ADHD medication use and long-term consequences

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ADHD MEDICATIEGEBRUIK EN LANGE TERMIJN CONSEQUENTIES

(Met een samenvatting in het Nederlands)

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Voor mamma en pappa

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Content

1

Introduction

Background

Ritalin® (methylphenidate) is one of the best known psychotropics used in children and adolescents today. This psychostimulant (named after his wife Rita) was designed around 1944 by the Italian chemist Leandro Panizon. In those days the drug was advised for curing chronic fatigue and mild depression [1]. A few years earlier Charles Bradley had written a paper enlightening the improvement of behavioural problems and school performance in some children with post-pneumoencephalography headaches that were treated with Benzedrine. Benzedrine, a psychostimulant, was originally introduced as an inhaler and bronchodilator in 1932 [2]. This unexpected finding provided pharmacological treatment options for children with disrupting behavioural problems such as -as it is called nowadays- attention deficit hyperactivity disorder (ADHD).

ADHD is a neurodevelopmental disorder, resulting from psychosocial, environmental, genetic and biological factors that can become visible in very early childhood, but also at older school or adult age [3]. ADHD is characterised by inappropriate problems with attention, concentration, impulsivity and hyperactivity causing impairment in daily life [4].

The exact aetiology of ADHD is unknown; however ADHD can be seen as a multifactorial disorder. Genetic as well as environmental factors play an intertwined role in the phenotypic expression of the disorder [5-7]. Relevant studies on family, twins and adoption suggest a multi-genetic transmission of genes in families. The heritability is estimated at 75% [8,9]. Genes of interest include DAT1 or SLC6A3 which code for the dopamine transporter and DRD4 which codes for the dopamine receptor D4. Further genes of interest are ADRA2A, a gene coding for the adrenergic alpha-2A receptor, the COMT gene, which codes for the enzyme catechol-O-methyltransferase and LPHN3, the gene which codes for latrophilin 3. These genes are supposed to be influencing the susceptibility to ADHD and may be involved in the response on ADHD medication [10,11].

Comparing patients with ADHD to control subjects, structural and functional abnormalities in the brain have been found, such as a significant smaller volume of the cerebrum, right caudate nucleus and globus pallidus, a smaller cerebral vermis, corpus collosum and white matter tracks, smaller anterior brain regions with larger posterior brain regions, reduction of white matter volumes and cortical thickness [12-14]. Recent Diffusion Tensor Imaging studies (DTI) show abnormalities in the

microstructural integrity of white matter brain tissue in patients with ADHD. These are most consistently found in the right anterior corona radiata, right forceps minor, bilateral internal capsule and left cerebellum areas [15]. Dopaminergic and noradrenergic dysfunction of the central nervous system is also found in patients with ADHD [9]. The anterior system (prefrontal cortex, anterior cingulated cortex, basal ganglia and corpus striatum) controls executive functions which are often disturbed in ADHD and require an intact dopaminergic system. Noradrenergic circuits influence the functioning of the posterior system (superior parietal cortex, thalamus and cerebellum) and play a role in processing of signals [9, 16].

Many environmental risk factors have been studied and they are assumed to play a role in the aetiology of ADHD. Factors that play a role are for example the exposure to heavy metals and chemicals such as phthalates, bisphenol A, tobacco smoke, polycyclic aromatic hydrocarbons, polyfluoroalkyl chemicals and alcohol. Nutrition, lifestyle and psychosocial factors are also known to influence the development of ADHD symptoms (such as low social-economic class and a disordered family environment) [9,17].

The prevalence of ADHD among preschoolers is estimated at 0.5-6.5%, whilst the prevalence among children and adolescents worldwide is estimated at 5%. Among adults at and elderly adults prevalence is estimated at 1-4.7% and 2.8% respectively [18-25]. The prevalence of ADHD in boys between 0-18 years old is three times higher than in girls of the same age group. For adults the prevalence in men is assumed higher than in women, although it is also reported that the prevalence in men and women is equal [18, 20, 21, 26, 27].

How is ADHD first diagnosed? One may presume that in most cases the first signs are of behavioural, learning or social problems at home, at school or elsewhere. These problems are only noticed if parents, caretakers, teachers, coaches or others are sensitive enough to perceive these behaviours as different from an “average” person in the same social surrounding. When behavioural or learning problems are interfering with daily life, in the Netherlands one will seek help from the general practitioner (GP) or from the youth health care medical practitioner. Depending on their knowledge, their experience and their referring possibilities, they might decide to refer a patient to a psychologist, psychiatrist, paediatrician, or to another expert. From there, the

diagnostic process will continue according to the Dutch protocol of ADHD diagnosis and treatment [28].

The Diagnostic and Statistical Manual of Mental Disorders (DSM) has been used worldwide for the classification of mental disorders such as ADHD. The various editions of the DSM describe ADHD differently over the years. The second edition of 1968 mentions an ADHD resembling disorder called 'hyperkinetic reaction of childhood' was mentioned [29]. Symptoms mentions therein were hyperactivity, a short attention span and restlessness. In the third edition of DSM, published in 1980 in the United States and in 1982 in the Netherlands, the 'hyperkinetic reaction of childhood' was referred to as 'Attention Deficit Disorder' (ADD) [30]. That edition distinguished two subtypes: inattention problems with or without symptoms of hyperactivity or impulsivity. The revised version ofthe DSM III (DSM-III-R, US 1987, the Netherlands 1988) included the Attention Deficit Hyperactivity Disorder (ADHD) with an obligate/ compulsory role of symptoms of hyperactivity without any subtypification [31].

The DSM-IV (US 1994, the Netherlands 1995) and DSM-IV-TR (US 2000, The Netherlands 2001) still mentions the disorder "ADHD", however, symptoms were divided in inattentive and hyperactive-impulsive symptoms. Furthermore, three subtypes were introduced: ADHD, primarily inattentive, ADHD, primarily hyperactive/impulsive and ADHD, combined type [32, 33].

Table 1 DSM definitions of ADHD

DSM	Year US/ the Netherlands	Name of disorder	Main symptoms
II	1968	Hyperkinetic disorder of childhood	hyperactivity, short attention span, restlessness
III	1980/1982	Attention Deficit Disorder (ADD)	2 subtypes: Inattention with or without hyperactivity/ impulsivity
III-R	1987/1988	Attention Deficit Hyperactivity Disorder (ADHD)	No subtypes, prominent role of hyperactivity
IV	1994/1995	Attention Deficit Hyperactivity Disorder (ADHD)	3 subtypes: ADHD, primarily inattentive; ADHD, primarily hyperactive/impulsive; ADHD, combined type
IV-TR	2000/2001	Attention Deficit Hyperactivity Disorder (ADHD)	3 subtypes: ADHD, primarily inattentive; ADHD, primarily hyperactive/impulsive; ADHD, combined type
5	2013/2014	Attention Deficit Hyperactivity Disorder (ADHD)	No subtypes, but current presentation like mainly inattentive or hyperactive/ impulsive or combined

The latest edition of the DSM, DSM 5, became available in 2013 [4].
The Dutch translation is expected in 2014. The main differences between the DSM-IV-TR and DSM 5 are [4, 33]:

→ Patients > 17 years at least 5 out of 9 symptoms/criteria required (DSM 5)
→ Differentiation between inattentive and/or hyperactive/impulsive "presentation" (DSM 5) instead of "subtype" (DSM IV-TR).
→ Several symptoms present < 12 years old (DSM 5) instead of < 7 years old (DSM IV-TR)
→ Symptoms interfere with or reduce the quality of social, academic and occupational functioning (DSM 5)
→ ADHD symptoms can be in partial remission (DSM 5)
→ ADHD must be classified as mild, moderate of severe (DSM 5).

The adjustment of the DSM criteria in DSM 5 are conforming to new insights based on current knowledge and life course of ADHD.
For example, symptoms of ADHD may change over time: children often show signs of daydreaming, distraction and inattention sometimes

combined with hyperactivity and impulsivity. During adolescence, hyperactivity and impulsiveness often reduce whilst problems regarding inattention, lack of concentration or planning persist (Warikoo 2013). In a meta-analytic study, Faraone demonstrated that for nearly two-thirds of the children with ADHD impairing ADHD symptoms remained in adulthood [34].

When diagnosing ADHD, all relevant individual, interpersonal, familial, intellectual, educational and somatic factors as well as comorbid disorders should be described. Also, they must be taken into account when designing a treatment program for the child, the adolescent and the parents/caretakers. According to DSM, 35-67% of the children with ADHD have a form of comorbid disorder. Many forms of comorbid disorder can occur, such as a depressive, anxiety or learning disorder, autism (as opposed to previous DSM version, DSM 5 scores comorbidity of ADHD and autism), an oppositional defiant disorder, conduct disorder or substance use disorder [9, 35-40].

There is a substantial public concern about the risk of overdiagnosing and underdiagnosing ADHD. This concern is reflected in the opinion of politicians, patients and parents, psychologists and psychiatrists [41-44]. Moreover, the Committee on the Rights of the Child of the United Nations, in October 2005, expressed concerns about the increase of ADHD classifications and the high levels of prescription of psychoactive drugs for children.

Many studies have shown that ADHD can have a major impact on a patient's daily life. Patients with ADHD are at risk to quit school without a diploma, to get a lower degree compared to their intellectual capacities or to lose their work. Families with an ADHD-family member experience more stress and conflicts. The risk of divorce among parents of ADHD children is higher. Parents of ADHD children tend to take more time off from their work. Children and adolescents with ADHD have poorer social relations with peers. Health care consumption and expenditure are higher in patients with ADHD than in normal controls. They are also more prone to injuries and drugs use or abuse is higher [9, 45-72].

Treatment of ADHD is focused on biological, environmental and psychosocial functioning. It is very important to discuss with the patient and with parents/caretakers which problems or symptoms need to be treated and in which setting (home, school, work, sport) and in which

order. Psycho-education about the disorder, the treatment options, the prognosis and the risks are supposed to be essential with respect to outcome. According to the Dutch national protocol, preferred treatment options are psycho-education and medication [28].

Other treatment options include parent management training, family therapy, individual or group psycho-therapy, help at school or coaching, diet (restricted elimination diet, artificial food colour exclusion or free fatty acid supplementation), cognitive training or neurofeedback [73]. In an extended meta-analysis of randomised controlled trials of nonpharmacological interventions, Sonagu-Barke (2013) found that only free fatty acid supplementation had a small effect in reducing symptoms of ADHD. Reducing artificial food colour only had effect in those with food sensitivities.

For ADHD symptoms, psychopharmacological treatment is one of the most effective treatment options currently available [9, 28]. Different types of medicine are prescribed for the treatment of ADHD: immediate or extended release stimulants such as methylphenidate or dexamphetamine, atomoxetin, tricyclic anti-depressant (TCA) or clonidine [3, 9, 28, 74-77, www.kenniscentrum-kjp.nl].

Prior to 2003, the Dutch authorities only approved methylphenidate immediate release (MPH IR, Ritalin®) for the treatment of patients 6-18 years old with ADHD and compounded dexamphetamine (Dexedrin®) for patients older than 3 years. Nortryptiline (Nortrilen®) and clonidine (Dixarit®) were used off-label. Later on, new long-acting medicines for ADHD treatment were assessed and approved to enter the Dutch market: in 2003, methylphenidate extended release (MPH-ER, Concerta®), in 2005 the non-stimulant atomoxetine (ATX, Strattera®), and in 2007 methylphenidate extended release (Medikinet CR® and Equasym XL®). Studies conducted in several countries, including the Netherlands, have shown a strong increase during the last two decades in prevalence and incidence in use of ADHD medication among preschoolers and school aged children, especially among boys between 6-12 years old, and among adults [78-93].

There is still much public debate about causes of the prescription rate increase, some of which are suggested are: a higher reference rates by the general practitioner, a better recognition of the disorder, increase in total

number of patients with ADHD, introduction of long acting ADHD medication or a tendency to earlier pharmacological treatment.

In the United States, the introduction of extended-release drugs increased drug prescription dramatically in children and adolescents as well as in adults [87, 92]. Possible positive effects of the introduction of extended release drugs are the increase of the compliance for ADHD drug use and the long term outcome in children and adults [34, 94-97]. One of the disadvantages of the new extended release drugs are the high costs. In The Netherlands, the majority of insurance companies did not cover the costs of extended release drugs.

Table 2 ADHD medication and year of availability

	Year of introduction International (I) or Netherlands (N)	**Effect neurotransmitter**	**Type of medication**
Methylphenidate IR (MPH IR, Ritalin®)	1954 (I)	► DA	Stimulant
Dexamphetamine (Dexedrin®)	1935 (I)	► DA	Stimulant
Nortryptilin (Nortrilen®)	1963 (I)	► NA	Tricyclic antidepressant
Clonidine (Dixarit®)	1966 (I)	◄ NA central alpha 2 adrenerge agonist	Anti-hypertensive drug
Methylphenidate extended release (Concerta®, MPH-ER)	2003 (N)	► DA	Stimulant
Atomoxetine (Strattera®, ATX),	2005 (N)	► NA	Noradrenergic reuptake inhibitor
Methylphenidate extended release (Medikinet CR® and Equasym XL®)	2007 (N)	► DA	Stimulant

Like many other countries, the Netherlands has a multi-cultural society, where family income is not equally divided among the different ethnic groups. It is therefore possible that ethnic background may influence use or using pattern of immediate or extended release ADHD medication. Not only lower income may influence medication use, but also culturally determined factors may play a decisional role, such as feelings of shame, ignorance of recognition of mental problems by parents and teachers and prejudices to mental disorders or treatment [98-100]. Little is known about

the effect of the introduction of new long acting ADHD medication, including extended release methylphenidate (Concerta®) in 2003 and atomoxetine (Strattera®) in 2005 on use and using patterns and the influence of ethnic background on use and using patterns in the Netherlands. Further, little is known about changes in prescription of ADHD medication in adults in the Netherlands.

Apart from the above mentioned public debate about the causes of increased prescription rates, there is also wide political and public debate about the psychopharmacological treatment ADHD. Firstly, there is disagreement about the short or long term side-effects of medication use affecting growth, weight, the functioning of the cardiovascular system and on the risk of cancer [101]. Secondly, debate centers around the question whether medication could protect an ADHD patient from developing other disorders, such as depression or anxiety. Thirdly, it is unclear if medication increases or decreases the risk of accidents, substance (ab)use or criminality [59, 70, 101, 102].

Previous studies have shown that those with ADHD or treated with ADHD medication are more prone to injuries. Compared to children and adolescents without ADHD or not treated with ADHD medication, the number and severity of accidents and hospital admissions is higher [51, 53, 54, 56-58, 61, 62, 65, 66].

Several factors can cause the increased risk of injuries, such as motor problems that are known to be associated with ADHD, ADHD related central nervous system symptoms and the core symptoms of ADHD (hyperactivity, impulsivity and attention problems). These factors allegedly contribute to unintentional injuries [103, 104]. Children with fine or gross motor problems, balance problems or problems with handwriting may benefit from use of stimulants [105-107]. The incidence rate of injuries may therefore decrease by using stimulants but studies supporting this argument have not been published yet. Little is known so far about the question whether psychotropic comedication modifies the risk of injuries in children and adolescents treated with ADHD medication [66].

ADHD is also associated with substance use, abuse and dependence [59, 65, 67, 71, 72, 108-110]. Recent meta-analyses confirmed that childhood ADHD is indeed a risk factor for substance use (nicotine, alcohol and marijuana), abuse or dependence (nicotine, alcohol, marijuana and cocaine) later in life [71, 72]. Despite its proven efficacy and increase in use, several concerns

and controversies regarding the use of stimulant medication exist. It remains unknown whether stimulant treatment modulates the established association between ADHD and the subsequent risk for addiction problems and substance use [111]. Meanwhile, there is evidence that stimulant use does not increase or alter the risk for substance use later in life but perhaps protects from substance use [112,113]. Little was known about the association between stimulant use and substance use or abuse in the Netherlands.

Thesis Objectives

1

The first objective is to describe patterns of the use of ADHD medication in the Netherlands in relation to the introduction of extended release ADHD medication and patient characteristics such as age, gender or ethnic background.

2

The second objective is to investigate short and long term outcomes of the use of ADHD medication, including the risk of injuries and the association with illicit drug use.

Thesis outline

The two specific objectives are divided in the following Chapters:

In the study described in **Chapter 2.1** the initial use of ADHD medication is investigated using data obtained from Dutch community pharmacies. Changes over time are described regarding incidence of prescriptions of ADHD drugs and the prescription profiles of patients younger than 45 years starting treatment with these medicines between 2001 and 2006 as well as effects of introduction of extended-release formulation of methylphenidate in 2003 and atomoxetine in 2005, which both increased treatment options.

In **Chapter 2.2** changes in patterns of ADHD medication use and in determinants thereof are assessed among children, adolescents and adults (<45 years), who all started ADHD medication since the introduction of extended release methylphenidate and atomoxetine. Usage patterns such as continuation, discontinuation, switching and addition of ADHD medication are evaluated at three, six and twelve months after initiation for three separate time-cohorts.

