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Non-stimulant interventions in ADHD

Mats Johnson, MD
Gillberg Neuropsychiatry Centre
Sahlgrenska Academy

Main supervisor Elisabeth Fernell
Co-supervisor Christopher Gillberg

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Study 1
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.

Study 2
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.

Study 3
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.

Study 4
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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Introduction

The parents of children with neuropsychiatric disorders such as ADHD are often met by claims in media about the effectiveness of alternative treatments

These claims have rarely been solidly supported by research

It is important for clinical researchers to contribute to knowledge about treatments, based on research of high quality, to be able to give families well informed advice

With this in mind we planned studies of new non-stimulant treatments which had shown at least some promising results in studies, but for which more research was needed to substantiate both effectiveness and safety

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Study 1

Omega-3/Omega-6 Fatty Acids for Attention Deficit Hyperactivity Disorder. A Randomized Placebo-Controlled Trial in Children and Adolescents

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.

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Study 1. Background

- Phospholipids containing polyunsaturated fatty acids (PUFA), such as Omega-3 and Omega-6, are integral parts of the neuronal cell membranes of the brain, and may have a role in facilitating the transmission of signals between neurons **(Sinn & Wilson, 2006)**
- Omega-3/Omega-6 has been discussed since the 1980s and used for MBD/ADHD (Tore Duvner in Sweden and David Horrobin in Britain)
- Trials with supplementation of the Omega-3 acids eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA) have reported significant symptom reductions in children with reading writing disorder, dyspraxia (i.e. motor coordination difficulties), and ADHD-related symptoms **(Richardson & Montgomery, 2005; Richardson & Puri, 2002; Stevens et al. 2003)**

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Study 1. Primary objective

- To assess whether supplementation with Omega 3/6 fatty acids was effective in reducing ADHD symptoms in children and adolescents with a clinical ADHD diagnosis
- and to assess effects in subgroups with different ADHD subtypes and comorbidities

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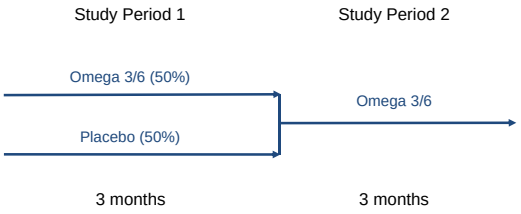
Study 1 design



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Study 1. Method

Study Period 1
Patients were randomized to active treatment with Omega 3/6 in a dose of three capsules twice daily = daily dose of 558 mg EPA, 174 mg DHA (both Omega-3 fatty acids), 60 mg gamma linolenic acid (an Omega 6 fatty acid), and 0.8 mg Vitamin E

OR to placebo (identical capsules containing olive oil)

Study Period 2
Open-label phase in which all patients were given active treatment in the same dosage as in period 1

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Study 1. Inclusion / Exclusion criteria

Inclusion

- Children and adolescents 8 to18 years
- DSM-IV criteria for ADHD any subtype

Exclusion

- Autism
- Other psychoactive medication, Substance use
- Serious medical condition
- Omega 3 treatment last 3 months
- Intellectual disability

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Study 1. Assessments

- Clinical assessments were made at three visits at the sites:
  - baseline
  - 3 months (before switching to open treatment with omega 3/6)
  - 6 months

- Primary outcome measures
  - ADHD Rating Scale (ADHD-RS) max score 54
  - CGI-S scale (Clinical Global Impression) max score 7

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Study 1. Patient characteristics (n=75)

Boys/girls	85%/15%
AD/HD	100%
• combined type (ADHD)	47%
• inattentive type (AD)	53%
Comorbidities	**78%**
• Developmental Coordination Disorder (DCD)	31%
• Autistic traits/Autism-like condition	26%
• Reading/Writing Difficulties (RWD)	43%
• Oppositional Defiant Disorder (ODD)	24%
• Learning Difficulties	12%
• Depression/anxiety	8%
• Tourette Syndrome	3%

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Study 1. Flow of participants

n = 75

Completed period 1	64
Completed period 2	59
Discontinued	16 (21%)
- unmotivated/ difficulty swallowing capsules	11 (5 Active, 6 Placebo)
- side effects (GI)	4 (3 Active, 1 Placebo)
- irritability	1 (Placebo)

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Study 1. Results

Overall, this is an essentially negative study: For the whole group of children and adolescents with ADHD, omega 3/6 supplementation for 3 months was not statistically superior to placebo in improving ADHD Rating Scale scores (although CGI scores showed significant improvement)

