Cross-sectional study of 24-hours blood pressure measures and left ventricular mass using echocardiograms in late adolescents and adults with ADHD.

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Primary Objective:To determine whether the long*term use of methylphenidate (> 3 years) increases the blood pressure and causes left ventricular hypertrophy (LVH) identified by echocardiography in late adolescent (>=15 years) and young adults...

Ethical review	Approved WMO
Status	Recruitment stopped
Health condition type	Other condition
Study type	Observational invasive

Summary

ID

NL-OMON37801

Source
ToetsingOnline

Brief title
ADDUCE: blood pressure and left ventrikel mass in ADHD.

Condition

- Other condition
- Cardiac disorders, signs and symptoms NEC

Synonym
Attention deficit disorder with hyperactivity; hyper active children

Health condition

Bloeddruk

Research involving
Human

Sponsors and support

Primary sponsor: Universitair Medisch Centrum Sint Radboud
Source(s) of monetary or material Support: Seventh Framework Programme for Research and Technological Development

Intervention

Keyword: ADHD, Adolescents/ jong volwassenen, Blood pressure, Left ventricular

Outcome measures

Primary outcome

• Hypertension defined on the basis of 24*hour blood pressure measures as systolic and/or diastolic blood pressure of a positive value >= 1.65 (equivalent to the 95th percentile).

• Left ventricular mass will be indexed by a partition. A partition value will be taken at the 95th percentile of measurements indexed to body size (whether, height, weight or body surface area). This has the attraction of simplicity and will be used as the primary outcome measure. This method essentially categorises individuals into *normal* or *increased* left ventricular mass without conveying the degree to which the abnormal measurement differs from the reference population. LVM will be indexed to the allometric height in meters raised to the power of 2.7 (g/m2.7). This been extensively reported, with a value of 38.6g/m2.7 denoting the 95th percentile (de Simone et al 1992; de Simone et al 1995).

Secondary outcome

• Continuous scores of 24-hour systolic and diastolic blood pressure.

• Z- scores of left ventricular mass. Z*scores record how many standard deviations above or below a size*specific population mean an individual measurement lies and has the attraction of conveying the degree of deviation of the observed measurement from the mean. This will be also assessed as a secondary outcome analysis (Foster et al 2008). LVM will be indexed for height to power of 2.7 using an online calculator (Parameter (Z), 2009).

Other study parameters

To meet our secondary objectives and explore the role of potential moderators, mediators and confounders, and analyze dose-response relationships, the following other study parameters will be collected:

Clinical and psychiatric information

• Demographic information

• Family Developmental, medical and Psychiatric History

• Developmental history

• Medication history

• Current psychiatric medication (including drug and dose)

• Schooling, SES

• Substance Misuse Questionnaire (including smoking and alcohol)

• Lifestyle, physical exercise

• Severity of ADHD (ADHD DSM-IV rating scale)

• Severity of psychiatric problems (YSR / YASR)

• CGI-Severity

• CGAS

Physical status

• Weight

• Height

• Physical examination

• Cardiac examination

• Biochemistry

Study description

Background summary

Attention deficit/hyperactivity disorder (ADHD) is one of the most common behavioural disorders of childhood, characterized by the early onset of age-inappropriate hyperactivity, impulsivity and inattentiveness, and a world-wide pooled population-prevalence of 5.3 % (Polanczyk et al. 2007). The current psychiatric disease classification system, DSM-IV, distinguishes three subtypes: a mainly inattentive, a mainly hyperactive-impulsive and a combined subtype (American Psychiatric Association (APA), 2000).
ADHD is strongly persistent over time. Approximately 15% of the patients still meet full ADHD criteria according to the DSM-IV in adulthood, whereas 40-60% remits only partially and has increased symptom counts as adults (Faraone et al. 2006). Given the high burden of ADHD and associated problems on the patient, the family environment and on society as a whole, the need for effective treatment is eminent. Clinical guidelines and practice parameters describe the pivotal role of medication in the clinical management of ADHD (National Institute for Health& Clinical Excellence (NICE), 2009; Scottish Intercollegial Network Guidelines (SIGN), 2009; Pliszka, 2007; Taylor et al. 2004; Banaschewski et al. 2006). These recommendations are based on numerous clinical trials that have shown both psychostimulant and non-stimulant medication to be highly efficacious in treating ADHD with a percentage of clinical responders around 70% or higher. Therapeutic effects of medication include a reduction of the hyperactivity, impulsivity, and inattention characteristic of patients with ADHD, and improvement of associated behaviors,