The study described in **Chapter 2.3** focuses on native Dutch, Moroccan, Turkish and Surinam patients and their differences with regard to initiating and discontinuation of ADHD medication. These groups constitute of ADHD patients, aged younger than 19 years and who are diagnosed between January 1999 and December 2010 at Altrecht. Differences are measured for ethnicity and adjusted for age, gender and socio economic status.

The study in **Chapter 3.1** describes differences in incidence of hospitalisation due to injuries, stratified for age and sex and compared to prior, during and after exposure to ADHD drugs. For this study a random sample of 150,000 persons (0-18 years) was obtained from the Dutch PHARMO Record Linkage System. An ADHD medication cohort as well as an up to six age/sex/index date sampled control cohort with no history of ADHD drug use was formed. Further, the influence of age, gender and comedication on this outcome is assessed.

Chapter 3.2 reports the results of a study that focuses on the association between stimulant treatment and life time or daily drug use in adults who were diagnosed with ADHD as a child or adolescent. Life time and

daily drug use is investigated in relation to gender, IQ, psychological treatment, age at the time of ADHD diagnosis and comorbid externalizing and internalizing disorders, For this analysis, data of children and adolescents was used who were diagnosed between January 1984 and December 2004 at the Department of Child and Adolescent Psychiatry at the University Medical Centre of Utrecht, the Netherlands. They were traced from September 2006 until February 2010. The data was provided by the Department of Clinical Child and Adolescent Studies at Leiden University and obtained using questionnaires asking about medication use and life time and daily drug use.

The general discussion in **Chapter 4** summarises the results of the different studies and puts the results into a broader context. It describes clinical perspectives and makes suggestions for future research.

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2

Prescription patterns of ADHD medication

2.1

33

Trends in incidence and characteristics of children, adolescents and adults initiating immediate- or extended-release methylphenidate or atomoxetine in the Netherlands during 2001-2006

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Abstract

Background Previous Dutch studies showed increasing psychostimulant use, especially methylphenidate immediate-release (MPH-IR), between 1995 and 2003. In 2003 the extended-release (ER) formulation of MPH and in 2005 atomoxetine (ATX) were introduced in the Netherlands, which increased treatment options.

Objective The aim of this study was to describe the change in incidence of attention-deficit/hyperactivity disorder (ADHD) drugs and the prescription profiles of patients younger than 45 years starting treatment with these medicines between 2001 and 2006.

Methods Data were obtained from Dutch community pharmacies as collected by the Foundation for Pharmaceutical Statistics, covering 97% of all dispenses for prescription medicines to outpatients in The Netherlands.

Results The overall incidence of ADHD drugs use increased 6.5-fold from 2001 to 2006 in men as well as in women. The absolute incidence was highest among 6- to 11-year-old boys. The percentage of first-time MPH-IR users decreased from 98.3% in 2001 to 75.9% in 2006. Likewise, MPH-ER use increased from 0% in 2001 to 18.9% in 2006 and ATX use increased from 0% in 2001 to 3.9% in 2006. The new nonstimulant drug ATX was prescribed more often to adults if they had been previously treated with selective serotonin reuptake inhibitors (SSRIs), benzodiazepines or antipsychotics. Youngsters < 17 years initiated on ATX were often previously treated with antipsychotics or clonidine/guanfacine.

Conclusion These findings demonstrate an increase in incidence in use of ADHD drugs between 2001 and 2006 in the Netherlands. The major proportion of all treated patients comprised boys, 6-11 years old; most of them were treated with MPH-IR. In a few years time, the use of extended-release drugs as part of all ADHD drugs prescriptions increased considerably, despite the lack of full reimbursement of these extended-release drugs. Psychostimulants and atomoxetine in children, adolescents, and adults are probably used to address different treatment needs.

Introduction

Attention-deficit/hyperactivity disorder (ADHD) is a neurobiological psychiatric disorder that occurs in childhood, adolescence and adulthood. The prevalence of ADHD among 0-18 year olds is estimated at 3.0-7.5% [1] and is three times higher among boys compared to girls in the general population [1]. The prevalence among adults is estimated between 1% [2] and 4.1-4.7% [3-5] and is possibly higher among men [4], although others found that the prevalence in men and women is equal [2,3,6].

In the last decade, many different aspects of ADHD have been studied worldwide, and concerns have been raised about the increase in diagnosing ADHD, the rise in stimulant use for the treatment of ADHD, and the lack of follow-up research on long-term effects of these drugs. In many countries, the use of stimulants for the treatment of ADHD has increased substantially over the previous two decades [7-14]. An increase is not only found among school-aged children [7], but also among preschoolers [8,13] and adults [15,16]. In the Netherlands, this increase was reported by several pharmacoepidemiological studies among children younger than 18 years, conducted between 1995 and 2003 [10,17,18]. Schirm et al. [10] found an increase of the prevalence of immediate-release stimulants of 1.5/1000 in 1995 to 7.4/1000 in 1999. Between 1995 and 2001 the use of all psychotropic medication among boys and girls younger than 18 years doubled, largely due to use of immediate-release stimulants by 5-14 year old boys [17]. Also, Faber et al. [18] found a two-fold increase in prevalence of immediate-release stimulants use from 6/1,000 in 1998 to 12/1,000 in 2002. Until 2003, short-acting stimulants such as methylphenidate immediate-release (MPH-IR, Ritalin®) and dexamphetamine (Dexedrine®) were available for the treatment of ADHD. In 2003, MPH extended release (MPH-ER, Concerta®) and in 2005 atomoxetine (ATX, Strattera®), a non-stimulant, as long-acting medication for the treatment of ADHD were introduced to the Dutch market. Both new medicines are, such as MPH-IR, approved for use in children 6-18 years old with ADHD. Atomoxetine is also approved for adults, although only for those patients who have been previously treated with ATX during childhood or adolescence. In the United States there was a dramatic increase in use of extended-release drugs after their introduction, especially in the paediatric (0-19 years), but also in the adult (> 20 years) population between 2000 and 2005 [16].

To our knowledge, no studies in the Netherlands have assessed the effect of the introduction of these new treatment options on the use of ADHD medication. Little is known about the extent and patterns of use of ADHD medication in adulthood. Therefore, the objective of this study was to assess trends in the incidence of ADHD drug use in the Netherlands in the period 2001-2006 and in the prescription profiles of ADHD drug users.

Methods

Setting

Data were obtained from the Foundation for Pharmaceutical Statistics (Stichting Farmaceutische Kengetallen, SFK). As of 1990, SFK has been collecting dispensing data from a growing number of community pharmacies in the Netherlands. In 2001, the catchment area of SFK consisted of 1,629 community pharmacies in both rural and urban areas all over the Netherlands, representing 90.7% of the total number of Dutch pharmacies. In 2006 coverage had increased to 92% the total number of Dutch pharmacies and 97% of the Dutch population [19]. For this study, we used data from those 745 pharmacies with a complete medication history of the patients from 2001 to 2006. Because the majority of patients in the Netherlands designate a single pharmacy to fill prescriptions from general practitioners or medical specialists, dispensing histories provide an almost complete account of prescription drug exposure in time [20].

Study medication and population

We identified all patients born after 1960 (i.e., < 45 years of age) that have been dispensed at least one prescription between January 2001 and December 2006, for drugs approved for use in the treatment of patients with ADHD (MPH-IR and MPH-ER, ATX, dexamphetamine). From here on, we will refer to these drugs as "ADHD drugs". Information about the prescribed medication contained patient identification (anonymous), dispensing date, number of units dispensed, and prescribed daily dose. For the present study, only incident users of an ADHD drug were included, where incident use was defined as having no ADHD drug dispensed in the prior 6 months. All patients were required to have at least 6 months of history in the SFK database prior to this prescription date.

Data analysis

For each year between 2001 and 2006, we calculated the incidence of ADHD drug use per 10,000 inhabitants by dividing the number of incident users per calendar year by the midyear population size of the corresponding year. The number of incident users per calendar year was corrected for the actual number of pharmacies in the Netherlands using a multiplication factor. Furthermore, the midyear population size of the corresponding year was corrected for the coverage provided by community pharmacies in the Netherlands. Data about number of inhabitants was provided by Statistics Netherlands [21]. The incidence was estimated separately for males and females in the four age cohorts: 0-5 years; 6-11 years; 12-17 years, and 18-44 years.

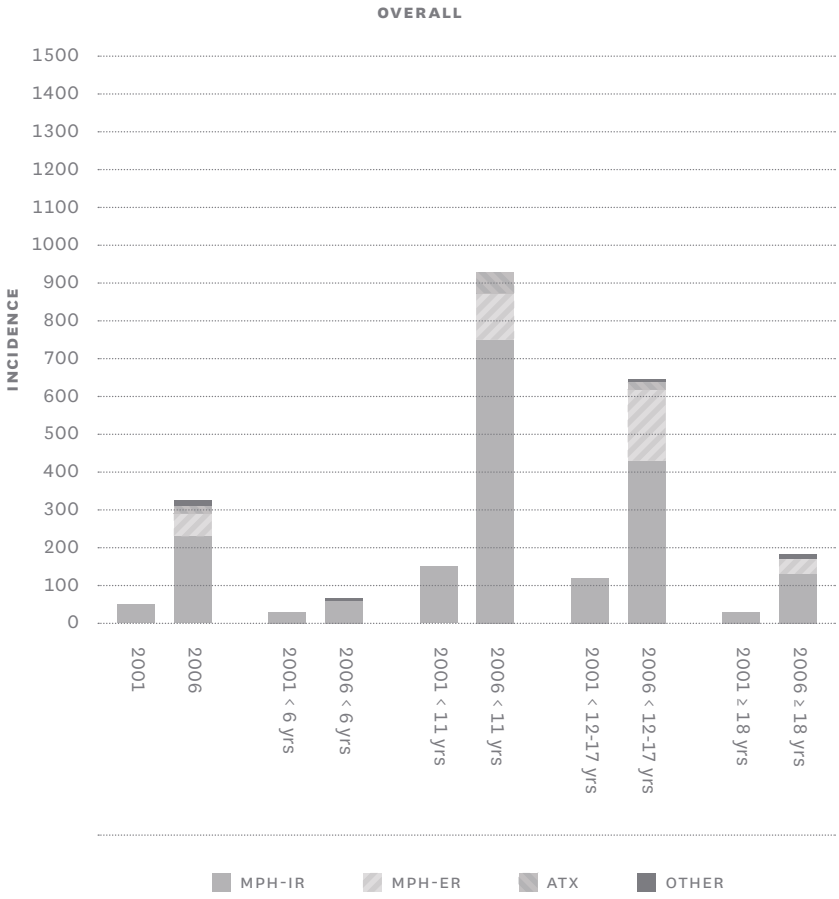
For each patient, we assessed the use of other psychotropics during the 6 months prior to ADHD treatment initiation. Drugs of interest were antipsychotics (typical and atypical), antidepressants (tricyclic, selective serotonin reuptake inhibitors [SSRI]), clonidine/guanfacine, drugs used in addictive disorders, lithium, benzodiazepines, and antiepileptic drugs (AEDs).

Differences with respect to psychotropics used prior to ADHD drugs between 2001 and 2006 were tested by means of a chi-squared test. We tested for differences by means of a chi-squared test between age groups, type of ADHD drug, and use of psychotropics, used prior to the start of that specific ADHD drug in 2005 and 2006. By that time, the newer extended-release ADHD drugs had been introduced. Differences were considered significant at $p < 0.05$ (two-tailed).

Results

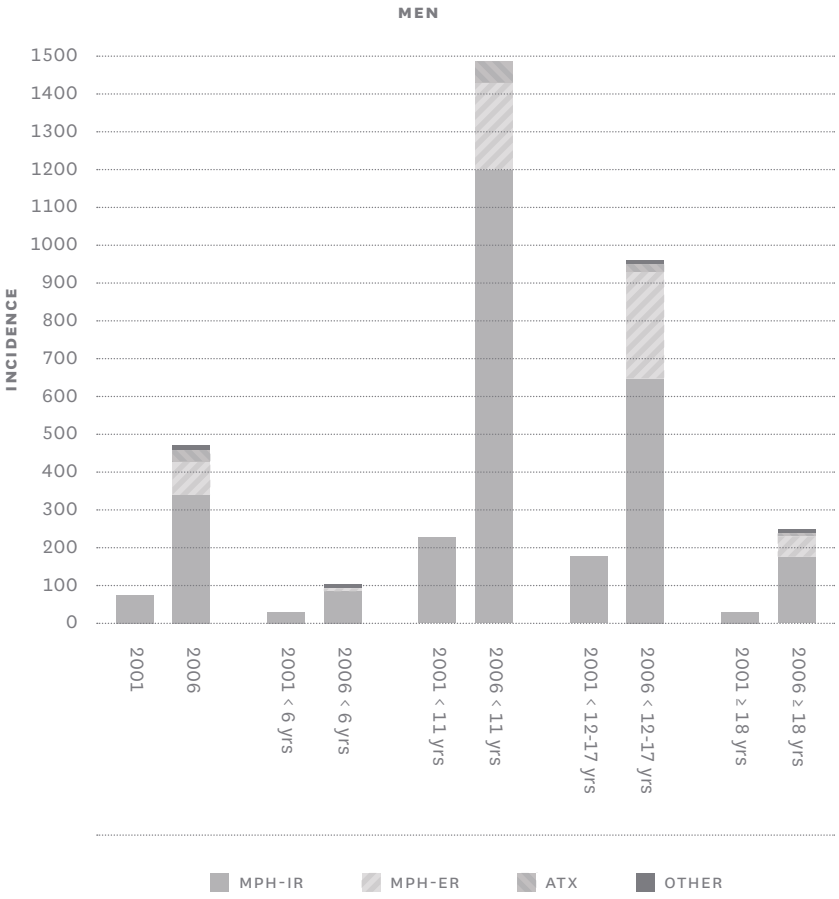
We identified 738,978 prescriptions for psychostimulants for 62,098 unique patients, of whom 34,335 (55%) were incident users. The overall incidence of ADHD drug use among males and females aged < 45 years increased 6.5-fold from 47.5 /100,000 (95% confidence interval [CI], 45.5-49.5/100,000) in 2001 to 309.6/100,000 (95% CI, 306.1-313.2/100,000) in 2006. This increase was the same in men and women, although the absolute incidence was 2.7-fold higher among men (68.6/100,000; 95% CI, 65.3-72.0/100,000) in 2001 to 447.4/100,000 (95% CI, 441.7-453.7/100,000) in 2006) than among women (25.6/100,000; 95% CI 23.6-27.8/100,000) in 2001 to 167.7/100,000 (95% CI, 164.0-171.5/100,000) in 2006). A five-fold increase in incidence is found among MPH-IR users for all ages (46.7/100,000; 95% CI 44.7-48.7/100,000) in 2001 to 234.6/100,000 (95% CI, 231.5-237.7/100,000) in 2006). The absolute incidence in 2006 was highest among boys aged 6-11 years (1,457.1/100,000; 95% CI 1,426.7-1,489.2/100,000). The (overall) increase in incidence was lowest among children < 6 years (2.9 times; 2001 20.9/100,000, 95% CI, 17.3-25.1/100,000 and 2006 59.7/100,000, 95% CI, 55.1-64.4/100,000). After introduction of extended-release ADHD drugs, the percentage of MPH-IR incident use compared to extended-release drug use declined between 2001 and 2006. Especially male and female adolescents were likely to be initiated on MPH-ER (**Figure 1, 2, 3**). Between 2001 and 2006 the relative percentage of MPH-IR initiations compared to all initiations decreased from 99.6% to 60.1%, although absolute number of starters of MPH-IR increased during the whole study period. The relative percentage of MPH-ER increased to 33.2% and of ATX to 6.1% (data not shown).

Figure 1 Overall incidence of attention-deficit/hyperactivity (ADHD) drug use per 100,000 inhabitants in the Netherlands in 2001 and in 2006.



