, seizure disorder, BMI < 18, hypertension, hyper- or hypothyroidism, other significant medical conditions or abnormal laboratory values, pregnancy or breastfeeding.

A total of 36 patients were assessed for study entry. Of these, 12 patients were excluded, due to depression (n=3), substance use disorder (n=4), psychosis (n=1), hypertension (n=1), or plans to move from the area or for long holidays (months) within the follow-up period (n=3). The remaining 24 patients (15 men, 9 women, mean age 32.3 years, range 19-47 years) consented to participate. Four of these were not included because they did not show for the baseline visit (n=3) or because of raised liver-enzymes at screening tests (n=1). Thus, a total of 20 patients (12 men, 8 women) were finally enrolled in the study. Of these, 14 patients had ADHD combined subtype and 6 patients inattentive subtype.

3.3.2 Study 3 outcome measures

The primary outcome measure was the investigator-rated CGI-S. Other instruments included the Conners' Adult ADHD Rating Scale, Self-report version (CAARS-S; Conners et al. 1999). Adverse events were recorded with an Adverse Events Scale listing possible medication side effects and by open questions. The outcome measures and adverse events reports were collected at all visits. Safety assessments included a blood and urine sample for routine hematology, chemistry and urinalysis at baseline, 10 weeks, 6 months and at study end. Pregnancy tests were required for all female patients at visit 1 and at any other visit if indicated. Height, weight, blood pressure and pulse were recorded at all visits.

3.3.3 Study 3 statistical analyses

The intention-to-treat analysis included all patients with at least one post-baseline evaluation, with the last observation carried forward to endpoint (LOCF). Average effect changes were measured for each patient with linear regression over visits, and the overall trend in the treatment group was then estimated by means of analysis of variance (ANOVA).

Safety analysis included all patients who took at least one dose of study drug. Secondary efficacy analyses and safety analysis of continuous measures were

performed using a LOCF approach to compare mean changes from baseline to endpoint using ANOVA.

3.4 Study 4

This was an open pilot study in which 17 families of children with ADHD, ODD and problematic behaviour received treatment with the Collaborative Problem Solving method (CPS; Greene 1998), now known as Collaborative & Proactive Solutions. Subjects were recruited via letters to the school nurses in the Skaraborg region in southwest Sweden. The school nurses contacted the families and referred them to the study team for possible participation in the study.

3.4.1 Study 4 participants

Eligible for inclusion were children aged 6-13 years, who met DSM-IV diagnostic criteria for ADHD of any subtype and ODD, and had considerable behavioural problems both at school and at home. Exclusion criteria were DSM-IV autistic disorder and/or intellectual disability, and recently started (<6 months) treatment with stimulants or other psychoactive medications.

Written informed consent was obtained. Before intervention, all eligible children were assessed by a paediatrician/neuropaediatrician. The assessment included a detailed developmental history, physical examination, and collection of questionnaire information. Clinical diagnoses were made according to DSM-IV criteria. Cognitive ability was evaluated by one and the same psychologist using the WISC-IV (Wechsler 2003). One and the same special education teacher assessed the child's school situation and academic skills.

Thirty-one children with challenging and explosive behaviours were referred to the project group. Of these, a total of 14 children were excluded from the study (for 6 of them, parent interviews made it clear that the child had significant ADHD and ODD symptoms only at school; 2 children were considered to be in need of pharmacological ADHD treatment without delay; 4 had other types of interventions ongoing and therefore chose not to participate; 1 had autistic disorder, and 1 was found to have mild mental retardation/intellectual disability). Thus, 17 children could be included in the study (12 boys, 5 girls, mean age 9.2 years, range 7-13 years). All had ADHD combined subtype and ODD. Two children (1 girl, 1 boy) of the 17 also had autistic traits (but did not meet criteria for an autism spectrum disorder diagnosis), and one boy met Gillberg (1991) criteria for Asperger syndrome (in addition to ADHD and ODD). One of the boys with ADHD and

autistic traits had been treated with methylphenidate for a couple of years, and continued with unchanged dosing during the study. All the other children were medication-naïve at the study start.

3.4.2 Study 4 intervention

The CPS intervention was provided in weekly sessions for 6-10 weeks (the number of sessions depending on each family's individual needs), by a special education teacher and a psychologist with long-term experience in the field of neuropsychiatry, and who had attended the CPS advanced training course, held by Ross Greene in Boston 2007. The book *Treating Explosive Kids* (Greene and Ablon 2005) was used as a manual.

At baseline, the therapists assessed the child's lagging cognitive skills and some problematic situations (unsolved problems) to work with, according to Ross Greene's instrument "Assessment of Lagging Skills and Unsolved Problems" (<http://www.livesinthebalance.org/paperwork>). The unsolved problems were then analysed in the three steps of the CPS model; (1) The "empathy step", where the unsolved problem is analysed in detail from the child's perspective to find a well-defined underlying factor causing the problem, (2) the "define the problem" step, where the adult's concern about the problem is addressed, and (3) the "invitation step", in which the adult and child exchange ideas of how to reach a mutually satisfactory solution to the problem. The sessions were divided to give separate attention to the parents, the child, and the whole family. The families then practiced the problem solutions at home between sessions.

3.4.3 Study 4 outcome measures

Outcome measures were collected at baseline (Time 1), post-intervention (1-2 months after intervention, Time 2), and 6 months later (6-month follow-up, Time 3).

Primary outcome measures were parent-rated ADHD and ODD symptom scores on the SNAP-IV scale (Swanson 1982, 1992), and the investigator-rated Clinical Global Impression-Improvement (CGI-I) scale (Guy 1976). This rating was performed by the paediatrician or neuropaediatrician who had not been involved in the intervention. Secondary outcome measures were the parent-rated Conners' 10-item parent scale (Conners 1969, Westerlund et al. 2009), and Family Burden of Illness Module (Riley et al. 2006, Prasad et al. 2007, Svanborg et al. 2009).

3.4.4 Study 4 statistical analyses

Descriptive statistics (mean, median and percentiles) were used to describe changes in outcome measure scores from baseline to post-intervention and to 6-month follow-up. Due to the small sample and variables with ordinal data, non-parametric tests were used.

To detect change between the three time points Friedman's test for related samples was used. Any significant differences were followed up by Wilcoxon pairwise test to detect at which time point a measurement differed from each of the other two. Mann-Whitney test applied on calculated individual changes between the time points was used to compare the magnitude of reduction in symptom scores across the group who received medication after the intervention period (Med group), and the group who did not (No-med group).

3.5 Study 1-4 ethics

All studies were approved by the regional ethical review board in Gothenburg.

3.6 Overview of instruments/outcome measures in all studies

3.6.1 ADHD Rating Scale-IV

The ADHD-Rating Scale-IV (ADHD-RS-IV) was developed by DuPaul et al. (1998). It consists of the 18 symptom criteria from DSM-IV. The frequency/severity for each symptom (item) is rated from 0 (rarely or never), 1 (sometimes), 2 (often), to 3 (very often). The maximum score is 54. ADHD-RS-IV can be rated by parents and teachers, or be used as a clinical interview. A clinical interview gives the opportunity to ask questions about every item and give examples of various situations and circumstances, to obtain global information about the frequency, impairment and difference compared with peers for every symptom.

ADHD-RS-IV was originally validated as a parent- and teacher-rated scale, and US norm data for gender and age were collected (DuPaul et al. 1998). Later the scale was validated as an investigator-rated interview to permit assessment of symptom severity in multiple settings, in relation to the clinician's total experience of patients with ADHD (Faries et al. 2001), and

has since been used in that way in numerous clinical trials (Michelson et al. 2001; 2004, Kratochvil et al. 2002, Coghill et al. 2013). In trials the scale has shown good test-retest reliability and correlation with CGI-scores (Zhang et al. 2005, Goodman et al. 2010).

The baseline ADHD-RS-IV score in clinical trials is usually above 32, and a common baseline mean score is 40. A reduction of the total score to <25 represents a robust effect, and improvement to a score of <18 means normalization (18 = mean score of 1 on each item).

3.6.2 CGI-S and CGI-I

The Clinical Global Impression (CGI) scales were developed by Guy et al. in 1976 as general global ratings for medical conditions. They have since been used as clinical interviews in a great number of clinical trials, among them many treatment studies in ADHD. CGI is a quick rating of the global severity (CGI-S) and improvement (CGI-I) of the patient's condition, based on all information available from all sources. With CGI-S the severity of the symptoms and impairment is rated at the current time point, related to the clinician's previous experience of patients with the same diagnosis. The scale ranges from 1 - normal, not at all ill; 2 - borderline mentally ill; 3 - mildly ill; 4 - moderately ill; 5 - markedly ill; 6 - severely ill; to 7 - extremely ill.

With the CGI-I the global improvement is compared to a previous time point, for instance at baseline before a treatment, and the score gives a direct illustration of how clinically meaningful an improvement is. The symptom picture and functional impairment in several environments where ADHD-symptoms usually cause problems are taken into account (school, with peers, family). The scale is scored from 1 – very much improved; 2 – much improved; 3 – minimally improved; 4 – no change; 5 – minimally worse; 6 – much worse, to 7 – very much worse.