However, there was a subgroup who responded with a **clinically meaningful** improvement in ADHD core symptoms **(= responders)**

Responder, definition:
Reduction of at least 25% on the ADHD Rating Scale–IV score

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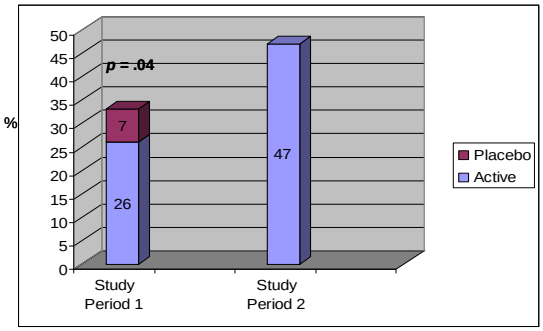
Study 1. Response rate in the whole group after 3 and 6 months (Chi-square test)



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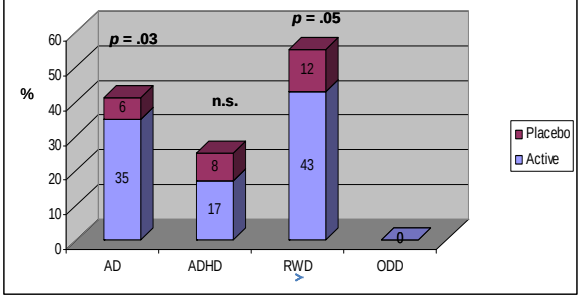
Response rates in diagnostic subgroups after 3 months



RWD = Reading Writing Disorder

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Study 1. Adverse events

Study period 1

- 6 patients (active) reported mild stomach discomfort or dyspepsia (+ the 3 who withdrew from the study: 2 active, 1 placebo)
- The blinded code had to be broken for 1 patient (placebo) due to markedly increased irritability

Study period 2

- One patient withdrew due to diarrhea

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Study 2

Fatty acids in ADHD: plasma profiles in a placebo-controlled study of Omega 3/6 fatty acids in children and adolescents

Johnson M, Månsson J-E, Östlund S, Fransson G, Areskoug B, Hjalmarsson K, Landgren M, Kadesjö B and 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.

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Study 2. Objective

To examine baseline levels and changes of fatty acid profiles in plasma phospholipids in children and adolescents with ADHD participating in Study 1

and to compare these fatty acid measures with treatment response

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Study 2. Plasma fatty acids in ADHD

Blood sample was drawn at

- baseline, 3 months, 6 months (n = 53)

- n-3 (Omega-3)
- n-6 (Omega-6)
- n-6/n-3 ratio
- EPA
- DHA

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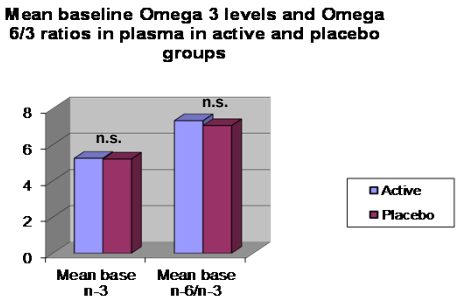
Study 2. Results Active/placebo groups



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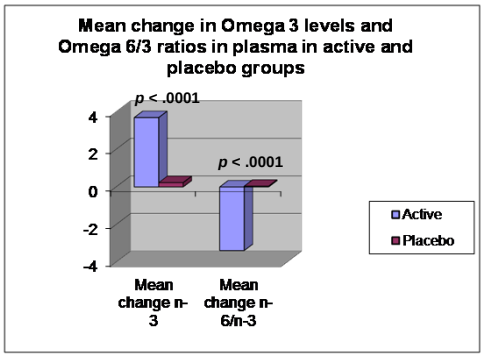

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Study 2. Results

Plasma fatty acids and treatment response

For the whole group, no significant correlation could be found between the degree of improvement in ADHD Rating Scale scores and the degree of change in the fatty acid plasma levels

However, analysis of 6-month responder vs. non-responder groups yielded some significant results

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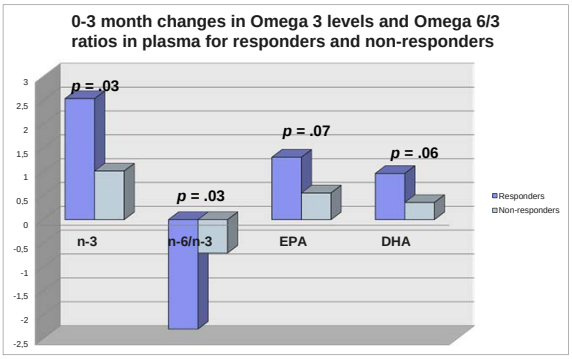