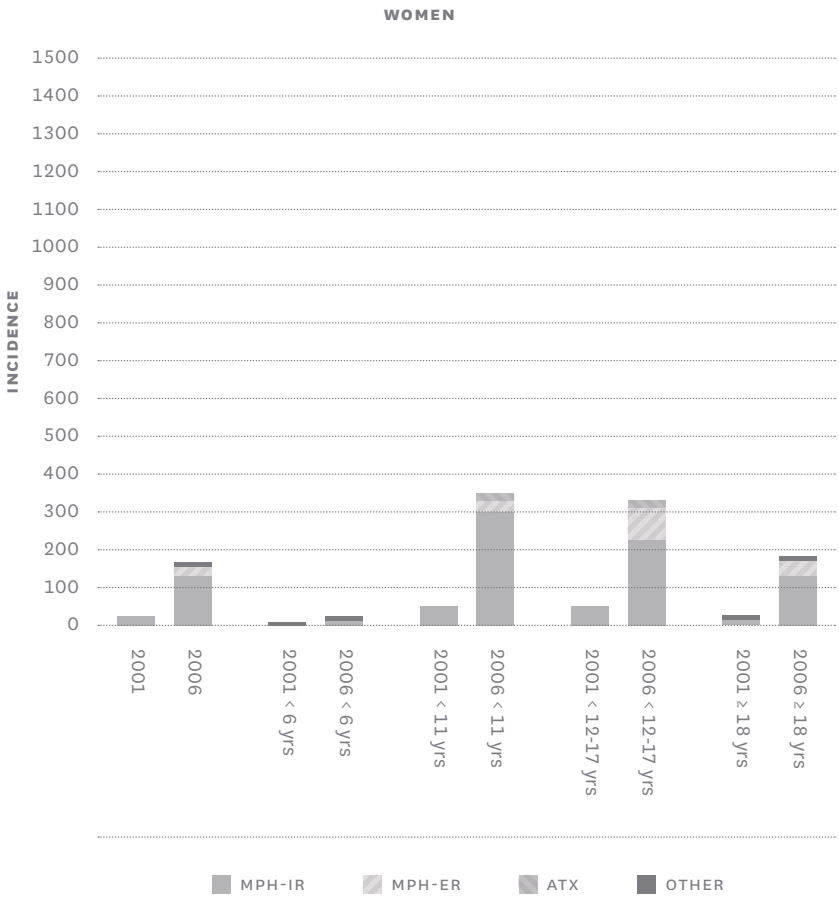
MPH-IR methylphenidate immediate-release
MPH-ER methylphenidate extended-release
ATX atomoxetine

Figure 2 Overall incidence of attention-deficit/hyperactivity (ADHD) drug use per 100,000 men in The Netherlands in 2001 and in 2006.



MPH-IR methylphenidate immediate-release
MPH-ER methylphenidate extended-release
ATX atomoxetine

Figure 3 Overall incidence of attention-deficit/hyperactivity (ADHD) drug use per 100,000 women in the Netherlands in 2001 and in 2006.



MPH-IR methylphenidate immediate-release
MPH-ER methylphenidate extended-release
ATX atomoxetine

The characteristics of the patients initiated on ADHD drugs are shown in Table 1. Use of any psychotropic prior to the start of MPH or ATX was highest among adults (41.5%), and mainly comprised antidepressants (25.4%, of which SSRIs 17.0%), and benzodiazepines (23.9%). Use of antipsychotics (10.4%) and clonidine/guanfacine (5%) was highest among children younger than 6 years.

Table 1 Characteristics of the incident users of ADHD drugs, 2001-2006

Characteristic	**Total N=34,335 100%**		**<6 years N=1,056 3.1%**		**6-11 years N=12,875 37.5%**		**12-17 years N=8,334 24,3%**		**>18 years N=12,070 35.2%**	
	N	**%**	**N**	**%**	**N**	**%**	**N**	**%**	**N**	**%**
Sex										
Male	25,455	(74.1)	895	(84.8)	10,592	(82.3)	6,452	(77.4)	7516	(62.3)
Female	8,880	(25.9)	161	(15.2)	2,283	(17.7)	1,882	(22.6)	4,554	(37.7)
Psychotropics use (in 6 months prior to initiation)										
No psychotropic drugs	27,013	(78.7)	880	(83.3)	11,718	(91.0)	7,360	(88.3)	7,055	(58.5)
Any psychotropic drugs	7,322	(21.3)	176	(16.7)	1,157	(9.0)	974	(11.7)	5,015	(41.5)
Anti psychotics	2,356	(6.9)	110	(10.4)	755	(5.9)	483	(5.8)	1,008	(8.4)
typical	1,202	(3.5)	88	(8.3)	364	(2.8)	218	(2.6)	532	(4.4)
atypical	1,332	(3.9)	28	(2.7)	427	(3.3)	287	(3.4)	590	(4.9)
Antidepressants	3,417	(10.0)	6	(0.6)	86	(0.7)	264	(3.2)	3,061	(25.4)
TCA	476	(1.4)	1	(0.1)	27	(0.2)	37	(0.4)	411	(3.4)
SSRI	2,297	(6.7)	3	(0.3)	51	(0.4)	187	(2.2)	2,056	(17.0)
Clonidine/ guanfacine	566	(1.6)	53	(5.0)	261	(2.0)	198	(2.4)	54	(0.4)
Drugs used in addictive disorders	298	(0.9)	1	(0.1)	1	(0)	2	(0)	294	(2.4)
Lithium	64	(0.2)	0	(0)	0	(0)	0	(0)	64	(0.5)
Benzodiazepines	3,134	(9.1)	17	(1.6)	93	(0.7)	136	(1.6)	2,888	(23.9)
AEDs	419	(1.2)	15	(1.4)	136	(1.1)	67	(0.8)	201	(1.7)

Abbreviations:
ADHD attention-deficit/hyperactivity disorder
TCA tricyclic antidepressant
SSRI serotonin reuptake inhibitors
AEDS antiepileptic drugs

Table 2 shows the psychotropics used during the 6 months prior to the start of MPH-IR and MPH-ER and ATX in 2005 and 2006 after introduction of the extended-release medicines. Adults received the highest percentage of other psychotropics, mainly SSRIs and benzodiazepines, before starting an ADHD drug. Among youngsters, aged 0-17 years, clonidine/guanfacine, typical and atypical antipsychotics were used significantly more often before starting ATX. Patients starting on ATX had a higher prevalence of use of almost all other psychotropics compared to MPH-IR and MPH-ER starters ($p < 0.05$).

Table 2 Psychotropic drugs used 6 months prior to initiation of ADHD drugs in 2005/2006 after introduction of MPH-ER en ATX (N=20,780)

		MPH- IR		MPH-ER		ATX	
		N	%	N	%	N	%
0-17 years	Typical antipsychotics	599	(3.0)	40	(2.0)	30	(7.1)
	Atypical antipsychotics	607	(3.1)	89	(4.4)	4	(11.0)
	TCA	51	(0.3)	8	(0.4)	6	(1.4)
	SSRI	212	(1.1)	22	(1.1)	4	(1.0)
	Clonidine/guanfacine	450	(2.3)	38	(1.9)	24	(5.7)
	benzodiazepines	226	(1.1)	17	(0.8)	2	(0.5)
	AEDs	194	(1.0)	18	(0.9)	6	(1.4)
>18 years	Typical antipsychotics	480	(4.7)	34	(3.0)	9	(7.0)
	Atypical antipsychotics	504	(5.0)	59	(5.2)	15	(11.7)
	TCA	340	(3.3)	23	(2.0)	9	(7.0)
	SSRI	1.804	(17.7)	147	(12.9)	20	(15.6)
	Clonidine/guanfacine	45	(0.4)	7	(0.6)	2	(1.6)
	Benzodiazepines	2.544	(25)	195	(17.1)	34	(26.6)
	AEDs	166	(1.6)	10	(0.9)	6	(4.7)

Abbreviations:

ADHD	attention-deficit/hyperactivity disorder
MPH-ER	methylphenidate extended-release
MPH-IR	methylphenidate immediate release
ATX	atomoxetine
TCA	tricyclic antidepressant
SSRI	serotonin reuptake inhibitors
AEDS	antiepileptic drugs

Discussion

This study showed a considerable change from 2001 to 2006 in the incidence and the pattern of prescribing ADHD drugs in the Netherlands.

A large increase in incidence of psychostimulant prescription as found in other (inter)national studies was confirmed by our study and was associated with gender and age [7-18]. Incidence increased most in boys, but also in females, young children and adults. A recent Dutch study by van Dijk et al. [22] confirmed a rise in ADHD drug prescription and diagnosing between 2002 and 2007 in boys and girls. Most patients were male in this study. Safer et al. [23], Schirm et al. [10], Vinker et al. [12] and Castle et al. [16] also concluded that there is an increase in use and prescription rate of stimulants among girls and women. The rapid growth in treatment with stimulants among girls is probably caused by better recognition of ADHD -mainly attention-deficit disorder (ADD) symptoms in girls by parents, teachers, and health-care professionals and higher diagnostic rates [24]. Rising prescriptions of ADHD drugs to the very young children are of public concerns [13] In our study, however, the increase in incidence was lowest among children <6 years. Prior to the start of psychostimulants in these young children, we found a high percentage of (off-label) prescriptions of typical antipsychotics, supposing a need for a psychopharmacological intervention due to severe behavioural symptoms in these youngsters. Recognition and referral increased in adults by a greater awareness among themselves and health-care professionals, as well as the development of diagnostic tools, medication guidelines and treatment opportunities [25-27]. A meta-analysis of Faraone et al. [28] showed that the persistence of ADHD from adolescence to adulthood (age 25) was almost 15% for the strict Diagnostic and Statistical Manual of Mental Disorders, 4TH edition (DSM-IV) [29] criteria. Although in partial remission, two thirds of the adult ADHD patients showed clinical impairment.

The prescription of MPH-ER and ATX was mainly due to the large increase in prescriptions of all ADHD drugs in our study. The relative decrease in use of MPH-IR, although the absolute numbers of prescriptions increased, was also found in the United States between 1996 and 2005 [16,30]. The rapid increase of prescriptions of extended-release drugs can be explained by perception of advantages by either patients, parents or doctors over MPH-IR with respect to less rebound effects, once-a-day administration, less stigmatisation at school, or reduced potential for

drug misuse [31-33] or other side effects and 24-hour coverage of ADHD symptoms by ATX. Substance abuse is a well-known co-morbid disorder in adolescents and adults with ADHD [24]. Immediate-release stimulants are at a greater risk to be misused, suggesting that MPH-IR should not be prescribed in drug abusers or an at-risk population [33]. Both male and female adolescents in our study, who go to secondary school at the age of 12 years in the Netherlands, were more likely to use MPH-ER comparing to other ages and may benefit of these advantages. Use of MPH-ER is associated with a greater continuity of treatment than immediate-release formulations in youth [31,32] and adults [34]. Scientific evidence, full reimbursement, but also marketing efforts, are as influential in this respect [35]. In the Netherlands, MPH-ER and ATX in general are not fully reimbursed despite the lobbying efforts of patient pressure groups and health-care professionals to persuade government, health-care insurers and Members of Parliament. Therefore prescription seem to be restricted to those who actually can afford this particular medication.

ATX was prescribed more often to children and adolescents when they had a patient history of antipsychotic or clonidine/guanfacine use. Antipsychotics in general are not recommended for the treatment of ADHD. Clonidine and guanfacine are third-line agents in the treatment of ADHD [36]. This suggests that ATX is used as a last resort. Is has been described in literature that newly introduced drugs are often prescribed to specific group of patients who, for example, did not respond well enough or with unpleasant side effects to the so called “old established drugs”. They are also prescribed to those who may benefit less from drugs in general or to patients as first–line drug because of side effects and risk profile [35,37]. Use of antipsychotics, SSRIs and benzodiazepines prior to the initiation on ATX in adults suggests a change in diagnosis of those patients toward ADHD or using it as a last resort or the presence of other more severe co-morbid disorders. This is in line with findings of Brunt et al. [38] who found that ATX was prescribed more often as treatment initiation to adults with ADHD with a prior diagnosis of bipolar disorder, alcohol dependence, previous use of antipsychotics or antidepressants compared to stimulants.

There are several limitations in this study. We did not have any information on the indication of ADHD drug use. Although MPH is the first choice pharmacotherapeutical intervention in the treatment of ADHD for children, adolescents [36] and adults [25,39], it can also be prescribed to adults for somatic problems such as a delirium or during

the palliative phase of a somatic disorder [40,41]. Results of the study can also be affected by the impossibility to analyse the data of dexamphetamine. Dexamphetamine is only available as compounded capsules prepared in a pharmacy, and its prescription can not be traced through the SFK. Little is known about the influence of studies or guidelines on ADHD drug treatment published in professional journals, (inter)national conventions or marketing strategies of pharmaceutical companies on the prescribing behaviour of health-care professionals or the perception on ADHD symptoms and medication of patients, parents, or teachers [35]. These factors may contribute to a more tolerant attitude towards ADHD drugs. Data for this study were obtained from a subset of 745 pharmacies having complete medication data during the study period. It seems unlikely this has resulted in selection bias because reasons for pharmacies not having a complete medication history are likely to be administrative only.

Conclusion

Between 2001 and 2006, a large increase was observed in the prescription rates of ADHD drugs in the Netherlands, not only in children and adolescents but also in adults. Shortly after their introduction and despite of the high costs, MPH-ER and ATX conquered an important share of the market. Clinicians, patients, and parents seem to make quite often a choice for extended-release drugs or non-stimulant ADHD drugs.
The economic implications of not only the rise of the prescriptions of ADHD drugs but also of untreated ADHD should be subject of future research. More research about factors influencing choices between immediate- or extended-release drugs is necessary. More research on efficacy and safety of ADHD drugs in adults and preschoolers is needed too. We only analysed data of adults from 18-45 years. It would be interesting to extend this study to elderly persons, as ADHD symptoms can even occur up to the age of 75 years [6].

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Less discontinuation of ADHD drug use since the availability of long acting ADHD medication in children, adolescents and adults under the age of 45 years in the Netherlands

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Abstract

Background Treatment options for ADHD in the Netherlands have increased with the introduction of the extended release formulations of methylphenidate (MPH ER, Concerta®) in 2003 and atomoxetine (ATX, Strattera®) in 2005, but data on the effect on drug usage patterns are scarce.

Objective to describe changes in patterns of ADHD medication use and determinants thereof among children, adolescents and adults (< 45 years) starting ADHD medication since the introduction of MPH ER and ATX.

Methods Data were obtained from Dutch community pharmacies as collected by the Foundation for Pharmaceutical Statistics, covering 97% of all dispenses for prescription medicines to outpatients in the Netherlands. Usage patterns (continuation, discontinuation, switching and addition) of ADHD drugs were evaluated at 3, 6 and 12 months after initiation for three separate time cohorts (patients starting ADHD medication in Jan-Dec 2002, Jan 2003-June 2004, respectively July 2004-Dec 2005).

Results We found that between 2002 and 2006 most ADHD drug users were initiated on methylphenidate IR. Discontinuation of any ADHD drug treatment decreased over time partly in favour of switching and addition. Discontinuation at 3 months decreased from around 33% to around 25%, at 6 months from less than 50% to almost 35%, and at 12 months from just fewer than 60% to less than 45%. Discontinuation was higher among females and in adults > 18 years. After the introduction of MPH ER and ATX (time cohort III), 16.5% of the incident ADHD drug users switched their medication and almost 9% added an ADHD drug to the prior ADHD drug

Conclusion Discontinuation of incident ADHD drug use is high after 3, 6 and 12 months. During the study period, the incidence of discontinuation decreased because of the availability of extended-release methylphenidate and atomoxetine.

Introduction

Attention Deficit Hyperactivity Disorder (ADHD) is a neurobiological psychiatric disorder that occurs in childhood, adolescence and adulthood. The prevalence of ADHD has been estimated at 3.0-7.5% among youth [1] and between 1.0 and 4.7% among adults [2-5]. Many patients are not outgrowing their ADHD, indicating that it is a lifetime disorder requiring chronic treatment [6]. Psychopharmacological treatment is one of the most effective currently available treatment options in ADHD [7,8]. During the last decade the pharmacotherapeutic options for the treatment of ADHD in the Netherlands have widened by the introduction of extended-release formulations of methylphenidate (MPH ER, Concerta®) in 2003 and the new active molecule atomoxetine (ATX, Strattera®) in 2005. Before 2003, only methylphenidate immediate release (MPH IR, Ritalin®) was approved in the Netherlands for the treatment of patients 6-18 years old with ADHD, while dexamphetamine (Dexedrin®), nortryptilin (Nortrilen®) and clonidine (Dixarit®) were used off-label for this indication.

Studies in several countries, including the Netherlands, have shown a strong increase during the last two decades in prevalence and incidence in use of ADHD medication among preschoolers, children and adults [9-26]. US data have suggested that the average duration of psychostimulant use ranges from 5 years for middle school students [27,28] to 8 years for high school students. Dutch studies have shown a shift towards longer duration of use from 1995 to 2006 [12,17,25]. Incidences and usage patterns differ between countries and within countries because there are differences regarding use of diagnostic classification systems, practice guidelines, cultural beliefs about use of medication, reimbursement possibilities, government regulations and drug advertising [22,24,29,30]. However, little is known how treatment patterns such as continuation or discontinuation, switching and combining ADHD drugs have changed after the introduction of the newer ADHD drugs.

The objective of this study was to assess changes in ADHD medication usage patterns (continuation, discontinuation, switching and addition) and determinants thereof in children, adolescents and adults < 45 years initiated on ADHD drugs in the Netherlands since the availability of the long acting ADHD drugs MPH ER and ATX.