The CGI scales have face validity and are clinically meaningful. A study based on two clinical drug trials showed good and consistent correlation between CGI-S/CGI-I and ADHD-RS ratings in children, adolescents and adults (Goodman et al. 2010).

3.6.3 SNAP-IV

The SNAP scale was first developed by Swanson, Nolan and Pelham (1982) as a scale for severity rating of the DSM-III ADHD criteria or symptoms (SNAP-III). It was revised as SNAP-IV in line with the DSM-IV diagnostic criteria (Swanson 1992) and used as an outcome measure in the Multimodal

Treatment of ADHD (MTA) study (MTA Cooperative group 1999), and in many other treatment studies. The long version covers the DSM-IV psychiatric disorders, and the short version (the one used in the MTA study) focuses on the DSM-IV ADHD and ODD criteria rated 0 (not at all), 1 (just a little), 2 (quite a bit) or 3 (very much). US norm data can be found on www.ADHD.net and in Bussing et al. 2008, along with psychometric evaluation.

3.6.4 FBIM (Family Burden of Illness Module)/FSI (Family Strain Index)

FBIM is a 6-item measure of family stress and burden of illness, developed by the ADORE (ADHD Observational Research in Europe) study group for use in a pan-European observational study (then called FSI; Riley et al. 2006), and was also used in two atomoxetine studies (Prasad et al. 2007, Svanborg et al. 2009). Items are scored from 0 (never), 1 (almost never), 2 (sometimes), 3 (almost always), to 4 (always), yielding a maximum score of 24. Factor analysis in the sample of 1477 FSI forms which were completed in the ADORE study (Coghill et al. 2008) indicated that the scale reflects an overall experience of worry, disruption and demand on parents of children with ADHD. All six items loaded strongly on a single factor, indicating excellent internal consistency (Riley et al. 2006, Svanborg et al. 2009)

3.6.5 CAARS-S (Conners' Adult ADHD Rating Scale, Self-report version)

The CAARS scales were developed by Conners et al. (1999) since measures of ADHD symptoms that were reliable and valid for adults were lacking at that time. Norm data for the self-report version (CAARS-S) were collected from a large sample (n=1026) of US and Canadian adults aged 18-80 years (Conners et al. 1999). The scale has been shown to be reliable across normative groups and has demonstrated validity in numerous studies.

3.6.6 Conners' 10-item scale

The Conners' 10-item scale was developed many years ago as a symptom measure of for use in clinical drug trials (Conners 1969). It consists of 10 items drawn from the Conners' Parent and Teacher Rating Scales. Each item is rated 0 (not at all), 1 (just a little), 2 (pretty much) or 3 (very much), yielding a maximum total score of 30. Norm data were collected in large samples of US school-aged children, and the studies indicated that the scale has a two-factor structure; hyperactivity/impulsivity and emotional lability (Parker et al. 1996, Rowe and Rowe 1997, Westerlund et al. 2009).

4 RESULTS

4.1 Study 1

Out of a total of 89 patients assessed for eligibility, 75 patients were included in the study. Figure 2 shows the flow of participants through the trial. Sixty-four patients (54 boys and 10 girls) completed the double-blind *Study Period 1*, and 59 patients (49 boys and 10 girls) completed the open-label *Study Period 2*. A total of 16 subjects (21%) discontinued from the trial: 11 (3 active, 8 placebo) during the double-blind phase (7 were unmotivated to continue or had problems swallowing the capsules [1 active, 6 placebo], 3 had side effects such as dyspepsia, vomiting, or diarrhoea [2 active, 1 placebo], and the blinded code had to be broken for 1 patient (placebo) due to markedly increased irritability). Five patients discontinued during the open-label phase (4 due to poor motivation and 1 due to diarrhoea). Another 6 patients reported mild stomach discomfort/dyspepsia on active treatment but did not discontinue. No other side effects were noted during the trial.

Compliance was generally high, with a mean of 93.4% (range 74-100%) for *Study Period 1*, and 93.3% for *Study period 2* (range 75-100%). All patients who completed a study period were also compliant for that period.

At baseline the mean ADHD-RS scores (total, inattentive or hyperactive/impulsive subscores) were not significantly different between the active and placebo group. From baseline to endpoint, the only significant active/placebo difference was greater improvements on the CGI-S for the active group at the end of the double-blind phase. No significant active/placebo differences were found in the ADHD-RS ratings. Thus the overall results of the study were considered to be negative. However, when analysing rates of clinically meaningful response in the whole group and in subgroups some significant findings appeared.

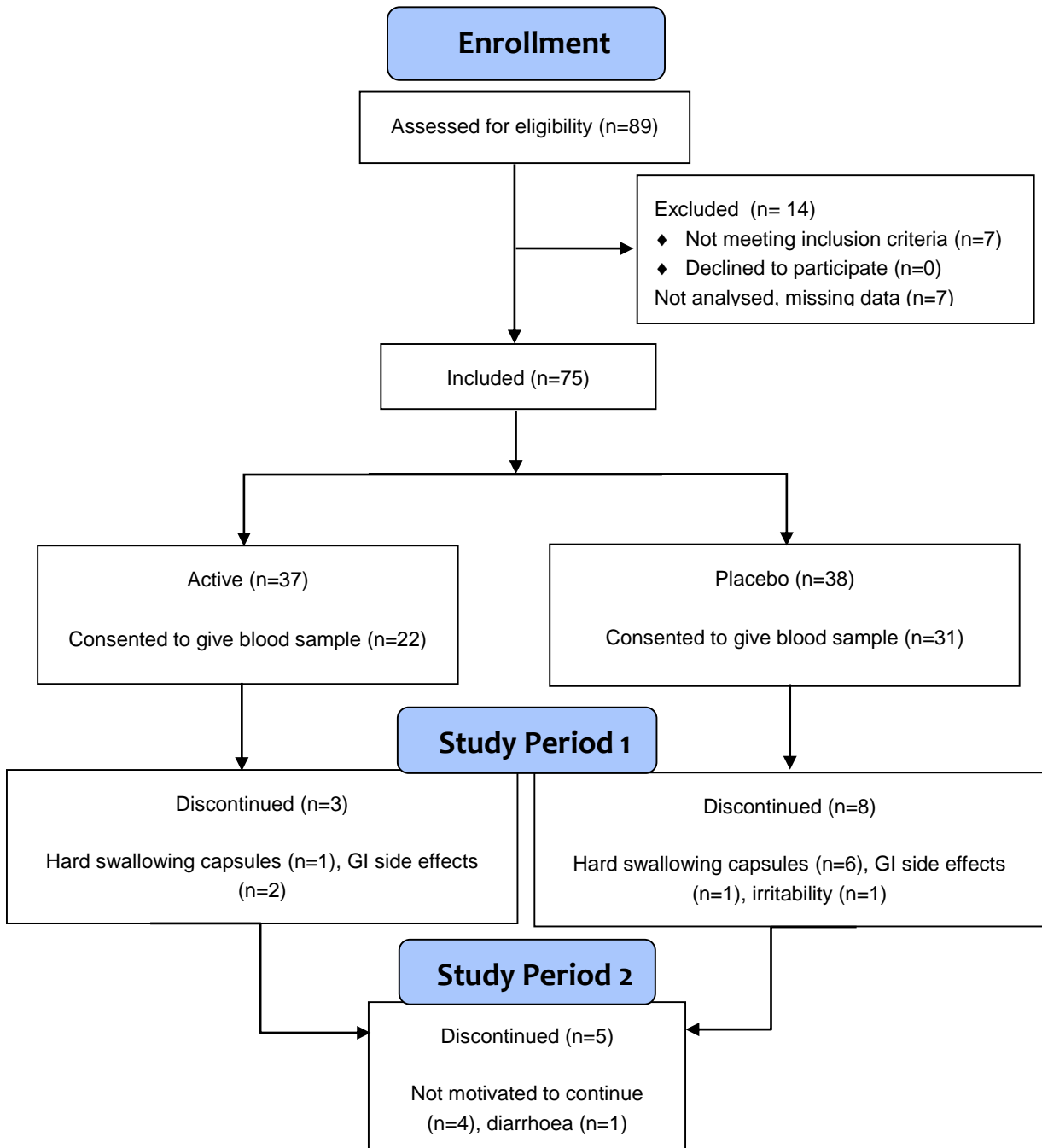


Figure 2. Study 1. Flow of participants.

4.1.1 Study 1 responders

“Responders” were subjects with an ADHD-RS-IV score reduction of at least 25%. At the end of the double blind phase 26% (9/34, all boys) in the active group vs. 7% (2/30, 1 boy, 1 girl) in the placebo group ($p=.04$) were responders (3-month responders) (Table 2). Four of the responders in the active group (12%, 4/34) had more than 50% reduction of ADHD symptoms, compared to none in the placebo group.

At the end of the open-label phase 47% (28/59) of all were responders compared to baseline (6-month responders) (Table 2), and among these were 7 patients (12%) who had more than 50% symptom reduction. Of the 11 subjects who were 3-month responders, 9 were also 6-month responders. The majority ($n=16$) of the 6-month responders had received active treatment during the entire study, but 12 of them had received placebo during the first 3 months.