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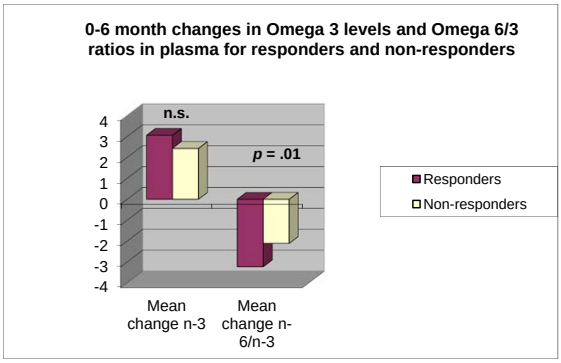

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Study 4

Attention-deficit/hyperactivity disorder with oppositional defiant disorder in Swedish children – an open study of Collaborative Problem Solving

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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The Collaborative Problem Solving (CPS) model

Theoretical basis:
Problem behaviours are caused by lagging cognitive skills
– for instance in emotion regulation and cognitive flexibility

The CPS model aims to:
- 1. Identify and train lagging skills
- 2. Find solutions to problematic situations
- 3. Improve compatibility between child and adult

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Study 4. Inclusion/exclusion criteria

Inclusion
- Children aged 6-13 years
- DSM-IV ADHD + Oppositional Defiant Disorder (ODD)

Exclusion
- Autistic disorder (but not autistic features)
- Intellectual disability
- Recently started (<6 months) treatment with stimulants or other psychoactive medications

At baseline all children underwent neuropsychiatric assessment and were tested with WISC-IV

Outcome measures: SNAP-IV, Conners' 10 items, Family Burden of Illness Module, CGI-I

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Study 4. Design

Open study

CPS intervention
- 6-10 sessions with CPS for parents and children during 3 months

Assessment
- Evaluation of outcome by independent assessors
  – post-treatment
  – 6 month follow-up

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Study 4. Outcome measures

SNAP-IV
- 18 DSM-IV-criteria for ADHD
- 8 criteria for Oppositional Defiant Disorder (ODD)
- All symptom criteria graded from 0-3

CGI-I (Clinical Global Impression-Improvement)
- **1 Very much improved**
- **2 Much improved**
- 3 Minimally improved
- 4 No change
- 5 Minimally worse
- 6 Much worse
- 7 Very much worse

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Results (n=17)

All17 families completed the treatment period
16 families remained at 6-month follow-up

Post-treatment
More than 30% reduction of:

SNAP-IV ODD-symptoms	**53% (9/17)**
SNAP-IV ADHD-symptoms	41% (7/17)
CGI-I 2-1	**53% (9/17)**

At post-treatment 8 families with children who had marked residual ADHD symptoms chose to add ADHD medication for their child.

6-month follow-up

CGI-I 2-1	**81% (13/16)**

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Future perspectives

Meta-analyses of several currently available trials including ours indicate that at least some trials of Omega 3/6 fatty acid treatment for ADHD in children show positive effects

However, interpretation of trial results is limited by small samples, variable study designs and variable Omega 3/6 formulations

Adequately powered studies with well-defined methodology, selection criteria, assessment of comorbidities, and Omega 3/6 formulations are essential to confirm effectiveness

Our Study 1 suggests that it would be relevant to examine children with ADHD inattentive subtype and comorbid RWD/other neurodevelopmental disorders

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Future perspectives

Study 4 showed that 53% of the children were much or very much improved after three months of CPS training.

Those who still had high levels of ADHD symptoms were subsequently treated with stimulants.

At six-month follow-up 81% of all children were much or very much improved

Based on the experiences from this small open pilot study, we have designed an RCT with CPS compared to Treatment As Usual (TAU) for 150 children and adolescents with neuropsychiatric disorders and problematic behaviours.

This trial is currently underway at the Gillberg Neuropsychiatry Centre (GNC)

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Acknowledgements

Research Teams

Study 1-2
Sven Östlund
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Sven Östlund
Gunnar Fransson
Magnus Landgren
Salmir Nasic
Björn Kadesjö
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Elisabeth Fernell

Thank you for your attention!