Methods

Setting and study population

Drug-dispensing data for this study were obtained from the Foundation for Pharmaceutical Statistics (Stichting Farmaceutische Kengetallen, SFK). As of 1990, SFK has been collecting dispensing data from a growing number of community pharmacies in the Netherlands. In 2001, the catchment area of SFK comprised 1,629 community pharmacies in both rural and urban areas all over the Netherlands, representing 90.7% of the total number of Dutch pharmacies. In 2006, coverage had increased to 92% of the total number of Dutch pharmacies and 97% of the Dutch population [31]. For this study, we used data from those 745 pharmacies with a complete medication history of the patients from 2001 to 2006. As the majority of patients in the Netherlands designate a single pharmacy to fill prescriptions from general practitioners or medical specialists, dispensing histories provide an almost complete account of prescription drug exposure in time [32]. Information about the prescribed medication contained patient data (anonymous ID, gender, year of birth), dispensing date, number of units dispensed and prescribed daily dose. From the SFK database, all patients born after 1960 (i.e. < 45 years of age) were identified with at least one prescription dispensed between January 2002 and December 2005 for a drug approved for the treatment of ADHD (methylphenidate IR and ER, atomoxetine). From here on, these drugs will be referred to as 'ADHD drugs'. The date of the first dispensing of an ADHD drug marked the start of follow-up. Only incident users of an ADHD drug were included in this study, where an incident user was defined as a patient having no ADHD drug dispensed during the 12 months prior. All patients were therefore required to have at least 12 months of history in the SFK database prior to this prescription date and also 12 months of follow-up after cohort-entry in order to be able to evaluate medication usage patterns. Three time cohorts were defined according to the year of ADHD drug initiation: I: January 2002- December 2002, II: January 2003- June 2004 and III: July 2004-December 2005.

ADHD drug usage patterns

For each included patient, all prescriptions for ADHD drugs were identified. The theoretical duration of use of each prescription was calculated by using information about the dispensing date, the number of units dispensed and the prescribed dosage regimen. For each subsequent dispensed prescription for an ADHD drug, the drug usage pattern was classified as continuation, discontinuation, switching or addition. Continuation was defined as continuing the initially prescribed ADHD drug. Discontinuation of ADHD treatment was defined as not having refilled a new prescription for any ADHD drug within 3 months after the theoretical end date of the previous prescription. Switching was defined as changing from one type of ADHD drug to another. Addition was defined as starting another type of ADHD drug while continuing the initially prescribed drug.

Data analysis

Demographic characteristics at baseline were compared between the three time-cohorts. Age was categorised in four age strata: 0-5, 6-11, 12-17 and 18-45 years.

Patients were followed up from cohort-entry to the first change in adhd treatment (discontinuation, switch, addition,) or censoring, whichever came first. The frequency of study outcomes for each time-cohort was assessed at 3, 6 and 12 months after cohort-entry. Cox regression analysis was conducted to assess the strength of the association between determinants and discontinuation and was expressed as a hazard ratio (hr) with 95% confidence interval (ci). The association between determinants (gender, age, initial adhd drug) and switching and addition was studied for time cohort iii only, because by that time both mph er formulations as well as atomoxetine were available on the Dutch market.

Results

We identified 62,098 unique patients and our study population comprised 13,489 incident users of ADHD drugs (Table 1). Overall, 72.6% were male and 44.2% were aged between 6 and 11 years of age. There were no major differences in the male/female ratio and age distribution between the three time cohorts. The absolute number of patients initiating ADHD drug treatment increased over time. The vast majority of patients (93.7%) were initiated on methylphenidate IR.

Table 1 Characteristics of incident users of ADHD drugs during 2002-2005 (N=13,489)

Characteristics	Time-cohort I Jan 2002-Dec 2002 N=1,849 (13.7%)		Time-cohort II Jan 2003-June 2004 N=5,555 (41.2%)		Time-cohort III July 2004-Dec 2005 N=6,085 (45.1%)		Overall 2002-2005 N=13,489 (100%)	
	N	%	N	%	N	%	N	%
Sex								
Male	1,288	(69.7)	4,089	(73.6)	4,412	(72.5)	9,789	(72.6)
Female	561	(30.3)	1,466	(26.4)	1,673	(27.5)	3,700	(27.4)
Age								
0-5 years	95	(5.1)	199	(3.6)	256	(4.2)	550	(4.1)
6-11 years	710	(38.4)	2,489	(44.8)	2,767	(45.5)	5,966	(44.2)
12-17 years	396	(21.4)	988	(17.8)	1,126	(18.5)	2,510	(18.6)
18-45 years	648	(35.0)	1,879	(33.8)	1,936	(31.8)	4,463	(33.1)
Type of initial adhd drug								
MPH IR	1,849	(100)	5,372	(96.7)	5,420	(89.1)	12,641	(93.7)
MPH ER	n/a	n/a	183	(3.3)	549	(9.0)	732	(5.4)
ATX	n/a	n/a	n/a	n/a	116	(1.9)	116	(0.9)

n/a not available at that time

Figure 1 shows the proportion of patients having one of the medication usage pattern events at 3, 6 and 12 months for the three time-cohorts. The number of patients continuing the initial ADHD medication decreased over time of follow-up, and this pattern was not different between the three time cohorts. After 3 months, around two-thirds of patients were still using the original ADHD drug, but at 1 year this proportion had dropped just under 40%. In contrast, continuation of any ADHD drug treatment increased from time cohort I to time cohort III with at each measurement point (3, 6, 12 months after initiation) a relative increase in continuation of 30-40%. The incidence of discontinuation of any ADHD drug was lower in the later time cohorts due to increased switching to and addition of the newer ADHD drugs. In time-cohort III, 25% of patients had an alteration of their initial treatment: in 16.5%, the medication was switched, and in almost 9% another ADHD drug was added to the initially prescribed drug. Overall, 90% of the switchers comprised MPH IR users, of whom almost 94% switched to MPH ER and 6% switched to ATX. Of the patients having an addition, 83% were MPH IR users and most of them were added MPH ER (data not shown).

Figure 1 Percentage of incident users having encountered one of the outcome events at 3, 6 and 12 months for the three time-cohorts I, II, III. Time cohort I January 2002- December 2002, time cohort II January 2003- June 2004, time cohort III July 2004- December 2005.

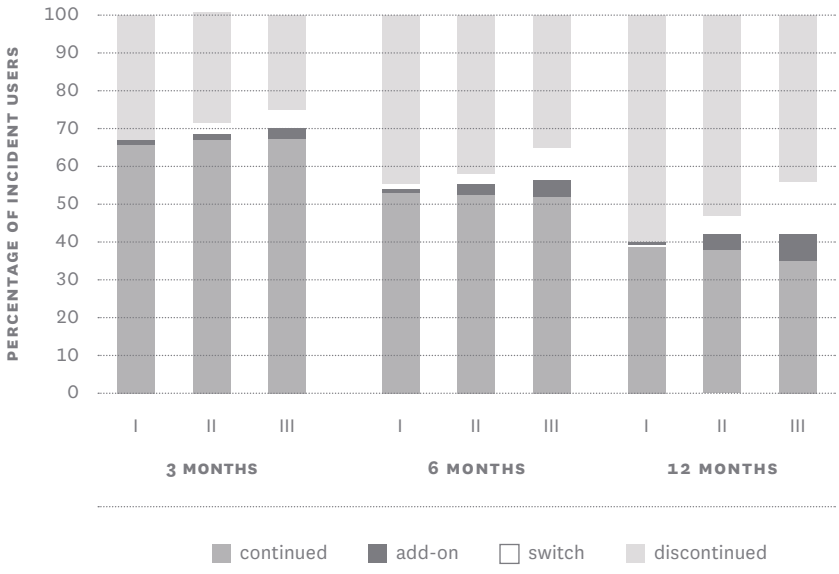

Table 2 shows that the proportion of patients of discontinuing of ADHD drug users was higher among females (72.0%) than among men (60.3%), yielding an adjusted HR of 1.09 (95% CI 1.04-1.15) and among adults > 18 years (adjusted HR 1.13, 95% CI: 1.06-1.19 vs. 12-17 year olds) in this particular study period. The influence of the determinants did not differ between the three time cohorts.

Table 2 Risk of ADHD treatment discontinuation during total follow-up (N = 13,489)

Characteristic	Number	% discontinued	Crude HR (95% CI)	Adjusted HR (95% CI)*
Time cohort				
Jan 2002-Dec 2002	1,458	78.9%	1.00 (reference)	1.00 (reference)
Jan 2003-June 2004	3,864	69.6%	0.86 (0.81-0.91)	0.98 (0.92-1.04)
July 2004-Dec 2005	3,248	53.4%	0.70 (0.66-0.75)	0.86 (0.81-0.92)
Sex				
Male	5,907	60.3%	1.00 (reference)	1.00 (reference)
Female	2,663	72.0%	1.39 (1.32-1.45)	1.09 (1.04-1.15)
Age category				
0-5 years	294	53.5%	0.64 (0.57-0.72)	0.67 (0.59-0.75)
6-11 years	2,910	48.8%	0.52 (0.49-0.56)	0.53 (0.50-0.56)
12-17 years	1,810	72.1%	1.00 (reference)	1.00 (reference)
18-45 years	3,556	79.7%	1.37 (1.29-1.45)	1.13 (1.06-1.19)

* Adjusted for other characteristics in Table 2

Discussion

First, this study showed that the discontinuation rate of treatment with ADHD drugs is high in all three time cohorts after 3, 6 and 12 months, especially among women and adults. Second, over time the discontinuation rate of any ADHD drug use decreased because of increased switching and addition following the availability of the newer ADHD drugs MPH ER and ATX.

The discontinuation frequency in our study is within the same range as found in other studies. Between 36 and 51% of the children discontinued their ADHD medication within 1 year after the start [23,33]. Only half of the children received their ADHD medication for less than 3 years [34]. On the other hand, 77% of the parents of children (6-18 years) diagnosed with ADHD reported in an online questionnaire that the length of treatment was more than 1 year [35]. In the Netherlands, a retrospective study of patients aged 6-21 years in an outpatient clinic for child and adolescent psychiatry showed that less than 10% discontinued their medication and half of the patients switched at least once between 2005 and 2006 [36]. Studies in adults also report high discontinuation rates. Only 24% of the patients initiated on methylphenidate were still on treatment after seven months [37]. About 20% of the adult ADHD patients in Norway still used their medication after 2 years between 1997 and 2003 [38].

In our study, risk of discontinuation was higher among females. This finding is in contrast with results from Faber et al. [17], who found no difference in duration of stimulant use between boys and girls, but supports data from Trip et al. [25], who found that boys tended to use their ADHD medication longer than girls. A recent Australian study [34] found a decline in duration of treatment with ADHD drugs from 2.5 years in 1990-2000 to 2 years in 2000-2006 with no difference between boys and girls aged less than 18 years. Their finding is consistent with studies by Reid et al. [13] and Barbaresi et al. [39]. Differences in outcome of discontinuation rates can be caused by study design, inclusion of different ages, the prescriber, the treatment setting, the motivation of patient and parents, duration of follow-up and as in our study the introduction of newer ADHD drugs.

In time cohort III, after introduction of MPH ER and ATX, 16.5% of the incident ADHD drug users switched their medication, mainly MPH IR to ER and almost 9%, of whom 17% was adult, added an ADHD drug to the prior

ADHD drug, mainly MPH ER to IR. This is consistent with the study of Pauw et al [36] in which eighty percent switched from MPH IR to ER.
Our hypothesis is that switching from MPH IR to ER is associated with a greater continuity of treatment than MPH IR. This is confirmed in studies in youth [40,41] and adults [42]. Switching to the non-stimulant drug ATX is probably because of side effects or too little effect of MPH IR.

There are several studies on pharmacological monotherapy versus combined therapy for ADHD in youth. Combined use of methylphenidate IR, ER or atomoxetine has not been the main subject of a study, although some data are available. Only 7% of the Australian children, 3-17 years old, received a combination of MPH IR and ER in 2004 [43]. Less than 2% of the children between 2006 and 2008 used more than one psycho-stimulant [44]. In adults, combined use of ADHD drugs was determined in 19.7% of initial atomoxetine users, in 21.0% of initial extended release stimulant users and in 23.1% of the initial immediate release stimulant users between July 2003 and June 2004 [45]. Hyperactivity predicted the combined use of ADHD medication in adults initiated on atomoxetine.

As if ADHD can be seen as a lifetime disorder, it should need chronic treatment. Medication is one of the most powerful treatment options in ADHD [6]. The high discontinuation rate in our study may reflect suboptimal treatment for ADHD. Untreated ADHD is a risk factor for traffic accidents, emergency room visits, school, work and marital problems, substance abuse and psychopathology [46-54]. Probably with the introduction of long-acting ADHD medication continuation of treatment can be optimised. In children (6-17 year) and adults, initial use of MPH ER was associated with a longer duration of treatment compared to the initial use of MPH IR [40-42]. There are indications that patients with more severe ADHD symptoms switch more rapidly to long acting drugs [55]. There are several reasons for discontinuation. Psychostimulants can have a rapid effect on ADHD symptoms and ADHD drug users can think that they are cured by the medication and stop. They can suffer from side effects or they disbelieve in the effects of medication. The type of prescriber or setting can influence their compliance. Probably, the ADHD drug user did not suffer from ADHD or other treatment opportunities were available and effective in reducing the ADHD symptoms.

Strengths of this study were that it was population based and involved a large sample of persons using ADHD medication. There are several limitations. We had no information on the indication for which ADHD

drugs were prescribed. Although methylphenidate is the first-choice pharmacotherapeutical intervention in the treatment of ADHD for children, adolescents [7,8] and adults [56,57], it can also be prescribed to adults for somatic problems [58,59]. Furthermore, persistence of ADHD treatment might have been affected by the prescriber, treatment setting or high costs of long-acting medication, which are not always covered by health insurance companies. Little is known about the influence of studies or guidelines on ADHD drug treatment published in professional journals, (inter)national conventions or marketing strategies of pharmaceutical companies on the prescribing behaviour of health care professionals or the perception on ADHD symptoms and medication of patients, parents or teachers [60]. These factors may contribute to a more or less tolerant attitude towards ADHD drugs. The Dutch clinical guideline was presented just before the introduction of atomoxetine in the Netherlands and could have influenced prescription behaviour.

In conclusion, discontinuation of ADHD drugs use is high within 1 year after initiation. It decreased over calendar time since the availability of long-acting ADHD drugs, which make it possible to switch or use more than one ADHD drug at the same time. Combined ADHD drug therapy is not very common in the Netherlands. More research on continuation, discontinuation, switching and addition must be performed after 2006 to investigate whether prescription of long-acting drugs further decreases the rate of discontinuation. Backgrounds of switching to MPH ER or ATX and effects of discontinuation of ADHD drugs on school performance, comorbidity, marital and family stress should be subject of future research.

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2.3

Differences in ADHD medication usage patterns in children and adolescents from different ethnic backgrounds in the Netherlands

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Abstract

Background ADHD medication use in children and adolescents has increased over the past decades in many countries. Differences in incidence and prevalence of ADHD medication use between ethnic groups have been reported. Whether there are also differences in usage patterns is, however, largely unknown.

Objective To determine whether there are differences in usage patterns of ADHD medication among native Dutch, Moroccan, Turkish and Surinam children and adolescents in the Netherlands between 1999-2010.

Methods A cohort of patients < 19 years diagnosed with ADHD was used to evaluate ADHD medication use. Incident use and discontinuation of ADHD medication was measured for ethnicity (native Dutch, Moroccan, Turkish and Surinam) and adjusted for age, gender and socio economic status.

Results A total of 817 children with a diagnosis of ADHD was identified. A higher proportion of ADHD diagnosed Moroccan (32%) and Turkish (42%) patients never used ADHD medication compared to Dutch natives (21%). One fifth of native Dutch and Turkish patients already used ADHD medication before the ADHD diagnosis date. Almost all patients, that used medication, around 80%, initiated on immediate release methylphenidate. Discontinuation of ADHD medication within 5 years was highest in Moroccan (HR 2.4 [95% CI 1.8-3.1]) and Turkish (HR 1.6 [95% CI 1.1-2.6]) patients. A sensitivity analysis with a postal code matched comparison between Dutch natives and non-natives showed similar results, suggesting this effect is probably not explained by socio economic status (SES).

Conclusion Differences are found in ADHD medication prescribing and use between ethnic groups. Native Dutch and Turkish patients start more frequently with ADHD medication before the ADHD diagnose date, which can be an indication of differences in either referral patterns and/or access to care. A higher percentage of Moroccan and Turkish patients never start using ADHD medication at all and if they start using medication, discontinuation rate is higher compared to Dutch natives and Surinams.

Introduction

Attention Deficit Hyperactivity Disorder (ADHD) is a highly prevalent neurobiological disorder characterized by developmentally inappropriate problems with attention, concentration, impulsivity and hyperactivity causing impairment in daily life and its presentation is influenced by psychosocial, environmental, genetic and biological factors [1-3].
The prevalence of ADHD among preschoolers is estimated at 0.5-6.5%, among children and adolescents worldwide at 5%, among adults at 1-4.7% and among elderly adults at 2.8% [4-11].

Studies in several countries, including the Netherlands, have shown a strong increase during the last two decades in prevalence and incidence of ADHD medication use among preschoolers and schoolchildren (especially among boys of 6-12 year old), and adults [12-29].