There appeared to be a difference between boys and girls, since all responders in the active group in *Study period 1* were boys, whereas the single responder among the girls was in the placebo group. However, the small sample of girls (10 girls completed *Study period 1*) makes this finding highly uncertain.

In the diagnostic subgroups responders were significantly more frequent (active vs. placebo) in the AD group ($p=.03$) but not in the ADHD combined type group (n.s.) (Table 2). Among the comorbid conditions, responders tended to be more frequent among patients with a ‘neurodevelopmental disorder’, i.e. RWD ($p=.05$), DCD, LD, or autistic symptoms (n.s.). In patients with other comorbidities (ODD, CD, depression, anxiety etc) there were no responders.

Most of the patients who had more than 50% reduction of ADHD symptoms had the inattentive ADHD subtype (AD) and some neurodevelopmental comorbidity (four patients at three months: 3 AD+RWD, 1 AD; seven patients at six months: 3 AD+RWD, 2 AD, 2 ADHD+DCD+RWD).

Table 2. Study 1. Patient characteristics and response rates in subgroups

Patient characteristics	N (base- line)	Responders 0-3 months		<i>P</i> (<i>chi</i> ²)	Responders 0-6 months % (n at endpoint)
		% (n at endpoint)			
		Active	Placebo		
Total	75	26% (9/34)	7% (2/30)	.04	47% (28/59)
<i>Gender</i>					
Male	64	30% (9/30)	4% (1/24)	.02	47% (23/49)
Female	11	0% (0/4)	17% (1/6)	n.s.	50% (5/10)
<i>Age groups</i>					
8-12 years	48	16% (4/25)	6% (1/18)	n.s.	43% (18/42)
13-18 years	27	56% (5/9)	9% (1/11)	.02	59% (10/17)
<i>ADHD subtype</i>					
Combined	35	17% (3/17)	8% (1/13)	n.s.	36% (10/28)
Inattentive	40	35% (6/17)	6% (1/17)	.03	58% (18/31)
<i>Associated conditions</i>					
Reading/writing difficulties	34	43% (6/14)	12% (2/17)	.05	52% (15/29)
DCD	23	25% (2/8)	9% (1/11)	n.s.	53% (10/19)
LD	9	0% (0/3)	0% (0/5)	n.s.	50% (4/8)
Autistic traits /ASP/ALC	17	20% (2/10)	0% (0/2)	n.s.	50% (6/12)
Any RWD, DCD, LD or autistic symptoms	54	27% (6/22)	8% (2/24)	n.s.	51% (22/43)
ODD	18	0	0		0
Conduct Disorder	2	0	0		0
Depression/anxiety	6	0	0		0

4.2 Study 2

No significant baseline differences in age, gender, ADHD subtype or comorbidity were found between the original group included in the clinical trial (Study 1) and the group who had blood samples taken. Mean baseline levels of n-3, n-6, n-6/n-3 ratio, EPA and DHA were similar in the active/placebo groups, and responder/non-responder groups.

4.2.1 Study 2 baseline to 3-month changes

Baseline to 3-month changes in n-3, n-6, n-6/n-3 ratio, EPA and DHA were significantly greater in the active group compared to placebo ($p < 0.01$) (Table 3).

Table 3. Study 2. Fatty acid composition of plasma phosphatidylcholine in the active and placebo groups (mean (SD)).

Fatty acid	Active	<i>n</i>	Placebo	<i>n</i>	<i>p</i> -value
n-3					
-baseline	5.34 (1.37)	22	5.21 (0.84)	31	0.81
-3 months	8.98 (1.80)	18	5.48 (1.64)	23	<0.001
-change	3.70 (1.48)	18	0.17 (1.31)	23	<0.001
n-6					
-baseline	36.10 (2.69)	21	35.42 (2.31)	31	0.33
-3 months	33.21 (2.71)	18	35.46 (2.77)	22	0.01
-change	-3.04 (2.08)	18	0.25 (2.95)	22	<0.001
n-6/n-3 ratio					
-baseline	7.58 (3.10)	22	6.95 (1.42)	31	0.32
-3 months	3.92 (1.20)	18	6.95 (1.88)	23	<0.001
-change	-3.44 (1.66)	18	0.13 (1.58)	23	<0.001
EPA					
-baseline	1.08 (0.42)	20	1.08 (0.42)	25	0.98
-3 months	2.97 (1.01)	17	1.28 (0.79)	20	<0.001
-change	1.95 (0.76)	17	0.17 (0.66)	20	<0.001
DHA					
-baseline	2.97 (0.82)	20	3.06 (0.73)	25	0.69
-3 months	4.42 (0.89)	17	3.25 (0.92)	20	<0.001
-change	1.48 (0.88)	17	0.08 (0.57)	20	<0.001

Differences were assessed using the Wilcoxon 2-sample test. Results are expressed as mol % of the total phosphatidyl choline fatty acid composition. (n-6) group consists of 18:2, 20:2, 20:3, 20:4, 22:4 and 22:5. (n-3) group consists of 18:3, 20:5, 22:5 and 22:6.

4.2.2 Study 2 correlations between change in ADHD symptoms and in plasma fatty acids

For the whole group, no significant correlations were found between the degree of improvement in ADHD-RS scores and the degree of change in the plasma fatty acid levels (Table 4). Analysis of the responder/non-responder groups, however (Table 5), showed that compared to non-responders, the 6-month responders had a significantly greater increase in n-3 levels at 3 months ($p=0.03$) and a significantly greater decrease in n-6/n-3 ratio at both 3 months ($p=0.03$) and 6 months ($p=0.01$).

Table 4. Study 2. Correlating changes in ADHD Rating Scale scores with changes in plasma fatty acid measures (Pearson correlations).

	Change 0-3 months (n=36)			Change 0-6 months (n=35)		
	Mean	SD	Corr	Mean	SD	Corr
ADHD-RS score	-2.75	7.45	1.00	-6.77	7.35	1.00
n-3	1.84	2.28	-0.03	2.64	1.56	-0.04
n-6	-1.44	2.92	0.03	-1.99	2.76	0.05
n-6/n-3 ratio	-1.62	2.40	0.06	-2.64	1.76	0.26
DHA	0.74	1.04	0.02	1.15	0.77	0.05
EPA	0.93	1.09	-0.11	1.28	0.73	-0.00

Table 5. Study 2. Fatty acid composition of plasma phosphatidylcholine in the responder and non-responder groups (mean (SD)).

Fatty acid	Responders at 3 months	n	Non-responders at 3 months	n	p-value	Responders at 6 months	n	Non-responders at 6 months	n	p-value
n-3										
-baseline	5.58 (1.46)	7	5.20 (0.97)	41	ns	4.99 (0.96)	21	5.46 (1.08)	27	ns
-3 months	8.28 (2.88)	7	6.75 (2.30)	34	ns	7.62 (2.49)	19	6.49 (2.32)	22	ns
-change	2.70 (2.04)	7	1.52 (2.25)	34	ns	2.54 (2.40)	19	1.02 (1.87)	22	0.03
-6 months	7.68 (1.79)	6	7.66 (1.80)	33	ns	7.72 (1.48)	17	7.62 (2.01)	22	ns
-change	2.06 (1.57)	6	2.50 (1.64)	33	ns	2.85 (1.11)	17	2.12 (1.89)	22	ns
n-6										
-baseline	36.50 (2.07)	7	35.86 (2.20)	41	ns	36.50 (1.87)	21	35.54 (2.32)	27	ns
-3 months	34.13 (4.27)	7	34.46 (2.64)	34	ns	34.32 (2.97)	19	34.47 (2.93)	22	ns
-change	-2.37 (2.49)	7	-1.13 (3.19)	34	ns	-2.11 (2.75)	19	-0.68 (3.27)	22	ns
-6 months	34.38 (2.19)	6	33.96 (1.95)	33	ns	34.39 (1.51)	17	33.75 (2.24)	22	ns
-change	-2.03 (1.67)	6	-1.90 (2.86)	33	ns	-2.35 (1.92)	17	-1.60 (3.18)	22	ns
n-6/n-3 ratio										
-baseline	7.02 (2.18)	7	7.17 (1.61)	41	ns	7.63 (1.77)	21	6.77 (1.52)	27	ns
-3 months	4.74 (2.12)	7	5.80 (2.21)	34	ns	5.14 (2.11)	19	6.03 (2.26)	22	ns
-change	-2.28 (1.81)	7	-1.26 (2.49)	34	ns	-2.29 (2.34)	19	-0.70 (2.24)	22	0.03
-6 months	4.73 (1.35)	6	4.73 (1.40)	33	ns	4.65 (1.07)	17	4.80 (1.59)	22	ns
-change	-2.31 (1.63)	6	-2.48 (1.81)	33	ns	-3.23 (1.40)	17	-1.86 (1.81)	22	0.01
EPA										
-baseline	1.15 (0.53)	7	1.03 (0.45)	41	ns	0.93 (0.27)	21	1.14 (0.56)	27	ns
-3 months	2.82 (1.63)	7	1.79 (1.12)	34	ns	2.27 (1.23)	19	1.69 (1.24)	22	ns
-change	1.67 (1.25)	7	0.75 (1.02)	34	ns	1.31 (1.17)	19	0.56 (0.94)	22	ns
-6-months	2.40 (1.06)	6	2.25 (0.74)	33	ns	2.24 (0.83)	17	2.29 (0.77)	22	ns
-change	1.25 (0.93)	6	1.24 (0.68)	33	ns	1.35 (0.71)	17	1.15 (0.71)	22	ns
DHA										
-baseline	3.27 (0.79)	7	2.98 (0.73)	41	ns	2.92 (0.71)	21	3.10 (0.76)	27	ns
-3-months	4.15 (1.20)	7	3.63 (1.06)	34	ns	3.99 (1.09)	19	3.48 (1.05)	22	ns
-change	0.88 (0.84)	7	0.60 (1.05)	34	ns	0.97 (1.04)	19	0.36 (0.92)	22	ns
-6-months	3.92 (0.87)	6	4.01 (1.04)	33	ns	3.99 (0.80)	17	4.00 (1.15)	22	ns
-change	0.60 (0.61)	6	1.07 (0.89)	33	ns	1.13 (0.57)	17	0.91 (1.04)	22	ns