including on-task behavior, academic performance, and social functioning (Greenhill et al. 2002).

The most commonly prescribed medications are the psychostimulants methylphenidate and other amphetamines. Methylphenidate and dexamfetamine belong to a group of drugs known as central nervous system stimulants. The mechanism by which stimulants act in reducing symptoms in ADHD is not completely clear, however it is believed that they inhibit the reuptake of dopamine and noradrenaline into the presynaptic neuron and increase their release into extraneuronal space thus increasing intrasynaptic concentrations (Faraone & Biederman, 1998).

However, as ADHD is a rather chronic condition, medication treatment typically will be extended over a long period of time, up to several years. The main goal of this protocol is to examine the long-term effects of methylphenidate on the cardiovascular system and in particular on blood pressure and on left ventricular mass. We focus on methylphenidate because it is the most often prescribed psychostimulant. Before we develop our research question in somewhat greater detail, we briefly review what is known about cardiovascular effects of methylphenidate.

Stimulants and heart rate and blood pressure

Stimulant medication is recognised to result in a small increase in heart rate averaging 1 - 2 beats per minute (Vetter et al 2008). Taking the average value in clinical studies hides a small proportion where the increment is larger; an increase of up to 50 beats per minute has been observed on rare occasions. Unfortunately, clinical trial data are rarely reported in a format that allows the incidence of clinically significant tachycardia to be quantified. In addition there is a lack of data on the longer term impact of methylphenidate on heart rate and the lack of appropriate controls in such studies. Methylphenidate, like other stimulant drugs, is also well known to have small, short term effects on blood pressure. In clinical trials, children treated with methylphenidate showed increases in systolic and diastolic blood pressure of 1-4 mmHg on average compared to those treated with placebo. A more relevant measure of risk, however, would be whether increases resulted in children entered the category of hypertension i.e. when blood pressure exceeds the 95th percentile, and if so how many children/young people are affected in this way. For this categorical measure, controlled trial data are not available for methylphenidate but data for atomoxetine (which has a comparable effect on mean blood pressure) suggested that elevations above the 95th percentile are seen in 6.8 % of patients (systolic) and 2.8% (diastolic) in comparison to 3% and 0.5% respectively in patients treated with placebo (Wernicke et al 2003). There are inadequate data at any stage of therapy, not just in the longterm and it remains to be established whether similar figures apply for methylphenidate. Because of the association between hypertension and socioeconomic status, studies will require socioeconomic status matched controls in addition to

untreated ADHD controls.

Study objective

Primary Objective:
To determine whether the long*term use of methylphenidate (> 3 years) increases the blood pressure and causes left ventricular hypertrophy (LVH) identified by echocardiography in late adolescent (>=15 years) and young adults with ADHD.

Secondary Objectives:
1) To explore the role of potential mediators, moderators and confounders e.g. age, sex, socioeconomic status, family functioning, comedication, negative lifestyle factors, weight and familial cardiovascular risk, in the relationship between methylphenidate treatment and the effects on blood pressure and echocardiogram.
2) To describe the dose*response relationship (dosage, duration of treatment, discontinuation vs. continued use) between methylphenidate exposure and the effects on blood pressure and echocardiogram.