Between ethnic groups differences have been found with respect to health care consumption, costs, use or dosage of psychotropics or medication for attention deficit hyperactivity disorder (ADHD) in children and adolescents. For example, the costs for psychotropic medication for African American children, coming into contact with U.S. Child Welfare Agencies, was almost 400 dollar lower than in a white child [30].
The percentage of African-American, Latin-American, non-Hispanic black or Asian children and adolescents getting a prescription for initial ADHD medication is lower than in Caucasian Americans [23, 31-40]. Differences in prescription rate or cost do not seem to be associated with differences in effectiveness of ADHD medication, since there is evidence that ADHD medication is as effective in Caucasian as in Afro American of Latin American children or adolescents [41,42]. Also, the persistence of ADHD symptoms from child to adolescence seems to be equal in patients with different ethnic backgrounds [43]. the Netherlands are a multi-cultural society, with clear differences between different ethnic groups in income, work, education and consumption of health care [44]. In the 1960s en 1970s two large groups of immigrants of Turkish and Moroccan background came to live in European countries such as the Netherlands. Surinam was a Dutch colony until 1975 and the immigration of Surinams to the Netherlands strongly increased during the period of decolonization. Among the immigrants there is a higher prevalence of risk factors for mental disorders such as low income, low socio economic status and bad housing.

Surprisingly, despite this higher risk for mental disorders, description rates of medication for high prevalent disorders appear to be lower in immigrant groups. Wittkampf [45] showed that the prevalence of ADHD medication prescriptions in Turkish and Moroccan Dutch immigrant populations was lower compared to that of the native Dutch population. One might therefore raise the question whether this differences in medication use reflect different intervention choices that might be due to cultural background.

To our knowledge, so far little is known about differences in use and usage pattern of ADHD medication like continuation or discontinuation among subjects of different ethnic backgrounds. Lipkin [46] found that a higher dosage of stimulants was prescribed in Medicaid non-African-American and in privately insured African-American children compared to Caucasian subjects. A higher percentage of Caucasian subjects continued use of stimulants from 1995-1996 to 2003-2004 than of Hispanics or African Americans [23]. Both studies suggest that differences in prescription and usage pattern migh excist between cultural or ethnic groups.

The subject of the present study is to analyze differences in initiation and discontinuation of ADHD medication between native Dutch, Moroccan, Turkish or Surinam youths with ADHD in the Netherlands.

Methods

Setting

The Psychiatric Casus Register (PCR) collects data of approximately 117,000 patients on age, gender, psychiatric diagnosis, type of psychiatric care, date of psychiatric diagnosis and start or ending of psychiatric treatment of patients of different psychiatric institutions in the province of Utrecht, the Netherlands. These data were linked to data obtained from the Achmea Health Database. Achmea is a large health insurance company in the middle of the Netherlands. The Achmea database contains demographic details, complete medication history and hospital admission information of 1.5 million insured patients. In the Netherlands each individual is required to have a health insurance.

Study population

For this study, all patients who had a diagnosis of ADHD at Altrecht between January 1999 and December 2010 and where younger than 19 years at the time of diagnosis, were identified from the Psychiatric Casus Register. Altrecht is a large institute for mental health care, a conglomeration of psychiatric hospitals and outpatient clinics that serves about 800.000 inhabitants in the central region of the Netherlands.

These patients were subsequently linked with patients from the Achmea Health Database on date of birth, sex and postal code. Patients who could not be linked uniquely or had no information about ethnic background were excluded. Furthermore, patients where only eligible for inclusion if they had at least six months of history in the composed database before the ADHD diagnosis and could be followed for at least six months afterwards.

Ethnicity

The Achmea Health Database registers the foreign nationality of first generation Moroccan and Turkish immigrants. Second or third generation immigrants were identified by use of a special designed computer program recognizing surnames and matching it with their background. Ethnic groups were classified as “native Dutch” (Dutch, Western and other non-Western nationalities), “Moroccan”, “Turkish” or “Surinam” [45].

ADHD medication use

For each patient, all prescriptions for ADHD medication (immediate release methylphenidate (IR-MPH like Ritalin® or Medikinet®) or extended release methylphenidate (ER-MPH like Concerta®, Medikinet CR® and Equasym XL®), dexamphetamine (Dexedrin®), atomoxetine (ATX, Strattera®), nortriptyline (Nortrilen®) or clonidine (Dixarit®) were identified from the Achmea Health Database. Concerta® was introduced in the Netherlands in 2003, atomoxetine in 2005 and Medikinet CR® and Equasym XL® in 2007.

The date of the first dispensing of any ADHD medication marked the start of treatment. Patients were considered to be incident users if they had at least six months of exposure history available prior to the first prescription of an ADHD drug. Patients were considered to be prevalent users if they did not fulfill this criterion.

The theoretical duration of use of each prescription was calculated by using information about the dispensing date, the number of units dispensed and the prescribed dosage regimen. Discontinuation of ADHD treatment was defined as not having refilled a new prescription for any ADHD drug within three months (90 days) after the theoretical end date of the previous prescription.

Assessment of covariates

We assessed the use of psychotropic comedication at the time of ADHD diagnosis, as well as at 6 and 12 months after this date. Drug evaluated included typical and atypical antipsychotics, antidepressants (tricyclic other than nortriptyline and SSRIs), lithium, benzodiazepines, prometazin and anti-epileptic drugs.

Psychiatric diagnosis

Other psychiatric diagnosis of interest, coded according to the Diagnostic and Statistical Manual of Mental Disorders IV and IV-TR, were disruptive behaviour disorder (oppositional defiant disorder (ODD), conduct disorder (CD) and behaviour disorder not otherwise specified), mood disorder (depression, dysthymia, bipolar disorder), autism spectrum disorders (autism, Aspergers syndrome, pervasive developmental disorder not otherwise specified (PDD NOS)), anxiety disorders (including obsessive compulsive disorder), learning disorder and mental retardation. Diagnoses of these conditions were assessed for all patients in the study population.

Data analyses

Differences between ethnic groups with respect to sex, age of ADHD diagnosis, comorbid psychiatric disorders or psychotropic comedication were tested by means of chi-square tests. Differences were considered significant at $p < 0.05$ (two-tailed). A cumulative frequency curve was made to show the time to ADHD treatment initiation for native Dutch, Moroccan, Turkish and Surinam patients according to the ADHD diagnosis date.

Among incident users of ADHD drugs, we assessed the time to treatment discontinuation. Cox regression analysis was used to calculate hazard ratios and 95% confidence intervals for the risk of discontinuation for Maroccon, Turkish and Surinam patients compared to Dutch natives.

As social-economic status is a potential confouder, we conducted a sensitivity analysis where we matched non-native patients with ADHD with native Dutch patients by the first numbers of the postal code and did similar analyses. The postal code was used as a proxy for information about mean income per person and grade of urbanization as defined and registered by Statistics Netherlands [44].

Results

Overall, there were 7,045 patients in the Psychiatric Casus Register with any psychiatric diagnosis that could be linked with data from the Achmea database. The study population comprised 817 (11.6% of total patients) patients that had a diagnosis of ADHD and had least six months of history in the composed database before and after the date of ADHD diagnosis.

Table 1 shows that almost three quarters of the study population were native Dutch, followed by Moroccan (17.5%), Turkish (6.4%) and Surinam (2.9%) patients. There are significantly more male (77.5%) than female (22.5%) patients with ADHD and especially more Moroccan (84.6%) and Turkish (92.3%) male patients. Overall, among 60% of the patients are diagnosed at the age of 6-11 year old with a mean age of 10.1 years (SD 3.5). The mean age at ADHD diagnosis of Dutch natives is 10.1 years (SD 3.5), of Moroccans 9.8 years (SD 3.3), of Turks 11.4 years (SD 3.8) and of Surinams 10.7 years (SD 3.7).

Learning disorders were significantly more frequently diagnosed in Surinam (29.2%) patients and mental retardation in Turkish (21.2%) and Moroccan (14.0%) patients with ADHD.

Use of psychotropic comedication at the time of ADHD diagnosis date and 6 and 12 months afterwards was low: between 0 and 1.8%. Use of anti psychotics was 2.9% at 12 months afterwards. No differences are found between native Dutch, Moroccan, Turkish and Surinam patients (data not shown).

Table 1 Characteristics of 817 patients 0-18 years old diagnosed with ADHD between 1999-2010

	Total	**Native Dutch**	**Moroccan**	**Turkish**	**Surinam**
	N=817 100% (N)	**N=598 73.2% (N)**	**N=143 17.5% (N)**	**N=52 6.4% (N)**	**N=24 2.9% (N)**
Gender*					
Male	77.5% (633)	74.4% (445)	84.6% (121)	92.3% (48)	79.2% (19)
Female	22.5% (184)	25.6% (153)	15.4% (22)	7.7% (4)	20.8% (5)
Age ADHD diagnosis					
0-5 year	5.6% (46)	6.2% (37)	4.9% (7)	3.8% (2)	0.0% (0)
6-11 year	62.8% (513)	63.0% (377)	67.1% (96)	50.0% (26)	58.3% (14)
12-18 year	31.6% (258)	30.8% (184)	28.0% (40)	46.2% (24)	41.7% (10)
	Mean (SD)	**Mean (SD)**	**Mean (SD)**	**Mean (SD)**	**Mean (SD)**
Age first contact (yrs)	9.58 (3.4)	9.5 (3.4)	9.5 (3.3)	10.4 (3.8)	10.1 (3.4)
Age ADHD diagnosis (yrs)	10.14 (3.5)	10.1 (3.5)	9.8 (3.3)	11.4 (3.8)	10.7 (3.7)
Comorbid psychiatric disorders					
Disruptive behaviour disorder	32.4% (265)	32.4% (194)	32.9% (47)	32.7% (17)	29.2% (7)
Mood disorder*	4.4% (36)	4.3% (26)	2.8% (4)	3.8% (2)	16.7% (4)
Autism and related disorders *	8.0% (65)	9.4% (56)	2.1% (3)	9.6% (5)	4.2% (1)
Anxiety disorder	31.1% (254)	32.3% (193)	26.6% (38)	36.5% (19)	16.7% (4)
Learning disorder*	11.3% (92)	12.4% (74)	6.3% (9)	3.8% (2)	29.2% (7)
Mental retardation*	10.3% (84)	8.5% (51)	14.0% (20)	21.2% (11)	8.3% (2)

*Significant $p<0.05$

Table 2 shows that a quarter of the 817 identified patients never used ADHD medication during the study period. This proportion is highest in Moroccan (32.2%) and Turkish (42.3%) patients with ADHD. Around 20% of the native Dutch (22.9%) and Turkish (19.2%) patients used incident ADHD medication before diagnosed with ADHD.

Table 2 Use of ADHD medication in 817 patients 0-18 years old diagnosed with ADHD between 1999-2010

	Total	**Native Dutch**	**Moroccan**	**Turkish**	**Surinam**
	N=817 100% (N)	**N=598 73.2% (N)**	**N=143 17.5% (N)**	**N=52 6.4% (N)**	**N=24 2.9% (N)**
Never used ADHD medication	24.7% (202)	21.2% (127)	32.2% (46)	42.3% (22)	29.2% (7)
Prevalent ADHD medication use	4.2% (34)	5.0% (30)	1.4% (2)	1.9% (1)	4.2% (1)
Incident ADHD medication use before ADHD diagnosis date	20.6% (168)	22.9% (137)	12.6% (18)	19.2% (10)	12.5% (3)
Incident ADHD medication use after ADHD diagnosis date	50.6% (413)	50.4% (304)	53.8% (77)	36.5% (19)	54.2% (13)

Figure 1 shows the time to ADHD medication treatment initiation in days for native Dutch, Moroccan, Turkish and Surinam patients with ADHD: around 20% of native Dutch and Turkish patients start with ADHD medication before the ADHD diagnosis date. A higher proportion of native Dutch patients continue to use ADHD medication (73.3%) for tree years after the ADHD diagnosis date.

Figure 1 Time to ADHD medication treatment initiation in days for Moroccan, Turkish, Surinam and native Dutch patients (N=581). T=0 as date of ADHD diagnosis.

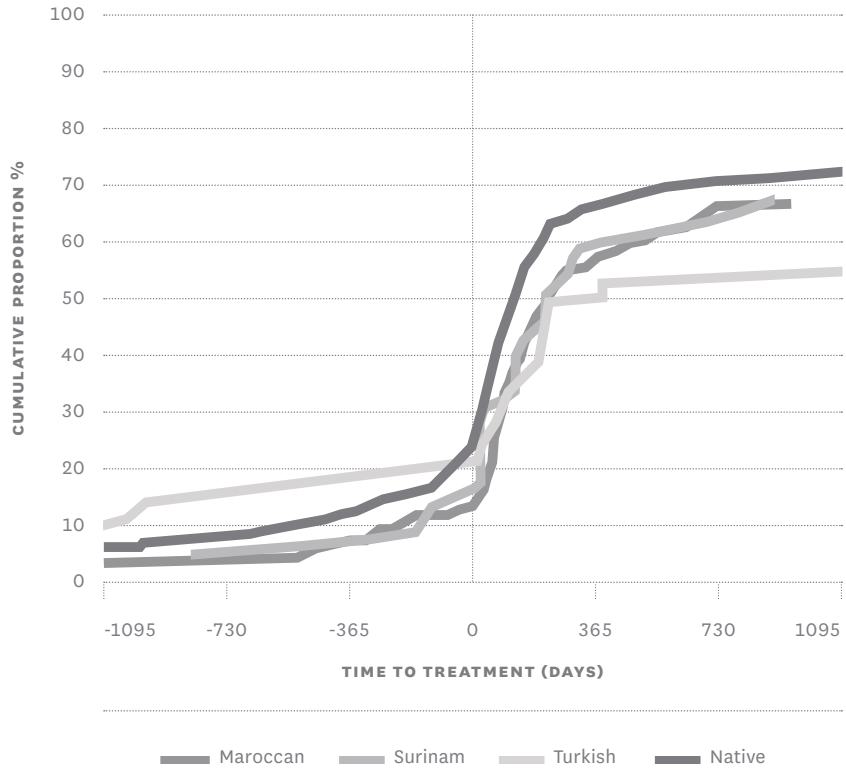


Table 3 shows that 581 (71.1%) of the 817 patients with ADHD were incident ADHD medication users having at least 6 months of exposure history available prior to the first prescription of an ADHD drug. Overall, almost three quarters of the patients is male. The percentage of non-native females initiating on ADHD medication is lower compared to native Dutch females. One fifth of the patients are getting incident ADHD medication prescribed by a general practitioner, almost three quarters by a medical specialist. The rate of pediatrician as first prescriber of incident ADHD medication was highest among Dutch natives (16.3%). Almost all patients start with methylphenidate, mainly immediate release methylphenidate (MPH IR) (around 80%). When starting with extended release methylphenidate, Dutch natives start with Concerta® (12.2%) and Moroccan patients with Medikinet CR® (11.6%) Almost no patients start with atomoxetine, nortriptyline or clonidine.