4.3 Study 3

This one-year open-label study of atomoxetine for ADHD in adults consisted of three phases. *Phase 1*: two-week assessment/washout phase. *Phase 2*: ten-week dose optimization and treatment. *Phase 3*: maintenance therapy period for patients who met primary efficacy criteria at the end of *Phase 2* (a reduction of the CGI-S score by ≥ 2 from baseline at the last two visits of *Phase 2*).

The flow of participants through the trial is shown in Figure 3. Of the 20 patients who entered the study, 10 patients met the efficacy criteria at the end of Phase 2 and continued into Phase 3, but 4 of these discontinued within a few weeks later because of side-effects, lack of efficacy, non-compliance, or moving from the area. Six patients (4 men, 2 women) continued for three months or more, but 5 of them stopped taking the medication within the following three months, because of side-effects or relative lack of effect. Only one individual (male, age 27 years) completed the whole one-year study.

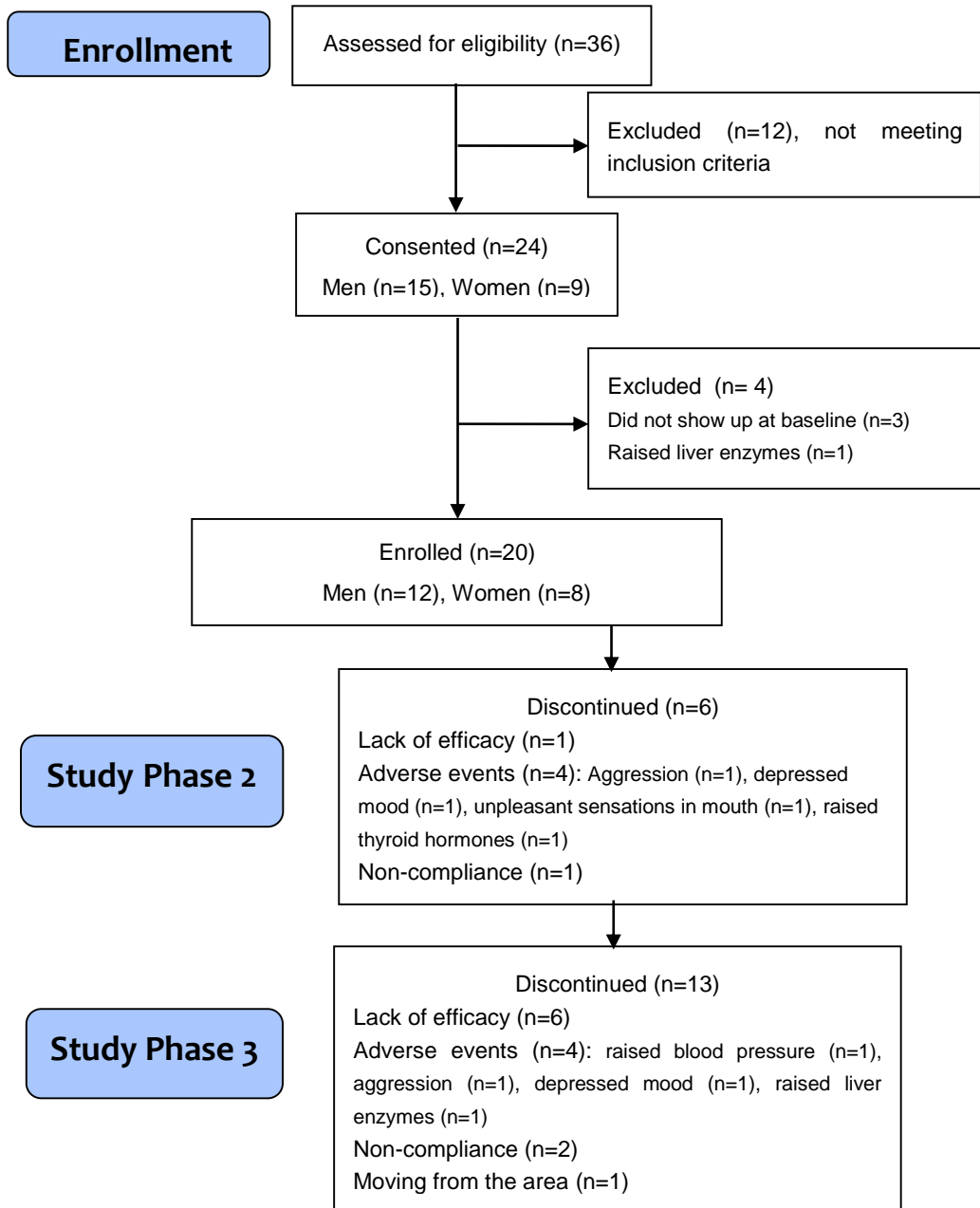


Figure 3. Study 3. Flow of participants.

4.3.1 Study 3 reasons for discontinuations

Four patients discontinued in *Phase 2* due to adverse events; aggression (n=1), depressed mood (n=1), unpleasant sensations in the mouth (n=1), and raised levels of thyroid hormones (n=1). One patient discontinued due to lack of efficacy, and one for non-compliance.

During *Phase 3* another 13 patients discontinued, due to lack of efficacy (n=6), adverse events (n=4; raised diastolic blood pressure (90), aggression, depressed mood, raised liver enzymes which normalized after treatment had stopped), non-compliance (n=2) or move to another part of Sweden (n=1). The overall proportion of patients discontinuing due to adverse events was 40% (20% in *Phase 2* and 20% in *Phase 3*).

Among the adverse events leading to discontinuations, none were severe. Two patients had moderate adverse events (raised hepatic enzymes, raised thyroid hormones, which normalized after treatment stopped). Six subjects had mild adverse events (aggressiveness n=2, depressed mood n=2, unpleasant sensations in mouth n=1, raised diastolic blood pressure n=1).

4.3.2 Study 3 adverse events

Of the adverse events reported by more than 5% of patients (Table 6), most occurred early or within the first 4-5 weeks (mouth dryness, fatigue, perspiration, erectile dysfunction, insomnia, reduced appetite, restlessness, depressed mood, urine retention, weight loss, vertigo, irritability, emotional lability, headache). Only one adverse event was most frequently reported later, at visit 10 (constipation).

Table 6. Study 3. Adverse events reported by more than 5% of patients (events recorded as occurring more frequently than “sometimes” in the adverse events scale)

Adverse event	Percent of patients	Max. frequency at visit
Mouth dryness	24	5
Fatigue	23	5
Perspiration	18	5
Erectile dysfunction	16	6
Insomnia	16	3
Reduced appetite	15	3
Restlessness	12	3
Depressed mood	11	3
Constipation	11	10
Urine retention	9	6
Weight loss	8	5
Vertigo	7	5
Irritability	7	5
Emotional lability	6	3
Headache	6	3

4.3.3 Study 3 vital signs

In the whole group there were no significant changes in heart rate or systolic/diastolic blood pressure. A small but significant weight reduction was observed (Table 7).

Table 7. Study 3. Vital signs (N=20), mean (SD) baseline to endpoint. ANOVA (LOCF)

Vital sign	Baseline Mean (SD)	Endpoint Mean (SD)	Change Mean (SD)	<i>p-value</i>
Heart rate, bpm	73.0 (9.0)	75.9 (5.7)	3.9 (10.4)	.1071
Systolic blood pressure, mm Hg	124.8 (12.7)	123.0 (12.2)	1.2 (10.2)	.5916
Diastolic BP, mm Hg	71.7 (6.7)	73.0 (10.8)	1.7 (10.2)	.4509
Weight, kg	81.6 (24.5)	74.6 (13.5)	-1.8 (2.7)	.0065

4.3.4 Study 3 CGI and CAARS outcomes

The subjects with 10 or more visits (n=14) had a mean CGI-S reduction from 5.4 (SD 0.5) at baseline to 3.3 (SD 0.7) at visit 10. Mean CAARS score was reduced from 47.1 (SD 14.8) at baseline to 23.6 (SD 13.1) at visit 10.