Study design

This is an observational study, conducted within The European Network for Hyperkinetic Disorders (EUNETHYDIS) a well established network of child and adolescent mental health researchers all of whom are experts in researching ADHD and many of whom are experts in paediatric psychopharmacology and pharmacovigalence. EUNETHYDIS has been recognized by the European Network of Paediatric Research at the European Medicines Agency (EnprEMA) and/or within the framework of IMpACT (International Multi-site persistent ADHD). IMpACT is a network of academic sites with strong clinical and research interest in adult ADHD in Europe (Nijmegen, Barcelona, London, Dundee, Budapest), Brasil and the USA (Boston). We will also recruit patients with ADHD from child and adolescent psychiatry clinics, in close collaboration with sites participating in observational studies in children and adolescents with ADHD in the framework of the ADDUCE grant.

This study will use a cross-sectional design to compare two groups of patient with ADHD: a group of late adolescent and young adult subjects with ADHD, treated with methylphenidate for > 3 years, and a matched group of late adolescent and adult subjects with ADHD who have never been treated with methylphenidate.

Study burden and risks

This is an observational study, and all procedures are very standard, and without increased risks. Benefits are formed by a systematic and thorough

monitoring of adverse events.

Contacts

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Trial sites

Listed location countries

Netherlands

Eligibility criteria

Age
Adolescents (12-15 years)
Adolescents (16-17 years)
Adults (18-64 years)
Elderly (65 years and older)

Inclusion criteria

Target group:
Patients with ADHD according to DSM-IV criteria (any subtype), based on clinical diagnosis, and confirmed by a structured interview [depending on local procedures: ADHD module of the K-SADS (Kaufman et al., 2000) or CAADID (Conners Adult ADHD Diagnostic Interview for DSM-IV) (www.mhs.com/) or DIVA (Diagnostic Interview for Adult ADHD) (www.divacenter.eu/Content/Downloads/DIVA_2.pdf).
• Aged between 15 and 25 years.

• Any comorbidity is allowed.
• Any comedication is allowed.
• Treated with methylphenidate (IR or ER preparations) for 3 years or longer, continuously.;Note: we will attempt to recruit at least 50% of the participants of the target group being treated continuously for 3 years with a minimum effective dose of 0.5 mg methylphenidate /kg/day). Being treated continuously means being prescribed methylphenidate continuously but may include the presence of drug holidays. We will measure adherence by asking questions about drug holidays and % of the overall dose taken. We will allow for some variation in dosages prescribed to be able to analyze dose-response relationships.;Control group:
• Patients with ADHD according to DSM*IV criteria (any subtype), based on clinical diagnosis.
• Aged between 15 and 25 years.
• Any comorbidity is allowed.
• Any comedication is allowed.
• Never been treated with methylphenidate.

Exclusion criteria

All Groups: Treatment with dexamfetamine or atomoxetine.
ADHD controls: Treatment with methylphenidate.

Study design

Design

Study phase:	4
Study type:	Observational invasive
Intervention model:	Other
Allocation:	Non-randomized controlled trial
Masking:	Open (masking not used)
Control:	Active
Primary purpose:	Treatment

Recruitment

NL

Recruitment status:	Recruitment stopped
Start date (anticipated):	12-08-2012
Enrollment:	320

Type:	Actual

Ethics review

Approved WMO Date:	31-08-2012
Application type:	First submission
Review commission:	CMO regio Arnhem-Nijmegen (Nijmegen)
Approved WMO Date:	23-04-2014
Application type:	Amendment
Review commission:	CMO regio Arnhem-Nijmegen (Nijmegen)
Approved WMO Date:	16-10-2014
Application type:	Amendment
Review commission:	CMO regio Arnhem-Nijmegen (Nijmegen)

Study registrations

Followed up by the following (possibly more current) registration

No registrations found.

Other (possibly less up-to-date) registrations in this register

No registrations found.

In other registers

Register	ID
CCMO	NL37942.091.11