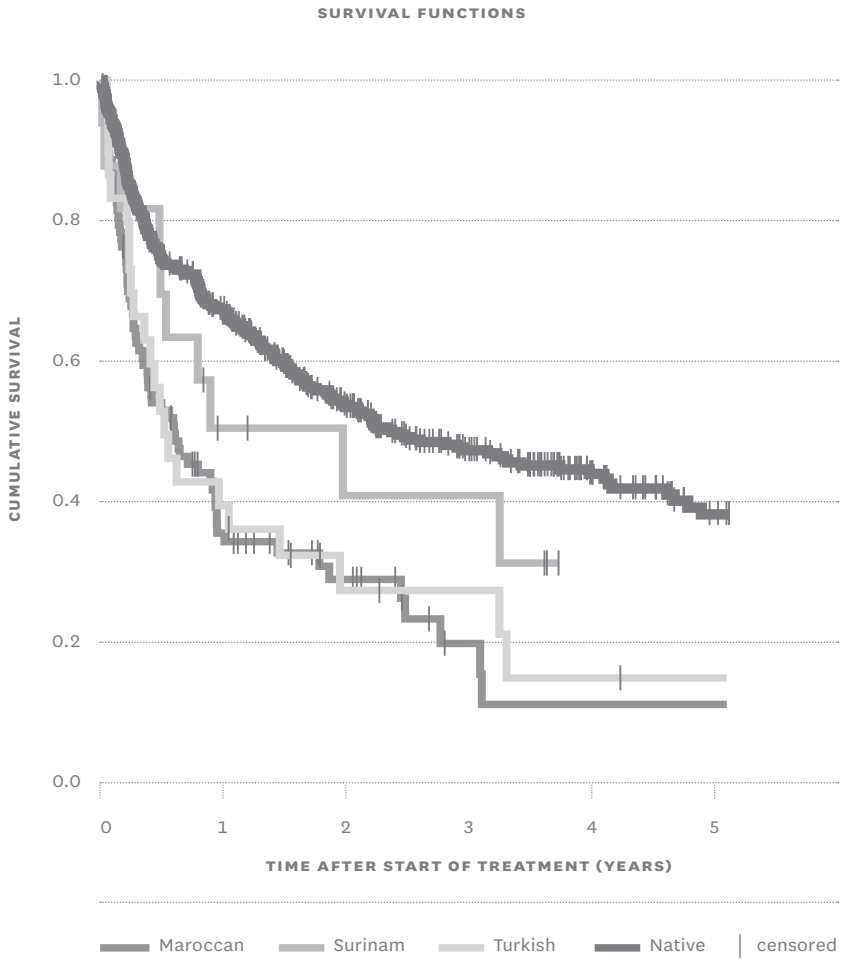
Table 3 Incident Use of ADHD medication in patients 0-18 years old diagnosed with ADHD between 1999-2010

	Total	**Native Dutch**	**Moroccan**	**Turkish**	**Surinam**
	N=817 100% (N)	**N=598 73.2% (N)**	**N=143 17.5% (N)**	**N=52 6.4% (N)**	**N=24 2.9% (N)**
Gender					
Male	78.3% (455)	76.4% (337)	81.1% (77)	96.6% (28)	81.2% (13)
Female	21.7% (126)	23.6% (104)	18.9% (18)	3.4% (1)	18.8% (3)
First prescribers incident ADHD medication					
General practitioner	21.5% (125)	21.1% (93)	20.0% (19)	31.0% (9)	25.0% (4)
Medical specialist:	73.3% (426)	75.1% (331)	69.5% (66)	62.1% (18)	68.8% (11)
pediatrician	14.3% (83)	16.3% (72)	7.4% (7)	6.9% (2)	12.5% (2)
CA psychiatrist	35.5% (206)	35.4% (156)	33.7% (32)	37.9% (11)	43.8% (7)
other/unknown	23.6% (137)	23.4% (103)	28.4% (27)	17.2% (5)	12.5% (2)
Other/unknown	5.2% (30)	3.9% (17)	10.5% (10)	6.9% (2)	6.3% (1)
Incident start of					
Methylphenidate IR and ER*	98.8% (574)	98.4% (434)	100% (95)	100% (29)	100% (16)
MPH IR	79.9% (464)	80.3% (354)	75.8% (72)	89.7% (26)	75% (12)
Concerta®	11.5% (67)	12.2% (54)	8.4% (8)	6.9% (2)	18.8% (3)
Equasym XL®	1.5% (9)	1.6% (7)	2.1% (2)	0.0% (0)	0.0% (0)
Medikinet CR®	4.1% (24)	2.5% (11)	11.6% (11)	3.4% (1)	6.2% (1)
Unknown IR or ER	1.7% (10)	1.8% (8)	2.1% (2)	0.0% (0)	0.0% (0)
Dexamphetamine	0.3% (2)	0.5% (2)	0.0% (0)	0.0% (0)	0.0% (0)
Atomoxetine	0.3% (2)	0.5% (2)	0.0% (0)	0.0% (0)	0.0% (0)
Clonidine	0.5% (3)	0.7% (3)	0.0% (0)	0.0% (0)	0.0% (0)
Nortriptyline	0.0% (0)	0.0% (0)	0.0% (0)	0.0% (0)	0.0% (0)

* methylphenidate ER: Concerta® or Equasym XL® or Medikinet CR®

Figure 2 illustrates that Moroccan and Turkish patients with ADHD are more prone to discontinue their incident ADHD medication within 5 years than native Dutch or Surinam patients. Discontinuation in Moroccan patients is, adjusted to age/gender, 2.4 times higher (95% CI 1.8-3.1) and in Turkish patients 1.6 times higher (95% CI 1.1-2.6) compared to native Dutch patients. Even after matching native Dutch and non native (Moroccan, Turkish or Surinam together) patients with ADHD using ADHD medication on SES (the first 4 numbers of their postal code), the same differences in pattern of discontinuation was found (data not shown).

Figure 2 Time in years to discontinue incident ADHD medication after 5 years (N=581)



Discussion

Our study shows differences in incidence and discontinuation of ADHD medication between native Dutch, Moroccan, Turkish and Surinam children and adolescents with ADHD. A significant higher percentage of Moroccan (32%) and Turkish (42%) patients never used ADHD medication during the study period compared to Dutch natives (21%). One fifth of the native Dutch and Turkish patients already used ADHD medication before they were diagnosed at a psychiatric institution with ADHD. Discontinuation of ADHD medication within five years is highest in Moroccan and Turkish patients and is not associated with socio economic status (SES).

Our finding that there is a difference in the percentage of ADHD medication use between ethnic groups is consistent with findings reported in (inter)national literature. In African-American, Latin-American, non-Hispanic black or Asian American children and adolescents the percentage that was prescribed ADHD medication is lower than in Caucasian Americans and it was shown that the prevalence of ADHD medication prescriptions in Turkish and Moroccan populations is lower compared to Dutch natives in a Dutch study as well [23,31-40,44].

We found that one fifth of the native Dutch and Turkish patients were initiated on ADHD medication before the ADHD diagnosis date. It is possible that native Dutch and Turkish children are diagnosed with ADHD elsewhere and that psychopharmacological treatment is already started before they are referred to Altrecht. This can be an indication of differences in referral patterns and access to care. In the Netherlands there are regional differences in the organization of assessment and treatment of patients with ADHD. In some regions only child- and adolescents psychiatrists diagnose and treat patients with ADHD, in other regions, like Utrecht, there are specialised pediatricians beside child- and adolescents psychiatrists, who prescribe medication and work together with first line psychologists, diagnosing ADHD and offering psychosocial treatment. Native Dutch and Turkish patients might be diagnosed and treated by them before they were referred to specialized care.

Risk of discontinuation of ADHD medication within five years significantly differed and was 2.4 times higher in Moroccan and 1.6 times higher in Turkish patients compared to Dutch natives. This finding is consistent with findings in the USA from Winterstein [23] who found a higher

percentage of Caucasian subjects continuing the use of stimulants compared to Hispanics or African Americans. In our study discontinuation is not explained by socio economic status (SES), so we conclude that it is related to ethnic background. Nuijen [47] concluded that, after consulting a mental health care institute, "non native" Dutch youngsters seem to have a higher drop out range of psychological or psychopharmacological treatment. To explain these high levels of drop out, he (and others) suggested that feelings of shame, fear for stigmata, prejudices to mental disorders or treatment, negative experiences with professional agencies and language or cultural discrepancies could play a role [48-53].

Further, we found significantly more comorbid mental retardation in Moroccan (14%) and Turkish (21.2%) patients with ADHD than in native Dutch and Surinam patients with ADHD. Studies has suggested that stimulants are less effective in intellectual disabled children with ADHD, although effect sizes of 0.39-0.52 were found [54]. The mean effect size of stimulants in children with a normal IQ is between 0.6 and 1.8, depending on the rater, [55]. It is possible that discontinuation in some Moroccan and Turkish patients with ADHD and mental retardation is associated with less effectiveness of stimulants.

These findings on discontinuation give cause for concern. Many studies have shown that ADHD can have a severe impact on daily life, daily functioning at school or at work, social and emotional development, family stress, health care consumption and expenditure, substance use, abuse and dependence and criminality and there are some indications that ADHD medication might reduce the risk and impact on life [56-74]. Non native patients with ADHD might be at an additional higher risk for negative outcomes later in life.

Strengths and limitations

Based on the fact that 27% of our research population was non Dutch native, we conclude that our group was representative for the Utrecht population that is known to have 20-21% non Dutch native inhabitants. We were able to include all patients with an ADHD diagnosis that were registered in the databases with a known ethnic background. This is an advantage over the studies that only include ADHD patients using medication. We expect that our conclusions therefore are based on a representative and adequate sample.

A limitation of our study was that we had no information where, when and by whom treatment was started in one fifth of native Dutch or Turkish patients with ADHD, who already used ADHD medication before being diagnosed. Further, it must be noted that the number of included native Dutch (N=598) and Moroccan (N=143) patients is much higher than the Turkish (N=52) or Surinam (N=24) patients. Therefor, the small group size might explain some findings of (not) being different from each other.

Conclusion

Differences are found in ADHD medication prescribing and use among native Dutch, Moroccan, Turkish and Surinam patients with ADHD. One fifth of the native Dutch and Turkish patients already used ADHD medication before being diagnosed at a specialized care clinic, which can be an indication that referral patterns and access to care in those groups differ from those in Moroccan and Surinam patients. It is preferable that access to care is indepent of ethnic background. Discontinuation of ADHD medication within five years is higher in Moroccan and in Turkish patients compared to Dutch natives and not different in Surinam patients although a small group size might explain this finding of not being different.

Future research should focus on underlying beliefs and prejudices influencing differences in incident use, discontinuation and effect of ADHD medication. Pathways of referral and differences between prescribers from different (mental) health care and other institutes must be analysed, because this might influence compliance. Little is known about long-term outcome of ADHD medication use among different ethnic groups, this should be subject for future research. At last, differences in (presentation of) effects or side effects of ADHD medication in patients of different ethnic backgrounds and whether differences have a genetical, biological or environmental origin should be studied.

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3

Short- and long-term outcomes of use of ADHD medication

3.1

Association between ADHD drug use and injuries among children and adolescents

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Abstract

Objective To study the association between attention deficit hyperactivity disorder (ADHD) drug use and the incidence of hospitalization due to injuries.

Methods A random sample of 150,000 persons (0-18 years) was obtained from the Dutch PHARMO record linkage system. An ADHD medication cohort as well as an up to six age/sex/index date sampled control cohort with no history of ADHD drug use was formed. Differences in incidence of hospitalization due to injuries were stratified for age and sex and compared prior, during and after exposure on ADHD drugs.

Results The overall incidence of hospital admissions for injuries was two times higher in the ADHD medication cohort [incidence rate ratios (IRR) 2.2 (95% CI 1.6-2.9)]. The incidence rate for injuries during exposure to ADHD drugs was lower in the exposed period compared to the period prior to ADHD drug use, although the difference was not statistical significant [IRR 0.68 (95% CI 0.29-1.60)]. The relative risk for injuries was almost five times higher in the ADHD medication cohort among those who concomitantly used other psychotropics [IRR 4.8 (95% CI 1.4-16.9)]. Risk for injuries was highest in 12-18 years olds.

Conclusion Children and adolescents using ADHD medication showed a twofold risk for hospital admissions for injuries. ADHD drug use might diminish the increased injury risk, but still overall risk is higher than in age/sex sampled children and adolescents without treatment with ADHD drugs. Use of ADHD and concomitant psychotropics increases the risk for injuries compared to only ADHD drug use.

Introduction

Attention Deficit Hyperactivity Disorder (ADHD) is a neurobiological disorder common in children, adolescents and adults, characterised by a persistent and inappropriate pattern of motor hyperactivity, impulsivity, impaired attention and distractibility [1, 2]. Many studies have shown that ADHD can have major negative impact on patients' daily life, daily functioning at school or at work, as well as on social and emotional development, family stress, healthcare consumption and expenditure [3-14]. Previous studies have shown that children and adolescents with ADHD or treated with ADHD medication are more prone to injuries, including the number and severity of accidents and hospital admissions compared to children and adolescents without ADHD or not treated with ADHD medication [8, 12, 15-22]. Treatment with stimulants, such as methylphenidate, dexamphetamine, or atomoxetine is one of the most effective treatment options for patients with ADHD [1, 23].
The incidence of ADHD drug use has clearly increased over the last 10-15 years [24-33]. However, little is known on how drug treatment with stimulants or other ADHD drugs modifies the increased risk of injuries in ADHD patients. Several factors such as motor problems or ADHD central nervous system symptoms can influence injury-proneness. It has been shown in a pediatric ADHD cohort that 60% of children had suboptimal motor performance and 30% were classified as probably having a developmental coordination disorder [34, 35]. Furthermore, the core symptoms of ADHD (hyperactivity, impulsivity and attention problems) can contribute to unintentional injuries [36]. Since it seems that the use of stimulants exerts a positive effect on motor problems and the central nervous system core symptoms, our hypothesis is that ADHD drug use decreases the incidence rate of injuries.

Information about influence of concomitantly used other psychotropics on injuries is scarce in child- and adolescent psychiatric psychiatry. It is known that at least 35-50% of the children with ADHD have a comorbid psychiatric disorder [37-39]. Little is known whether psychotropic comedication modifies risk of injuries in children or adolescents treated with ADHD medication [22]. Use of anxiolytics and hypnotics has been associated with an increased risk of injuries in adults and there is some evidence that depressive disorders in children and adolescent are linked to an increased risk of injuries [18, 40, 41]. From some psychotropic drugs, like antipsychotics, it is known that these influence attention and are sedative.

Further, being male is suggested to be one of the risk factors for injuries during outdoor play [17, 42]. As the prevalence of ADHD among 0-18 year olds is estimated at 3.0-7.5% and is three times higher among boys compared to girls in the general population [43], it can be expected that boys with ADHD are more prone to injuries.

The objective of this study was to assess the association of ADHD drug use with the incidence of hospital admissions due to injuries in children and adolescents and to investigate the influence of age, gender and comedication on this outcome.

Methods

Setting

Data for this study were obtained from the PHARMO record linkage system (RLS) (http://www.pharmo.nl). PHARMO RLS includes the demographic details and complete medication history of more than two million community-dwelling residents of more than 25 population-defined areas in the Netherlands from 1985 onwards, further linked to hospital admission records. PHARMO RLS does not contain information about psychiatric diagnoses. Since almost all patients in the Netherlands are registered with a single community pharmacy, independent of prescriber, pharmacy records are virtually complete with regard to prescription drugs [44].

For this study, drug dispensing data and hospitalization data were used. The computerised drug dispensing histories contain information concerning the dispensed drug, dispensing date, the prescriber, amount dispensed, prescribed dosage regimen, and the estimated duration of use. The duration of use of each dispensed drug is estimated by dividing the number of dispensed units by the prescribed number of units to be used per day. Drugs are coded according to the Anatomical Therapeutic Chemical (ATC) classification. The hospital admission register comprises all hospital admissions in the Netherlands, including detailed information concerning the primary and secondary discharge diagnoses, diagnostic, surgical and treatment procedures, type and frequency of consultations with medical specialists and dates of hospital admission and discharge. All diagnoses of hospital admissions are coded according to the International Classification of Diseases, 9th edition (ICD-9-CM).
This study was approved by an independent Privacy Committee PHARMO.

Participants and exposure definition

For this study, a random sample of 150,000 subjects from the PHARMO RLS born in 1977 or later was used. The study period was from January 1998 to December 2008. From these subjects, an ADHD medication cohort (N = 1,289) was identified comprising all children and adolescents (< 18 years), who started with at least one prescription for a drug approved for the treatment of ADHD ['ADHD drugs': methylphenidate immediate (IR) and extended release (ER) release, atomoxetine]. Dexamphetamine is not licensed in the Netherlands. The date of the first dispensing of any ADHD drug was the index date. A reference cohort (N = 7,332) was sampled by selecting up to six controls for each subject in the ADHD medication cohort with the same age, sex and calendar time distribution, but without any history of ADHD drug use during the study period. For the reference cohort an index date was randomly assigned. Subjects were included in the study only if they had at least 12 months of history in the PHARMO RLS prior to the index date.

For each patient in the ADHD medication cohort, treatment episodes of ADHD drugs were calculated. Treatment episodes were defined as series of subsequent prescriptions independent of switching between different types of ADHD drugs. A new episode was assumed if there was a gap larger than 90 days between the theoretical end date of a prescription and the next one.

Outcome definition

The occurrence of hospital admissions for injuries or poisoning [(ICD-9 codes 800-995, excluding ICD-9 codes 905-909 (late effects of injuries, poisonings, toxic effects and other external causes)] and specifically fractures (ICD-9 800-829), intracranial injuries (ICD-9 850-854) and open wounds (ICD-9 870-897) was assessed.

Potential confounders

For each subject, the use of other psychotropic drugs in a 6-month period prior to the index date was assessed. Psychotropic drug assessed included antipsychotics, antidepressants, antiepileptic drugs, benzodiazepines and promethazine.

Statistical analysis

Subjects were followed up from the index date until the end of the study period or January 1st of the year the patient turned 18 years old, whichever came first. Incidence rates of injuries in both the ADHD medication cohort and reference cohort were obtained by dividing number of events by person-years of follow-up. To assess the effect of drug treatment, the observation time of the patients in the ADHD medication cohort was classified as prior, during and after use of ADHD drugs, based on the constructed treatment episodes. To limit potential effects of ageing, this analysis was restricted to the year before and after the index date. For the reference cohort the year before and after the index date was analyzed. Poisson regression analysis was used to calculate incidence rate ratios (IRR) and 95% confidence intervals (95% CI). Analyses were stratified according to sex and age at index date (0-5, 6-11, 12-18 years). Further, analyses were adjusted for psychotropic co medication. The population-attributable risk, a measure of the excess incidence of injury in a population that is associated with taking ADHD medication, was also calculated.

Results

The study population comprised 1,289 persons in the ADHD medication cohort and 7,332 persons in the reference cohort (Table 1). Overall, almost 80% were boys and almost 65% were between 6 and 11 years of age. The use of psychotropic drugs was higher in the ADHD medication cohort (9.2 versus 2.1%).