Ten patients (50%, 10/20) met primary efficacy criteria (reduction of CGI-S score by ≥ 2) at the last two visits of *Phase 2*, and continued into *Phase 3*. From baseline to endpoint (=at any time when the patient discontinued), ten patients had such a decrease in CGI-S score. The patient who completed the whole one-year trial had a CGI-S reduction from 6 at baseline to 2 at visit 10, followed by a slight increase to CGI 3 at end of study.

All patients with at least one post-baseline measurement were evaluated with linear regression, showing that 11 out of 20 slopes yielded a significant decrease in CGI-S. Eight out of 20 had a significant reduction in CAARS scores, of whom 5 also had a significant decrease in CGI.

Efficacy estimates for the whole group resulted in highly significant F-tests for both CGI-S and CAARS. Mean CGI-S was reduced by 27% from 5.33 (SD 0.56) at baseline to 3.95 (SD 0.94) at endpoint ($p < .0001$), and CAARS

by 36% from 47.25 (SD 15.44) at baseline to 30.1 (SD 19.40) at endpoint ($p < .0001$) (Table 8).

Table 8. Study 3. Symptom measures. Analysis of variance: ANOVA (LOCF)

Measure	N	Baseline	Endpoint	Change	<i>p-value</i>
		Mean (SD)	Mean (SD)	Mean (SD)	
CAARS S:SV total	20	47.25 (15.44)	30.1 (19.40)	-18.90 (15.52)	<.0001
CGI-S	20	5.33 (0.56)	3.95 (0.94)	-1.45 (1.00)	<.0001

4.4 Study 4

All 17 families completed the CPS intervention. The boy with Asperger syndrome discontinued the study after the intervention period due to lack of efficacy. The remaining 16 subjects completed the 6-month follow-up.

For the whole group SNAP-IV ODD scores were significantly reduced from baseline to post-intervention and to 6-month follow-up (Table 9). The SNAP-IV total ADHD symptom scores and subscores were also significantly reduced across all time points, except the inattention subscore baseline to post-intervention decrease, which was close to significance.

The Conners' 10-item scale total score and "restless/impulsive behaviour" subscale were significantly reduced from baseline to post-intervention and from baseline to 6-month follow-up, but not between post-intervention and 6-month follow-up. However, the Conners' "emotional lability" subscale was significantly reduced across all time points (Table 9).

The FBIM scores were significantly improved from baseline to post-intervention and to 6-month follow-up, but not from post-intervention to 6-month follow-up (Table 9).

At *post-intervention* CGI-I scores of 1-2 (much to very much improved) were reached by 53% (9/17) of the subjects, a score of 3 (minimally improved) by 18% (3/17), and a score of 4 (no change) by 29% (5/17). At the *6-month follow-up* CGI-I scores of 1-2 were recorded for 81% (13/16) of the subjects, while the remaining 3 children had a score of 4.

Table 9. Study 4. Outcome variables for the whole group (SNAP-IV, FBIM and Conners' scores). Significant p-values in bold.

Outcome Measure	Assessment Median (1-st and and 3-rd quartile)			<i>p-value</i> ¹		
	Baseline ^a (n=17)	Post-intervention visit ^b (n=17)	6-month follow-up ^c (n=16)	a vs b	b vs c	a vs c
ODD (SNAP-IV)	20 (17-22)	14 (8-16)	7 (4-14)	0.001	0.020	0.000
ADHD (SNAP-IV)	39 (35-47)	35 (27-39)	18 (12-30)	0.004	0.010	0.001
Hyperactivity (SNAP-IV)	23 (18-26)	16 (13-19)	10 (6-16)	0.001	0.008	0.001
Inattention (SNAP-IV)	19 (17-23)	18 (13-19)	7 (6-15)	0.052	0.006	0.001
FBIM	14 (10-16)	12 (5-15)	5 (3-11)	0.035	0.069	0.016
Conners total	22 (19-25)	17 (8-19)	9 (6-18)	0.002	0.096	0.001
Conners restless/impulsive ²	14 (11-15)	10 (6-13)	6 (5-13)	0.016	0.406	0.004
Conners emotional lability ³	9 (9-10)	7 (4-8)	4 (1-6)	0.002	0.007	0.001

¹Pairwise comparisons by Wilcoxon's test for paired data

² Conners- Subscale restless/impulsive

³ Conners- Subscale emotional lability

4.4.1 Study 4 Med vs. No-med group

From post-intervention (Time 2) to 6-month follow-up (Time 3) eight children received ADHD medication (*Med group*) because of insufficient ADHD symptom control, while 7 children remained medication naïve (*No-med group*). The medication was long-acting methylphenidate, titrated from 0.5 mg/kg to an optimal dose according to response and tolerability. At post-intervention, the *No-med group* showed significant improvements on SNAP-IV ODD and ADHD scores (Figures 4-5), and Conners' restless/impulsive and emotional lability scores (not shown). In contrast, the *Med Group* had almost no improvement in ADHD scores (Figure 5) and on the Conners' restless/impulsive subscales. It was only with medication from the post-intervention time point to the 6-month follow-up that the *Med group* showed a trend towards significant ADHD symptom improvement (Figure 5).

Comparison *between* the groups showed that during the CPS intervention, the *Med group* had significantly less improvement than the *No-med group* (p-value <0.05) on all outcome measures. From post-intervention to 6-month follow-up, however, no significant differences in symptom reductions between the two groups could be found.

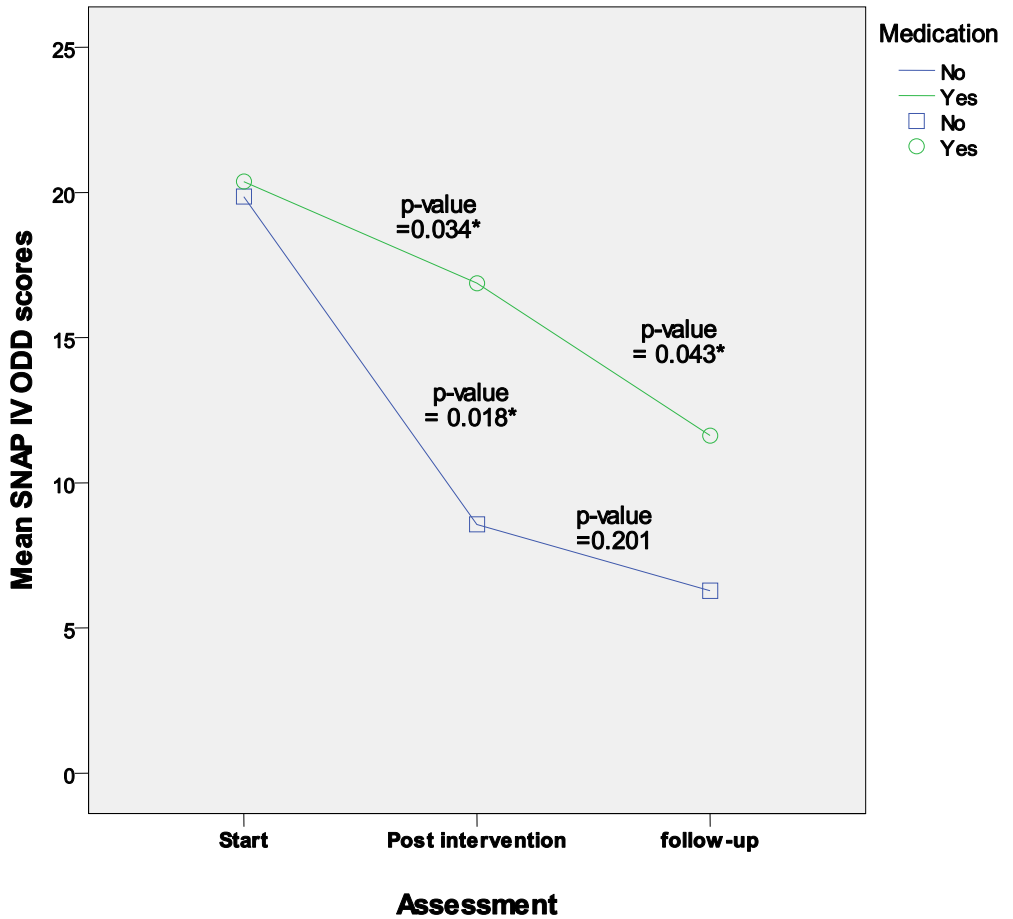


Figure 4. Mean ODD (SNAP-IV) scores over time by Med/No-Med group (p-values refer to comparisons within the groups).

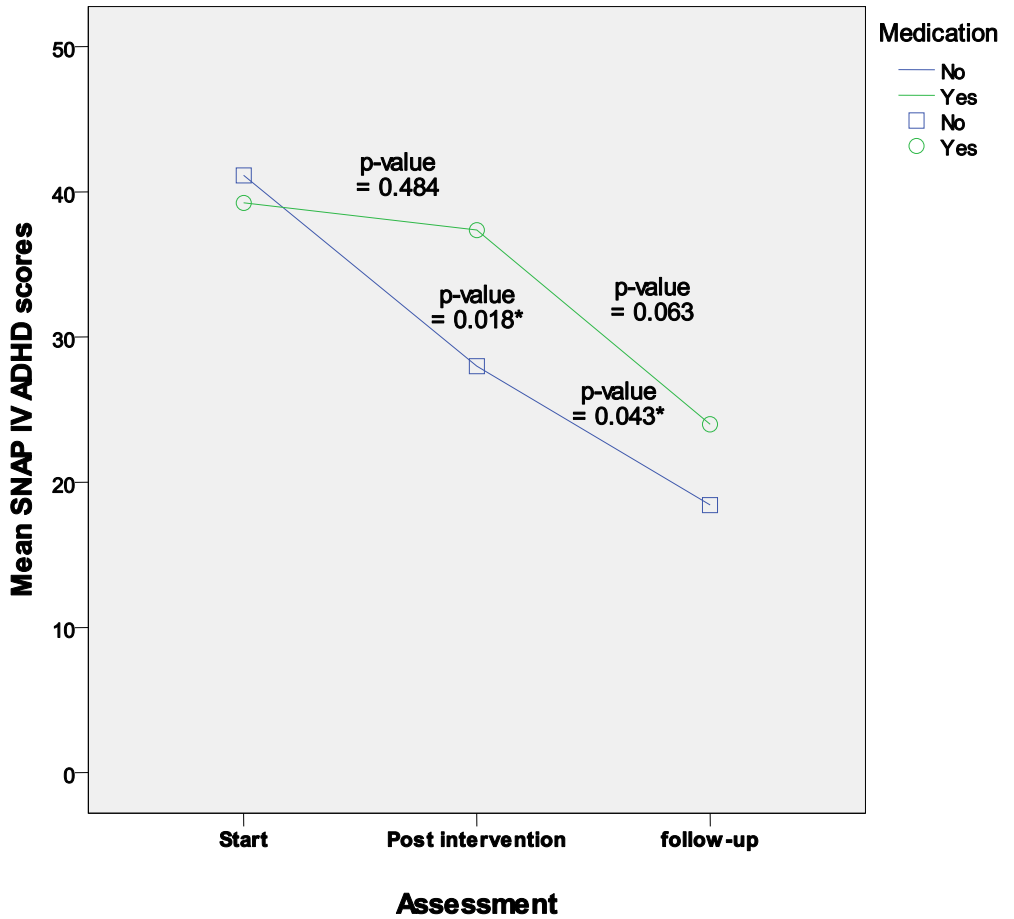


Figure 5. Mean ADHD (SNAP-IV) scores over time by Med/No-Med group (p-values refer to comparisons within the groups).

5 DISCUSSION

In this thesis, three different non-stimulant treatment/intervention approaches have been trialled in ADHD. The studies were “supplementation”, pharmacological, and behavioural in nature. They looked at outcomes in young children, adolescents, and adults. They employed either an RCT (including placebo) or open design. All were of moderate to relatively long duration. The Omega 3/6 RCT in ADHD was the first of its kind and the demonstration of clinical effects linked to plasma fatty acid change is a particular asset. The two open label studies (of atomoxetine in adults, and of behavioural intervention in children with ADHD) were among the first of their kind outside the US. Given that there remains a clinical need for alternative treatments (non-stimulant) in ADHD, the results of the thesis should be of interest to clinicians and researchers.

5.1 Study 1

The overall results of the double-blind randomized placebo-controlled part of Study 1 were essentially negative. Omega 3/6 treatment was not statistically superior to placebo in improving core ADHD symptoms as measured by the investigator-rated ADHD-RS-IV scale. However, there were some indications suggestive of effects of active treatment, since the CGI scores did show global improvements superior to placebo.

A fundamental question in clinical trials is if the treatment is clinically meaningful, i.e. does it make a real-life difference for the individual? In an effort to address this issue many trials use the concept of “responders”. Common cut-off levels for defining response in ADHD trials are between 25% - 50% improvement in ADHD symptom scores.

Using a response definition of more than 25% improvement of ADHD-RS-IV scores in Study 1 we found some significant results. At the end of the double-blind *Study Period 1*, 26% (all boys) in the active group vs. 7% in the placebo group were responders ($p = .04$). In the active group 12% actually reached more than 50% ADHD symptom reduction, while none did so in the placebo group. An improvement of this magnitude (>50%) most probably makes a remarkable difference in everyday life.

By the end of the following open-label treatment period (*Study Period 2*), 47% were responders compared to baseline, and 12% of all had more than 50% symptom reduction.

Clinical response tended to be most common in subjects with AD and a 'neurodevelopmental disorder', i.e. RWD, DCD, LD, or autistic symptoms. This finding is of theoretical interest since it might illustrate improvement of common core mechanisms affecting attention and other cognitive processes and motor functions.

Since our study was published, several reviews and meta-analyses have made detailed comparisons of presently available trials, also including our own trial. One review (Raz and Gabris 2009) concluded that placebo-controlled RCTs in children with ADHD generally had been unsuccessful in showing treatment effects with PUFA supplements.

A meta-analysis of ten Omega 3 or Omega 3/6 studies of ADHD in children showed an overall effect size of 0.31 (Bloch and Qawasmi 2011). The results in the individual studies, however, were variable and often negative. Sample size calculation indicated that the sample needed to detect such a modest effect size with power 80% at alfa-level 0.05, would be 330 children (Bloch and Qawasmi 2011). Thus the individual studies were clearly underpowered, and the modest effect may therefore have gone undetected.

Other factors limiting the interpretation and comparison of study results are the varying compositions of PUFA supplements, varying dosage, potential methodological issues with randomization and blinding (Bloch and Qawasmi 2011, Sonuga-Barke et al 2013), heterogeneous samples of subjects and lack of definition of comorbidities.

Meta-regression analysis showed a dose-response relation since studies with a higher dose of EPA had higher effect sizes (Bloch and Qawasmi 2011). In view of the mild side effect profile, this suggests that higher EPA doses could be tested to find the optimal dose range.

Another review and meta-analysis (Sonuga-Barke et al. 2013) examined trials of a wide range of non-pharmacological treatments of ADHD. The authors made a systematic investigation of the effects of unblinded or blinded assessments in trials of diet, cognitive training, neurofeedback, behavioural interventions, Omega 3 and Omega 3/6 supplementation, etc. The analysis showed that in several studies, significant effects observed with unblinded assessments were substantially reduced, often to non-significant levels, when only using blinded assessments. The Omega 3 and Omega 3/6 trials, however, showed significant but small effects with blinded assessments.

The authors (Sonuga-Barke et al 2013) also note that interpretations are limited by the heterogeneity of study designs, outcome measures and results, and they conclude: “Free fatty acid supplementation and artificial food color exclusions appear to have beneficial effects on ADHD symptoms, although the effect of the former are small and those of the latter may be limited to ADHD patients with food sensitivities. Evidence for the value of behavioural interventions is limited to unblinded ratings made by individuals likely to have an investment in treatment success”.

A Cochrane review (Gillies et al 2013) of 13 trials of Omega 3, Omega 3/6 and also Omega 6 supplements with a total of 1011 participants, showed no significant differences compared to placebo in parent-rated ADHD symptoms (5 trials 413 subjects) or in teacher-rated symptoms (4 trials, 324 subjects). The authors concluded that overall there was little evidence that PUFA supplementation improves ADHD symptoms in children and adolescents. However, trials with Omega 3/6 formulations showed improvement. Here again, it is noted that the studies have the problems of small sample sizes, variable selection criteria, different supplement formulations and doses, and methodological flaws, thus clearly limiting conclusions.

A very recent meta-analysis by Puri and Martin (2014) of 18 trials of PUFA treatment for ADHD in children showed a small effect overall (standardized mean difference (SMD) -0.192). This analysis included trials with variable compositions of Omega 3 or Omega 3/6, and trials with Omega 6 (GLA). Significant effects were found only in parent ratings, not in teacher or clinician ratings. Multivariable meta-regression analysis indicated that longer study duration and PUFA containing GLA or EPA + GLA were associated with significant improvements in inattention, but not in hyperactivity/impulsivity. This analysis included a couple of new studies (Perera et al. 2012, Milte et al. 2012), that were not assessed in earlier meta-analyses.

It should be noted that all these meta-analyses included one or more trials in which the children did not have clinically diagnosed ADHD. One of these trials focused on DCD, but several of these children also had some ADHD symptoms (Richardson and Montgomery 2005). Another included children with high scores of ADHD symptoms recorded by parents in rating scales (Sinn and Bryan 2007).

Side effects of PUFA treatment have been overlooked or underreported in some earlier studies, but several trials have now demonstrated that side effects of Omega 3 or Omega 3/6 are mild, and generally confined to gastrointestinal symptoms such as nausea, diarrhea, indigestion and stomach

discomfort. No severe adverse effects have been reported (Raz and Gabris 2009, Manor et al. 2013).