Table 1 Characteristics of the ADHD medication cohort and the reference cohort during 1998- 2008

Characteristics	ADHD medication cohort N=1,289(%)		Reference cohort N=7,332(%)	
Age				
< 6 years	72	(5.6)	404	(5.5)
6-11 years	846	(65.6)	4,833	(65.9)
12-18 years	371	(28.8)	2,095	(28.6)
Gender				
Male	1,029	(79.8)	5,842	(79.7)
Female	260	(20.2)	1,490	(20.3)
Index date				
1998-2001	219	(17.0)	1,247	(17.0)
2002-2005	443	(34.4)	2,522	(34.4)
2006-2008	627	(48.6)	3,563	(48.6)
Mean follow-up (years)	4.5	(SD 2.6)	4.5	(SD 2.6)
Type of incident adhd drug prescriber				
Psychiatrist	445	(34.5)		
Pediatrician	325	(25.2)		
General Practitioner	236	(18.3)		
Other	236	(18.3)		
Unknown	47	(3.7)		
Comedication used in the 6 months prior to the index date				
Any psychotropic drug	118	(9.2)	157	(2.1)
Antipsychotics	72	(5.6)	35	(0.5)
Antidepressants	20	(1.6)	11	(0.2)
Anti epileptic drugs	19	(1.5)	37	(0.5)
Benzodiazepines	19	(1.5)	29	(0.4)
Promethazine	17	(1.3)	63	(0.9)

Overall, subjects in the ADHD medication cohort were more frequently hospitalised for injuries compared to those in the reference cohort (**Table 2**). This pattern was observed for all included types of injuries, in both boys and girls and in all age categories. The overall incidence rate of hospital admissions for injuries was two times higher in the ADHD medication cohort (11.5 vs. 5.3/1,000 person years), yielding a crude IRR of 2.2 (95% CI 1.6-2.9). Adjustment for concomitant use of antipsychotics and benzodiazepines at baseline had a modest effect: adjusted IRR 2.0 (95% CI 1.5 to 2.7). The risk was higher in girls (adjusted IRR 2.4, 95% CI 0.91-6.5) than in boys (adjusted IRR 1.9, 95% CI 1.4-2.6), but did not reach statistical significance. The highest absolute incidence rate for hospital admissions for any injury (16.3/1,000 person years), but also for fractures, intracranial and internal injuries or open wounds (data not shown) was found for 12-18 years old. The incidence rate of hospital admissions for subjects in the ADHD medication cohort also using other psychotropic drugs was almost five times higher compared to the reference cohort [21.6 vs. 4.5/1,000 person years; crude IRR 4.8 (95% CI 1.4 to 16.9)]. The population-attributable risk was 1.84%, indicating that nearly 1 out of 50 hospital admissions of youngsters < 19 years is associated with taking ADHD medication.

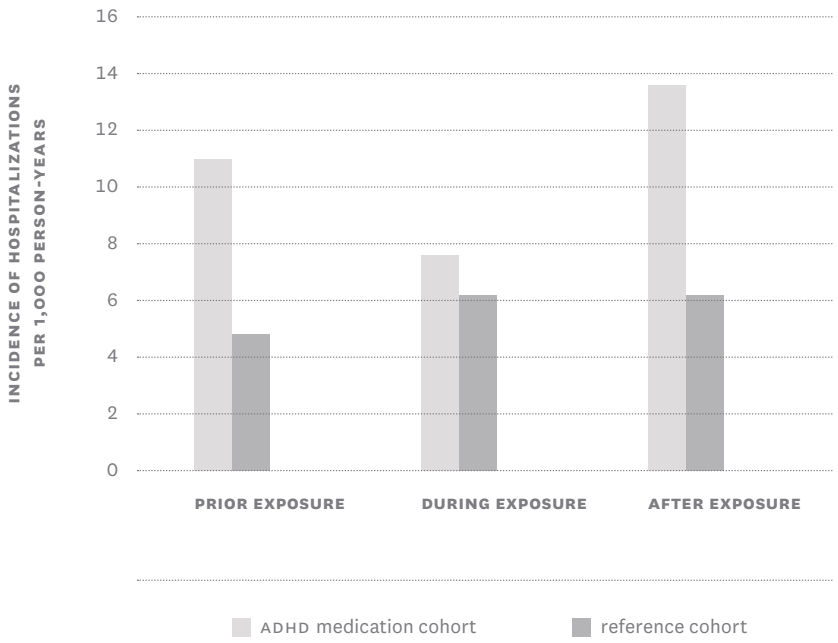
Table 2 Incidence of hospitalizations per 1,000 person years of any injury, fractures, intracranial injury, internal injury or open wounds in the ADHD medication cohort and the reference cohort

	ADHD medication cohort		**Reference cohort**			
Characteristics	# events	inc/1,000 py	# events	inc/1,000 py	Crude IRR	Adjusted IRR
Overall	**N=1,289**		**N=7,332**			
Any injury	64	11.5	163	5.3	2.2 (1.6-2.9)	2. 0 (1.5-2.7)[b]
Fractures	30	5.4	99	3.2	1.6 (1.1-2.5)	1.6 (1.1-2.4)[b]
Intracranial Injury	13	2.3	25	0.80	2.9 (1.5-5.7)	2.5 (1.2-5.0)[b]
Open wounds	5	0.90	11	0.36	2.5 (0.88-7.3)	2.2 (0.7-6.8)[b]
Boys	**N=1,029**		**N=5,842**			
Any injury	54	11.9	150	6.0	2.0 (1.5-2.7)	1.9 (1.4-2.6)[b]
Girls	**N=260**		**N=1,490**			
Any injury	10	9.6	13	2.3	4.3 (1.9-9.8)	2.4 (0.91-6.5)[c]
< 6 years [a]	**N=174**		**N=979**			
Any injury	1	4.2	6	4.6	0.9 (0.1-7.7)	n/a
6-11 years	**N=987**		**N=5,633**			
Any injury	23	8.0	75	4.6	1.7 (1.1-2.8)	1.5 (0.93-2.5)[b]
12-18 years	**N=792**		**N=4,421**			
Any injury	40	16.3	82	6.1	2.7 (1.8-3.9)	2.4 (1.6-3.6)[b]
Use of psychotropics	**N=118**		**N=157**			
Any injury	12	21.6	3	4.5	4.8 (1.4-16.9)	n/a
No use of psychotropics	**N=1,171**		**N=7,175**			
Any injury	52	10.4	160	5.3	2.0 (1.4-2.7)	n/a

py	person years
psychotropics	antipsychotics, antidepressants, benzodiazepines, prometazine, AEDs
n/a	not applicable
n/s	not significant
a	Totals add up to >100% because subjects contribute in multiple age categories due to long follow-up
b	adjusted for use of antipsychotics
c	adjusted for use of antipsychotics and benzodiazepines

Subsequently, we assessed the effect of ADHD drugs on the incidence of any injury. The mean time for exposure was 229 days, counted by using the first date of the first episode and the last day of the last episode of a prescription of a stimulant. **Figure 1** shows that the incidence rate of hospital admissions in the ADHD medication cohort prior, during and after exposure to ADHD drugs was, respectively, 11.0 (prior), 7.8 (during) and 13.8/1,000 person years (after) and for the reference cohort 4.8 (prior), 6.2 (during) and 6.2/1,000 person years (after). When comparing the incidence of any injury prior and during use of ADHD drugs the risk in the ADHD medication cohort was (not significant) decreased with >30% (IRR 0.68, 95% CI 0.29-1.60).

Figure 1 Incidence of hospitalizations per 1,000 person years of injury prior, during and after exposure on stimulants in the ADHD medication cohort and the reference cohort



Discussion

Our study shows a twofold increased risk for hospital admissions for injuries in children and adolescents using ADHD medication compared to controls. To our knowledge, this is the first study that shows that the incidence of injuries before, during and after use of ADHD medication is influenced by use of ADHD medication. ADHD drug use might diminish the increased injury risk, but still overall risk is higher than in age/sex sampled children and adolescents without treatment with ADHD drugs.

The increased risk for injuries in children and adolescents treated for ADHD with medication is in line with previous findings [8, 17, 19, 22]. Different factors can play a role in explaining the increased risk of injuries.

Firstly, the core symptoms of ADHD hyperactivity, impulsivity or attention problems can contribute to these incidents [36, 45]. Supportive for such an association is that hyperactive and impulsive children need more hospital admission or ER (Emergency Room) visits for reduction of their fractures than less hyperactive and impulsive children [46, 47]. Secondly, associated problems like diminished motor skills or timing of behaviour could result in a higher risk for accidents than in the general population [48]. Studies report that 30-60% of children with ADHD have poor motor coordination skills [34, 49-53]. Children and adolescents with ADHD also have motor timing deficits, which are related to impulsiveness, suggesting that they have problems adjusting their speed to the demanded speed in a motor task [54, 55]. Barkley concludes that children with ADHD show more risk-taking behaviour [56].

Thirdly, comorbid symptoms or disorders such as defiant, aggressive or antisocial behaviour, oppositional defiant disorder (ODD) or a conduct disorder (CD) could result in more accidents than in normal controls [16, 48]. Rowe [18] found that ADHD, but also ODD, is associated with unintentional injuries such as burning, poisoning, head injuries and fractures. Studies show that at least 30% of children and adolescents with ADHD suffer from ODD or CD [57-59]. Differences in risk for injuries before, during and after use of ADHD medication, found in our study, can be understood because hyperactivity, impulsivity and attention problems diminish with use of stimulants or atomoxetine [1, 15]. Symptoms of oppositional defiant disorder or conduct disorder are also less while using stimulants or atomoxetine [60-62]. Further, there is some evidence that stimulants

improve fine of gross motor or balance problems and therefore decrease risk of accidents [35]. Increase of incidence after exposure on ADHD drugs can be understood as age effect in both the ADHD medication cohort as well as in the reference cohort. We found in our study that girls treated with ADHD medication does not show a lower risk of hospital admissions compared to boys. Some researchers suggest that girls with ADHD in treatment settings are more severely affected by their ADHD than boys [63]. Girls with ADHD seem to experience more motor difficulties than boys [34]. Therefore, the background risk for injuries between "normal" girls could be lower when compared to girls with ADHD, so the contrast in behaviour symptoms can be higher in girls, comparing this to boys with and without ADHD. Further, we found in our study that adolescents treated with ADHD medication, 12-18 year old, compared to controls, are most prone of all age categories for hospital admissions for injuries and poisoning. Increased risk for adolescents is in line with the risk in the general population (http://www.cbs.nl/). Also, in adolescents with ADHD motor deficiencies are comparable with those observed in children, implying that they do not disappear with age [34]. Besides hypotheses mentioned above, additional hypotheses about this higher risk in adolescents could be that care takers could supervise their adolescents less than younger children or that adolescents, possibly taking more part of the traffic, could be influenced by alcohol of drugs. Adolescents with ADHD are at risk for substance use and abuse [64]. Finally, the proportion of subjects using psychotropic drugs at the index date was higher in the ADHD medication cohort than in the reference cohort. Use of psychotropic drugs beside ADHD mediation increased the risk for hospital admissions for injuries. This could indicate that these patients were suffering from other comorbid psychiatric disorders beside ADHD or a more severe variant of ADHD. The increased risk by use of anxiolytic/hypnotic comedication in children and adolescents has also been confirmed by Marcus [22]. So, it is possible that psychotropic drugs itself influence the risk on accidents and/or the psychiatric comorbid disorder.

The strengths of this study are that it includes new information about the possible influence of a disorder and medication on injuries; it is population-based, is geographically diverse and includes a large number of subjects that were followed for an average of 4.5 years. Furthermore, hospital admissions were used as an objective outcome measure for serious events. There are some limitations as well. Firstly, we had no medical diagnosis of ADHD, but identified subjects on the basis of use of ADHD drugs just like in studies by Brehaut [8], Scharnetzky [17],

Swensen [19] and Marcus [22]. Several studies concluded that prescription of stimulants is a valid indicator for the diagnosis of ADHD [19, 65, 66]. Canadian studies concluded that at least 90% of the methylphenidate prescriptions were for ADHD [65, 66]. However, this approach may have resulted in some misclassification of ADHD in both cohorts. The risk we found, could be an underestimation of the true risk because the ADHD medication cohort could contain subjects who did not have ADHD, but were treated with stimulants resulting in an underestimation of the true incidence of injuries and the reference cohort could contain subjects, not diagnosed with ADHD, while suffering from ADHD or suffering from ADHD but not treated with medication, so the real incidence of injuries in this cohort could be lower than found in our study. Second, outcome events assessed were only the ones that required hospital admission. Injuries treated in the ER or by the general practitioner were not assessed, possibly resulting in an underestimation of the true incidence of injuries. However, it seems unlikely this has any impact on the observed differences between patients with ADHD and controls. Third, we had no data about other treatment options such as for example physiotherapy or psychotherapy that could influence accident proneness. The ADHD medication cohort possibly covers children and adolescents with more severe cases of ADHD, while mild and moderate cases are either not diagnosed or, if diagnosed, they are managed, according to scientific recommendations, with predominantly psychosocial and educational methods. It is possible that the ADHD medication cohort is a special group of children with severe cases of ADHD, rather than all spectrum of children with ADHD.

Fourth, we did not know whether the injuries were intentional, for example a suicide attempt or child abuse, of unintentional. It seems likely that most events are unintentional. Fifth, we can not be sure that a child actually takes medication while prescribed on the day of the injury. However, it seems more likely that a subject swallows a pill when the prescribed medication is actually collected at the pharmacy, than that a subject swallows a pill if the prescribed medication is not collected. At last, we had no data about children and adolescents treated with ADHD medication for more than one year after the inclusion date of December 2008.

Clinical implications of our study are that the finding that children and adolescents are more accident prone and probably need more protection in outdoor play should be stressed in health education about ADHD to

patients and parents. Second, it is important to assess the effect of ADHD medication on motor coordination, hyperactive, impulsive or inattentive behaviour and whether the child or adolescent has less accidents in and around the house, school or during sports during evaluations. Third, a combination of ADHD medication and antipsychotics increases the risk on injuries, so monotherapy of only ADHD medication is preferred. Fourth, when a clinician diagnoses poor motor skills, specialised physiotherapy can be advised. Finally, clinicians of the ER should be aware to refer hyperactive, impulsive or inattentive children or adolescents with injuries for an assessment to a child- and adolescent psychiatrist of -psychologist.

It is clear that children and adolescents with ADHD, identified by use of ADHD medication, compared to controls are at higher risk for hospital admissions for injuries, poisoning, fractures, intracranial injuries and open wounds. The highest risk is among adolescents 12-18 years old. There are differences in the risk for injuries before, during and after use of ADHD drugs. ADHD drug use might diminish this increased injury risk, but still the overall risk is higher than in age/sex sampled children and adolescents without use of ADHD medication. In those using ADHD and any other psychotropic drugs risk for injuries is higher compared to those who only use ADHD drugs. Future research should further evaluate whether the risk for serious accidents is influenced by differences between subgroups of ADHD drugs, the dosage and length of use, the start age and/or other interventions such as physiotherapy or psychotherapy.

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3.2

Association between stimulant treatment for ADHD and daily or life time drug use: a follow-up from childhood into adulthood

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Abstract

Background Youngsters and adults with ADHD are at risk for substance use and abuse. A relation has been suggested between stimulant treatment and risk for substance use and abuse.

Objective To describe the association between stimulant treatment and life time (ever used) or daily drug use in adults who were diagnosed with ADHD as a youngster. Life time and daily drug use was investigated in relation to gender, IQ, psychological treatment, age of ADHD diagnosis, comorbid externalizing and internalizing disorders.

Methods A prospective cohort study designed to evaluate outcomes in adulthood of subjects who received psychiatric care as a youngster at the Department of Child and Adolescent Psychiatry at the University Medical Centre of Utrecht, the Netherlands, between January 1984 and December 2004 (T1). Subjects were traced from September 2006 until February 2010 (T2). Subjects meeting the following criteria were included for follow-up: (1) ADHD diagnosis based on DSM III, III-R, IV or IV-TR criteria at T1, (2) ages 18 years or younger at T1, (3) ages 18 years or older at T2. Data were obtained using questionnaires concerning medication use and life time and daily drug use.

Results 50% of the responders (N=398) reported life time use of cannabis, party drugs and/or hard drugs. Risk for life time drug use in general (cannabis, party- and hard drugs) and life time cannabis use was increased in those with a lifetime history of stimulant treatment, controlled for potential confounders (HR 1.8 [95% CI 1.3-2.5]; HR 1.6, [95% CI 1.1-2.2]). No effects of stimulant treatment were found on daily use of drugs. Irrespective of stimulant use, participants who at T1 were not only diagnosed with ADHD but also with ODD or CD showed increased risk for life time drug use in general (HR 1.6 [95% CI 1.2-2.3]); and especially for life time and daily cannabis use (HR 1.7 [95% CI 1.2-2.5]); (HR 2.0 [95% CI 1.2-3.3]). The later in life a subject was diagnosed with ADHD, the higher the risk for life time hard drug use at follow-up, independent of stimulant use (HR 1.1, [95% CI 1.0-1.2]).

Conclusion A history of stimulant treatment increased the risk for life time drug use, particularly for life time cannabis use, in adults diagnosed with ADHD at childhood. A comorbid externalizing disorder diagnosed at young age increased the risk for life time use of drugs in general and life

time and daily cannabis use in adulthood. Early diagnosis of ADHD might protect against hard drug use in adulthood.