In summary, previous study results are mixed and comparisons between trials are limited by several factors. Meta-analyses indicate that Omega 3 and Omega 3/6 supplements show some promise, and suggest that the EPA dose may be important. For the future well-designed, properly powered studies with carefully characterized samples and well-defined fatty acid formulations are essential to document any effects. A dose-response design is also needed to tell us which doses are most effective and safe.

More recent studies have made promising efforts to improve methodology. A trial by Manor et al. (2012) had a relatively large sample size (200 children with clinically diagnosed ADHD), and made detailed recordings of comorbidities and adverse effects. They tested a formulation of phosphatidylserine (PS) containing Omega 3 (daily dose of 300 mg PS and a relatively low dose of EPA/DHA (120 mg; ratio 2:1)), in a 15-week double-blind placebo-controlled phase, followed by a 15-week open-label extension phase. Significant improvement on the Global: Restless/impulsive subscale of the Conners' Parent Rating Scale was reported on active treatment compared to placebo, but no effect overall, or on other subscales. The effect size on total ADHD symptom severity in the study, as estimated in the meta-analysis by Sonuga-Barke et al. (2013), did not favor treatment vs. control.

In a double-blind RCT by Milte et al. (2012) comorbidities, learning difficulties, and adverse effects were recorded, blood samples for fatty acid profiles were taken, and cognitive tests performed. The 4-month trial included 90 children aged 7-12 years, with an ADHD diagnosis or a high parent-rated ADHD score on the Conners' Parent Rating Scale (CPRS). They were randomized to three treatment arms, one receiving an EPA-rich oil (EPA 1.1 g/day), one a DHA-rich oil (DHA 1.0 g/day), and a control group receiving an Omega-6 rich oil (safflower oil). The EPA and DHA doses were thus relatively high in this study. Overall, no significant differences between the groups in the primary outcomes (reading/spelling and CPRS scores) were found, but fatty acid profiles in the blood samples showed correlations with improved symptoms and cognitive functions (see below, Study 2).

The results from our trial can also be compared to the recent Mexican open-label RCT which compared treatment with methylphenidate (MPH), MPH and Omega 3/6, and Omega 3/6 alone, during 12 months in 90 children with any subtype of ADHD (Barragán et al. 2014). The Omega 3/6 composition and dosage was the same as in our study, the children were 6-12 years of age and treatment naïve. The trial suggested that Omega 3/6 was effective and

safe, albeit somewhat less effective than MPH, and with a somewhat slower onset of efficacy. The combination of Omega 3/6 and MPH was not superior to MPH alone but permitted lowering of the MPH dose, and resulted in significantly less adverse events.

The responder definition used in the Mexican trial was slightly different from our study (>30% reduction of ADHD-RS score vs. >25% reduction), and the proportion of Omega 3/6 responders slightly higher in the Mexican study (60% at 12 months, compared to 47% in our study at 6 months), but this difference is suggestive of a slower trajectory of efficacy development for Omega 3/6, since the treatment period was considerably longer in the Mexican study, and about half of the subjects in our trial had received placebo during the first 3 months.

5.1.1 Study 1 limitations

The small sample sizes, particularly for subgroup analysis, make results uncertain, and it is possible that significant results may be obscured. Compliance estimates are uncertain since they were not measured with pill counts. About half of all participants in our study had the inattentive ADHD subtype, in contrast to most drug trials which have mostly subjects with ADHD combined type (our study results are therefore not directly comparable to the drug trials). The infrequent clinic visits could limit the recognition of early efficacy, and may obscure effects since memories of long-term changes may be vague.

5.2 Study 2

Blood samples for analysis of fatty acid profiles in plasma phospholipids were collected from 53 participants in Study 1 (active n=22, placebo n=31). Baseline levels were similar across groups, but from baseline to 3 months the active group had a significantly greater increase in n-3, EPA and DHA, and decrease in n-6 and n-6/n-3 ratio, compared to placebo. This indicates that the oral intake of Omega 3/6 really did make a difference in the plasma fatty acid profile.

Significantly greater increase in n-3 levels and decrease in n-6/n-3 ratio were seen in the 6-month responder group compared to non-responders, suggesting a relation between clinical symptom response and plasma fatty acid change. The most consistent result was the reduction in n-6/n-3 ratio, which remained significant through the entire study.

Other studies have given indications that plasma and red blood cell fatty acid composition can be changed by PUFA treatment, and that the fatty acid changes in the blood may be associated with behavioural and cognitive improvements. However, interpretations are again limited by variations in study designs and in fatty acid supplement compositions.

In a placebo-controlled trial of 50 children with ADHD symptoms but not confirmed DSM-IV ADHD diagnosis, Stevens et al (2003) demonstrated that 4 months treatment with a daily dose of 480 mg DHA and 80 mg EPA significantly reduced the n-6/n-3 ratio and increased EPA and DHA in red blood cells and plasma in the active group. The blood fatty acid changes could also be correlated to reductions in disruptive behaviours.

A small 8-week open trial of high-dose (16.2 g) EPA/DHA daily to 9 children with ADHD (Sorgi et al 2007) demonstrated marked reduction of the arachidonic acid (AA)/EPA ratio and associated improvement in rated behaviour (inattention, hyperactivity, conduct). The high dose seemed to be well tolerated, with only one case of loose stools reported.

A three-month placebo-controlled trial compared two preparations of low-dose EPA/DHA daily (ca. 155/95 mg), one conjugated to phospholipid, the other to fish oil, in 86 children who had diagnosed ADHD and low scores on the computerized attention test TOVA (Vaisman et al. 2008). An increase in EPA and DHA in plasma and a correlation between this increase and improved TOVA scores was found mainly in the group taking the phospholipid preparation.

In a 15-week placebo-controlled trial with 0.5 g EPA daily in 92 children with ADHD, Gustafsson et al (2010) found greater reductions in the n-6/n-3 ratio in a subgroup with oppositional behaviour who were treatment responders.

In their three-group RCT of EPA, DHA or Omega-6 treatment in children with ADHD symptoms Milte et al. (2012) found correlations, especially in the subgroup with learning difficulties, between increased DHA in erythrocytes and improvements in reading/spelling, oppositional and ADHD symptoms. These findings lend support to the results in our Study 1, suggesting that children with neurodevelopmental disorders/learning difficulties may have special benefits of Omega 3/6.

5.2.1 Study 2 limitations

The small sample size, particularly in the subgroups of responders, limited the statistical power, and findings should be regarded as suggestive. Replication in adequately powered trials is needed. The large standard deviations of several measures increase the uncertainty of the results and may possibly obscure significant findings.

5.3 Study 3

This long-term open-label study of atomoxetine treatment for adults with ADHD showed fair efficacy at 10 weeks, with 10 of 20 individuals meeting the primary efficacy criteria (reduction of CGI-S score by ≥ 2). However, several subjects discontinued during the following months, mostly because of insufficient efficacy or adverse events, and after 1 year only one patient remained in the study.

Comparison with other trials suggests that high baseline symptom severity may be an important factor related to lack of efficacy. This relation was observed in the recent US/Canadian open-label 4-year trial with 384 adults (Adler et al. 2005, 2008). The patients discontinuing due to lack of efficacy in that study had higher baseline scores on CAARS and CGI-S than those who did not. The baseline CGI-S scores (mean 5.3) in our study indicate high symptom severity, and although the reduction in CGI-S score was substantial (mean -1.45), the score at endpoint (mean 3.95) did not reach the levels of improvement (CGI-S 1-2) which represent an almost normalized symptomatology, and which are known from other trials to be satisfactory for most participants. It is probable that the relatively high endpoint symptom level in our study was perceived by the subjects as insufficiently beneficial, and that this contributed to the high discontinuation rate. However, poor long-term compliance is a common problem in ADHD studies, especially in adults (SBU 2013), who no longer have parent support helping them maintain treatment adherence. In the US/Canadian study 33% of the patients completed 97 weeks and 18% the whole 221 weeks of the study (Adler et al. 2005, 2008). In a 6-month placebo-controlled trial with 501 adults (Adler et al. 2009), and in a large study in 18 countries (n=2057) with an open-label phase followed by a randomized withdrawal phase, a majority of patients did not complete the trials (Upadhyaya et al. 2013).

5.3.1 Study 3 limitations

Conclusions should be drawn with caution due to the small sample size and the open-label nature of the study.

5.4 Study 4

Our small open study of CPS for children with ADHD and ODD indicated that 3 months of training with the CPS method was effective for 53% (9/17) of the participants, who were much or very much improved on the investigator-rated CGI-I, with only mild symptoms remaining (CGI-I 1-2). At that time point families of children who had marked residual ADHD symptoms (7/17) chose to add ADHD medication for their child. Six months later 81% of all were much or very much improved. The results are only suggestive, given the open nature of the study and the small sample size, but they are promising and instructive, giving hints about future directions of research in this area.

Our results are in line with the outcome of the US trial (Greene et al. 2004) in which CPS was compared to Barkley's (1997) behavioural parent training (BPT) program, in 50 children aged 4-12 years with ODD and affective dysregulation (subthreshold features of bipolar disorder or major depression). Equivalent to superior outcomes were found for CPS compared to BPT on ODD symptoms and other measures of functioning at post-treatment and 4-month follow-up. Parent rated CGI-I was much or very much improved (CGI-I 1-2) for 70% of the children at post-treatment and for 80% at 4-month follow-up (compared to 53% at post-treatment and 81% at 6-month follow-up in our study). The post-treatment outcome differences between the trials may be affected by differences in medication regimes. In the US trial, medication and medication changes were allowed during the treatment phase, while in our study only one child had medication (long-term unchanged) during the treatment phase. From the post-treatment time point in our study a subgroup with high residual levels of ADHD symptoms started ADHD medication, and at 4-month and 6-month follow-up, results were very similar between the trials (80% vs. 81% reached CGI-I 1-2).

Other noteworthy methodological considerations are that in the US trial, raters were parents and therapists. In our study, raters were assessors not involved in the treatment, and thus possibly somewhat more independent. However, none of the studies had blinded assessors.

Study 4 thus suggests that CPS is effective for reducing oppositional behaviour in some children with ADHD and ODD, and that this improvement is relatively long-term stable, i.e. it is maintained at 6 month follow-up, with no additional treatment. The results also indicate that a subgroup of children with relatively severe core ADHD symptoms may benefit from the combination of CPS and ADHD medication. This is in line with the success reported from other studies combining behaviour therapy and medication.

One well-known example is the MTA study, in which the combined (multimodal) treatment group received stimulant medication in combination with intensive behavioural supportive treatment, resulting in that 86% of this group reached “normalization” of ADHD symptoms after 14 months (MTA Cooperative group 1999, Swanson et al. 2001). Also the Cologne Adaptive Multimodal Treatment (CAMT) study showed that behaviour therapy and/or stimulant medication for ADHD (adaptive and individually tailored multimodal treatment) produced marked reductions in ADHD symptomatology, which were maintained at 18-month-follow-up (Döpfner et al. 2004, 2014).

It has not yet been demonstrated how well CPS works for challenging behaviours in children across diagnostic categories and comorbidities, for instance autism, ADHD + autism, Tourette syndrome, ADHD + Tourette, or for children with more severe variants of Conduct Disorder (CD). None of the children in the US trial or in our Study 4 met full diagnostic criteria for CD. Further studies with well-defined clinical samples would be valuable in this respect.

Many studies with children of all ages have indicated that BPT models have positive effects on parenting strategies and child behaviour, and some studies show that parental stress can be reduced. BPT thus meets the APA research criteria for a well-established treatment in children and adolescents with disruptive behaviour and ADHD (Pelham and Fabiano 2008, Döpfner 2010, Evans et al. 2013).

However, BPT effects on ADHD core symptoms are less clear, and reviews of BPT trials show that careful study design and methodology is essential to avoid bias. The above-mentioned review and meta-analysis by Sonuga-Barke et al. 2013 assessed several trials of BPT and parent/child training in children with ADHD, but found that the positive effects on ADHD symptoms recorded by unblinded raters evaporated completely with blinded raters. A Cochrane review (Zwi et al. 2011) looking at RCTs of parent training interventions for 5-18 year-old children with ADHD found that only few studies met inclusion criteria for the review, and noted that methodological weaknesses such as partial reporting and insufficient blinding limited the confidence in assessments of clinical effects. Results suggested positive effects on general behaviour, but little effect on ADHD symptoms. For similar reasons, a review by the Swedish Council on Health Technology Assessment (SBU 2013) concluded that the research support for BPT effects on ADHD core symptoms was insufficient.

Promising parent training models are now being examined in trials with large samples and improved methodology, focusing on clinically important factors such as ecological validity, long-term results, broader outcome measures, and the perspectives from various raters. Instructive examples (although not specific for ADHD) are studies of the Prevention Programme for Externalizing Problem behaviour (PEP). One was an effectiveness trial by Hautmann et al. (2008, 2009) of PEP training given in routine care settings for 270 children 3-10 years old with externalizing problem behavior, which also included a long-term (one year) follow-up (effectiveness trials assess if a treatment has effect in real-world conditions, an important distinction from efficacy trials, which test the effect of a treatment under rigorously controlled conditions). Outcome measures of child behaviour, ADHD symptoms and parenting were used (but rated by mothers only). The other PEP study was a large RCT (n=155) by Hanisch et al. 2010 for parents and preschool teachers to children with disruptive behavior, in which broader measures of child symptoms, parent functioning and quality of life were rated by mothers, teachers and observers. Another example is the large (n=329) multicenter RCT of the adapted New Forest Parenting Programme (NFPP) for preschool children with ADHD (McCann et al. 2014), which will compare adapted-NFPP to the Incredible Years programme and to Treatment as Usual (TAU).

A key point regarding CPS is that the training is expected to give a long-term improvement of the cognitive lagging skills, thus building abilities to handle an increased number of previously problematic situations, and also permanently changing the mindset of both the adults and the child towards a strategy of mutual problem solving, instead of finding themselves in a vicious cycle of opposition and coercion. If so, this would be a very important finding, since the problem with most treatments is that the effect “wears off”, lasting only for short time periods. Long-term follow-up studies are warranted to demonstrate if CPS effectiveness lasts.

5.4.1 Study 4 limitations

This was a small open pilot study of an exploratory kind. It did not have a control group or blind raters. The findings should therefore be considered only as suggestive, and in need of replication in an adequately powered RCT, preferably with a longer follow-up period.

6 CONCLUSION

Study 1 and 2. Overall, the double-blind randomized placebo-controlled part of the trial of Omega 3/6 for ADHD in children and adolescents (Study 1) was negative. Active treatment was not superior to placebo. However, participants with clinical response (more than 25% reduction in ADHD Rating Scale score) were significantly more common in the active group than the placebo group, and response tended to be most common in subjects with AD and ‘neurodevelopmental disorders’, i.e. RWD, DCD, LD, or autistic symptoms. The active group had a significant rise in the plasma level of Omega 3 (n-3) and reduction of the Omega 6/3 (n-6/3) ratio, and the changes in plasma fatty acids appeared to be associated with clinical response.

Study 3. The open-label trial of ADHD in 20 adults demonstrated that atomoxetine produced substantial improvement for 50% of the patients after 10 weeks, but before 1 year of treatment all but one of the patients discontinued, mostly due to lack of efficacy or adverse events.

Study 4. This open study of 17 children with ADHD and ODD showed that 53% of the children were substantially improved (with only mild symptoms remaining, i.e. CGI-I scores 1-2) after three months of CPS training. Those who still had high levels of ADHD symptoms were subsequently treated with stimulants. Six months later 81% of all children were substantially improved.

7 FUTURE PERSPECTIVES

Study 1 and 2. Meta-analyses of currently available PUFA trials indicate that at least some trials of Omega 3/6 fatty acid treatment for ADHD in children show indications of positive effects. Overall, however, the interpretation of trial results is limited by small samples, variable study designs and variable PUFA formulations. Further research is needed to confirm effectiveness and to show which patients might benefit the most.

In future research it is therefore essential to use more uniform methodology, well-defined selection criteria (for instance with clinically established diagnoses and assessment of comorbidities and of functional impairment), and well-defined PUFA formulations. Our Study 1 suggests that it might be rewarding to examine children with neurodevelopmental disorders (such as ADHD inattentive subtype, reading/writing or learning disorders). In addition, more long-term studies are warranted, preferably with more focus on functional and quality of life outcomes. The possibly confounding factor of variable PUFA content in the everyday diet of the participants should also be controlled for.

Larger, adequately powered randomized placebo-controlled trials are recommended, and the evidence for a dose-response relationship of EPA suggests that higher doses of EPA should be tried. Associated studies of Omega 3 and 6 in plasma or erythrocytes may give useful information about baseline levels in children with ADHD and of the impact of treatment on blood levels correlated to clinical response.

If effectiveness can be confirmed in such studies, and in view of the mild side effect profile, PUFA may have a place in the treatment of ADHD when medication is not wanted, or as an adjunct to medication.

Study 3. Efficacy of atomoxetine in adults with ADHD has been well established in short-term trials, in which treatment compliance can be held high. Long-term compliance is, however, a major problem in atomoxetine trials (as well as in other drug trials). This finding highlights the importance for future research to focus on developing multimodal programs with supportive strategies that may enhance treatment adherence, especially for adult patients, who may not have close support from parents or relatives.

Study 4. As mentioned in the Introduction, the American Psychiatric Association (APA) has rated the CPS model as *probably/possibly efficacious*, based on currently available research. A larger study of 134 children with

ODD has recently been completed at the Child Study Center, Virginia Polytechnic Institute, showing equivalent results of CPS compared to Barkley's (1997) BPT program (Ollendick 2011, Ollendick et al. submitted). Effectiveness demonstrated in properly powered randomized controlled trials may shift the APA rating for CPS to the level "*well established*". Our small open pilot study, the first study in Sweden, shows promising results. Based on the experiences from that study, we have designed an RCT with CPS compared to Treatment As Usual (TAU) for 150 children and adolescents with neuropsychiatric disorders and challenging behaviour. This trial is currently underway at the Gillberg Neuropsychiatry Centre, Sahlgrenska Academy.

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