Introduction

Attention Deficit Hyperactivity Disorder (ADHD), probably one of the most prevalent childhood onset neuropsychiatric disorders, is characterised by inattention, hyperactivity, impulsivity and distractibility [1,2]. ADHD is persistent from childhood into adulthood in approximately half of the patients [3]. Many studies have shown that ADHD can have a severe impact on daily life, daily functioning at school or at work, social and emotional development, family stress, health care consumption and expenditure [3-15]. Moreover, ADHD has been associated with substance use, abuse and dependence [3, 12-14, 16-19]. Recent meta-analyses confirmed that childhood ADHD is a risk factor for substance use (nicotin, alcohol, marijuana), abuse or dependence (nicotin, alcohol, marijuana, cocaine) later in life [18,19]. Moreover, clinical and epidemiologic studies of adolescents and adults with drug- or alcohol use disorders have shown high rates of ADHD: between 15% to 25% of these adults meet the criteria of ADHD in adulthood [20,21].

In many countries, including the Netherlands, the use of stimulants for treatment of ADHD has increased substantially over previous decades, not only among school-aged children, but also among preschoolers and adults [22-31]. Despite its proven efficacy and increasing use, several concerns and controversies regarding the use of stimulant medication exist, for instance whether stimulant treatment modulates the established association between ADHD and the subsequent risk for addiction problems and substance use [32].

Lambert found that a history of stimulant treatment for more than one year in childhood is correlated with an increased risk for later nicotine and cocaine abuse [33]. Another study by Lambert showed that stimulant treatment and tobacco smoking increased the risk for cocaine dependence and life time use in adult participants who had tried cocaine on at least one occasion [34]. However, findings are not unequivocal. Wilens, in a meta analysis, and subsequent empirical studies found evidence suggesting that in children with ADHD, the use of stimulant medication, nor its time of onset, duration or dosage influenced the risk for alcohol, drug or nicotine use or abuse in late adolescence or adulthood [16, 32, 35-39]. It has even been

studied that stimulant treatment could act as a protective factor in ADHD, resulting in the reduction of risk for substance use or abuse later in life [40]. Studies by Faraone and Biederman, however, showed no protective effect of methylphenidate use in children from substance use disorder (SUD) (abuse and dependence) in adulthood [41,42]. A recent study and meta-analysis showed no protection nor a contribution of ADHD medication use to SUD in adolescence in ADHD [43,44]. The age at which stimulant treatment was started might influence its effect on later recreational drug use, abuse or dependence: the later in life stimulant treatment is started, the higher the chances are to develop a SUD [16,45]. This could imply that early diagnosis and pharmacological treatment of ADHD might be a protective factor for substance use or SUD's. In addition, Fischer and Barkley found that stimulant treatment in adolescence might have a protective effect on hallucinogen abuse in adulthood [37] Starting stimulant treatment after diagnosing ADHD at an even earlier age might be even more protective.

Because of the contradictory findings regarding the effects of stimulant medication on substance use and abuse and the questions unanswered, the present study aims to elucidate whether there is an association between use of stimulant medication in patients diagnosed with ADHD at childhood and substance use and abuse later in life, while the influence of age of diagnosing ADHD and several other potentially influential factors namely gender, psychological treatment, IQ, comorbid internalizing disorders and externalizing disorders are evaluated [14, 19, 46-55]. Based on literature so far, our hypothesis is that stimulant medication use is associated with a lower risk on substance use or abuse in adults diagnosed with ADHD in childhood or adolescence.

Methods

Setting, study population and study design

This study is part of a prospective cohort study designed to evaluate outcomes in adulthood of subjects who received psychiatric care during their childhood or adolescence at the Department of Child and Adolescent Psychiatry at the University Medical Centre of Utrecht (UMCU), the Netherlands, between January 1984 and December 2004 (T1). The data at T1 comprised information on gender, IQ, age of diagnosis, comorbid externalizing disorders such as oppositional defiant disorder (ODD) or conduct disorder (CD) and internalizing disorders including depression

and anxiety disorders. Subjects were traced by information from their former or current general practitioner or by the Civil Registry of the concerning municipality from September 2006 until February 2010 (T2). They received a letter and if possible were contacted by phone to encourage participation. Subjects meeting all of the following criteria were approached for follow-up: (1) an ADHD diagnosis based on DSM III, III-R, IV or IV-R criteria at T1, (2) aged 18 years or younger at T1, (3) aged 18 years or older at T2. This resulted in 1,088 subjects eligible for follow-up in the present study.

The ethical principles of the Helsinki Declaration were followed and ethical approval was obtained from the Medical Ethical Committee of the University Medical Centre of Utrecht (number 05-319/K).

Data collection

A self report questionnaire concerning outcomes in adult life was sent to the cohort members eligible for follow up in the period from 2006 until 2010. The questionnaire contained 17 items addressing psychological and pharmacological treatment history, drug use, current behavioural or emotional problems and present situation of living, working, education and subjective quality of life. There were three questions concerning the use of cannabis, party drugs (ecstasy=XTC) and hard drugs (heroine/ cocaine/ amphetamine/ Lysergic acid diethylamide=LSD): 1) did you ever use a drug? (never/once/once in a while/monthly/weekly/daily), 2) age of onset of drug use 3) if applicable, at what age did you stop using a drug? Two outcome parameters of drug use were analysed: life time and daily drug use (both dichotomous: yes/no). Life time drug use was defined as use of one or more substances (either cannabis, hard drugs or party drugs) ever (once/once in a while/monthly/weekly). Daily drug use was defined as a history of use of one or more substances (either cannabis, hard drugs or party drugs) on a daily basis for a certain period of time. As for medication use, subjects were asked whether they currently used or had ever used medication for mental problems and what kind of medication. For each subject medication use was categorised in: antidepressant, antipsychotic, psychostimulant medication, ADHD non-stimulant medication, benzodiazepines and other medication. As for psychological treatment subjects specified whether they had received this, and if so, the kind of treatment and the duration. Subjects who returned the questionnaire were divided into two groups according to whether they had a history of stimulant medication use or not. ADHD stimulant medication use was defined as having ever used methylphenidate immediate or extended release.

Data analysis

Group comparisons (stimulant treatment: yes/no) at follow up on demographic characteristics were done using Pearson Chi Square tests and ANOVA for binary and dimensional variables respectively. Differences in starting ages of drug use between stimulant and non-stimulants groups were performed using ANOVA. Further, the Cox proportional hazards model was used to assess the association between predictor variables (gender, age of ADHD diagnosis, use of (one or more) other types of medication at follow up, comorbid externalizing or internalizing disorders and psychological treatment) and drug use. This model also accounts for subjects who did not develop drug use, but who are not yet beyond the period of risk [56,57]. Because apart from historical datasets the final status for all observations or the time to reach final status was not known, data contained censored and uncensored cases, which is compatible with assumptions of Cox regression. A binary variable for each drug was created to establish a measure of life time drug use. The earliest age of onset of use of drugs was used as the survival time for case subjects and the age at the most recent interview T2 as the time of censoring for non case subjects. First, separate univariate survival analyses were conducted for each of the predictor variables (covariates) with each of the following outcomes: life time drug use in general (cannabis, party- and harddrugs), life time and daily cannabis use, life time party drug use and life time hard drug use. For daily party and hard drug use the number of daily users was too small to analyze effects. Covariates with p-values less than 0.20 were entered into the proportional hazards analysis [57]. Covariates in this analysis that showed p-values less than 0.05 (two tailed) were rerun in a final proportional hazards multivariate analysis. Finally, interaction effects between stimulant use and age of ADHD diagnosis were analyzed. Interactions significant at the 5 percent level were then added jointly to the main effects model. The remaining significant interactions were included in the final model. All analyses were conducted using SPSS, 16.0 (SPSS, Inc., Chicago, IL).

Results

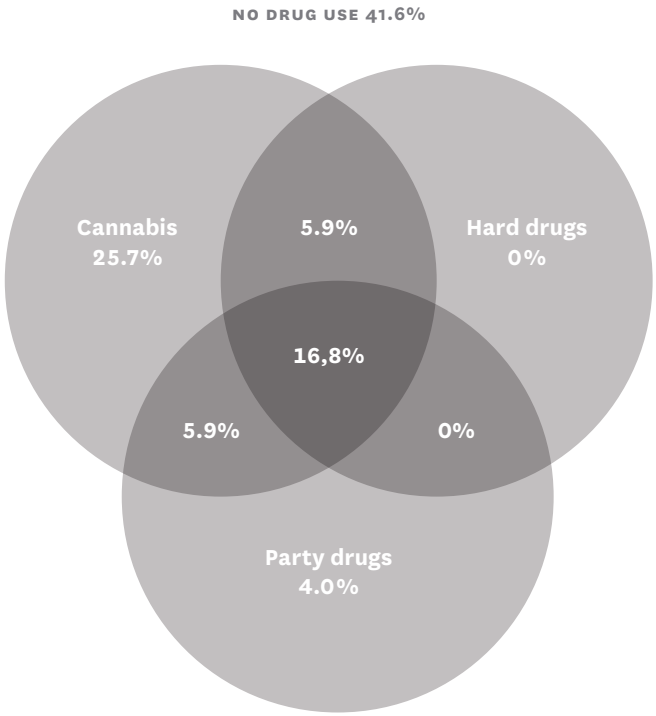
Almost 40% (N=398) of the 1,088 eligible subjects returned the questionnaire at T2. Differences in baseline psychopathological and demographic characteristics of the initial sample (N=1,088) of subjects with ADHD were analysed with frequency distributions to compare those who did return (follow up group) or did not return (non-responders) the questionnaire. There were no significant differences between the follow up group and the non-responders for gender, externalizing or internalizing comorbid disorders or total IQ, except for a significant difference in age at T1 (follow up group: 10.5 (SD=3.2) years vs. non-responders: 9.7 (SD=3.2) years, $p < .001$). Around 85% of the responders comprised of males. The mean age at T2 was between 22.9 and 26.1 years. A little more than a quarter of the responders had a history of stimulant use. At T1, more than one fifth suffered from comorbid ODD or CD and less than ten percent of comorbid depression or anxiety disorder.
Table 1 shows differences in demographic characteristics between the groups with versus without a history of stimulant medication. Differences were only significant for psychological treatment and mean duration of follow up. Those who had a history of stimulant use, received psychological treatment more often (57.3% vs 33.4%, $p < 0.01$). The mean follow-up period was 12.4 (SD=3.4) years for the group that used stimulant medication and 15.6 (SD=4.5) years for the group without a history of stimulant medication.

Table 1 Demographic characteristics of all ADHD patients with and without a stimulant medication history at T2

	Stimulant medication history (N=101)		No stimulant medication history (N=297)			
Characteristics	**N**	**%**	**N**	**%**	**x^2**	**p**
Male	86	83.5	259	86.3	.50	.48
Comorbid externalizing disorders T1	24	23.3	62	20.7	.32	.58
Comorbid internalizing disorders T1	9	8.7	25	8.3	.02	.90
Psychological treatment ever	59	57.3	78	26.0	33.4	<.01
	Mean	**SD**	**Mean**	**SD**	**t**	**p**
Age of diagnosis T1	10.5	3.0	10.5	3.2	.04	.97
Age at follow up T2	22.9	3.6	26.1	5.5	6.0	<.01
Total IQ T1	99.9	12.3	94.5	16.7	-2.2	.04

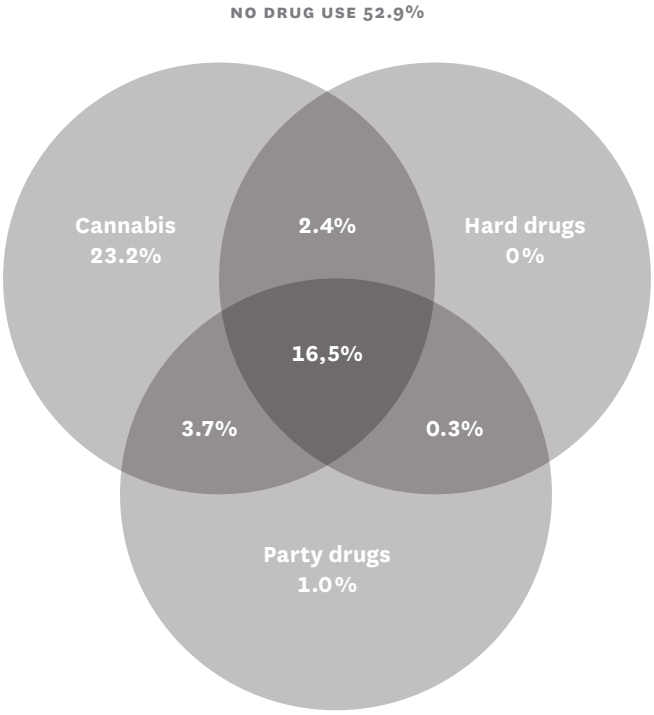
Drug use was reported by 199 subjects (50.0%), of which half pertained to single life time and/or daily drug use (51.3%) and half to multiple drugs (≥2 drugs) (48.7%). **Figure 1a and 1b** show proportions of life time and/or daily drug use within the groups with- and without a history of stimulant use, respectively. The frequency of single and multiple drug use was 29.7% and 28.7% within the group who received stimulant treatment, and 24.2% and 22.9% within the non stimulant group. Of the total sample, 16.6% reported life time and/or daily use of all three types of drugs (i.e. cannabis, party- and hard drugs); 16.8% for the stimulant group and 16.5% for the non-stimulant group. The largest group consisted of life time and/or daily users of cannabis (23.9%); 25.7% for the stimulant group and 23.2% for the non-stimulant group.

Figure 1a Life time and/or daily drugs use reported by all ADHD patients at T2 with a history of stimulant use ever



TOTAL: N=199 (drug users) MISSING: N=9

Figure 1b Life time and/or daily drugs use reported by all ADHD patients at T2 without a history of stimulant use ever (N=140)



TOTAL: N=199 (drug users) MISSING: N=9

The mean age at which cannabis use was started was 15.6 (SD 2.1) years in the stimulant treated group and 17. 0 (SD 3.7) years in the non-stimulant group ($F(1,148)=5.8$; $p=.02$); for party drugs this was: 17.0 (SD 2.7) vs 19.0 (SD 4.1) years ($F(1,69)=4.4$; $p=.04$); and for hard drugs: 17.6 (SD 3.6) vs 19.1 (SD 3.9) years (ns).

Cox proportional hazards regression analysis revealed that subjects with a history of stimulant use ever, showed an increased risk for life time drug use in general (cannabis and/or party drugs and/or hard drugs), compared to those who did not use stimulants, while controlling for relevant demographic and clinical variables (HR 1.8 [95% CI 1.3-2.5]) (**Figure 2**). Further analyses showed that particularly the life time use of cannabis was significantly predicted by a history of stimulant use (HR 1.6, [95% CI 1.1-2.2]) (**Figure 3**). No association was found between a history of stimulant use and daily use of cannabis. For party and hard drugs the number of daily users was too small to analyze effects. We found no modification by covariates on the association between stimulant use and life time or daily drug use.

Figure 2 Cumulative incidence to life time drug use (cannabis, party-, hard drugs) of ADHD patients by use of stimulant medication ever as reported by age of first use of drugs (in years)

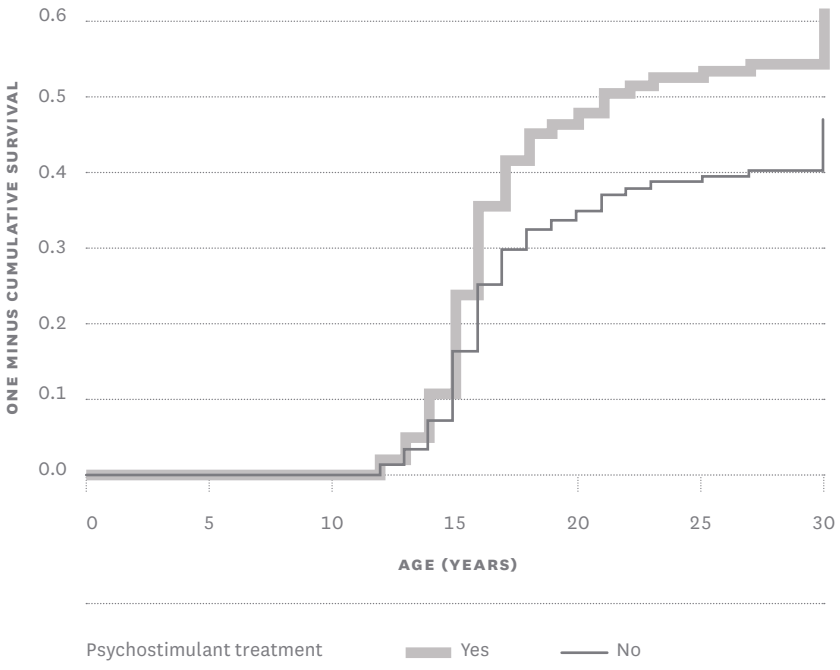
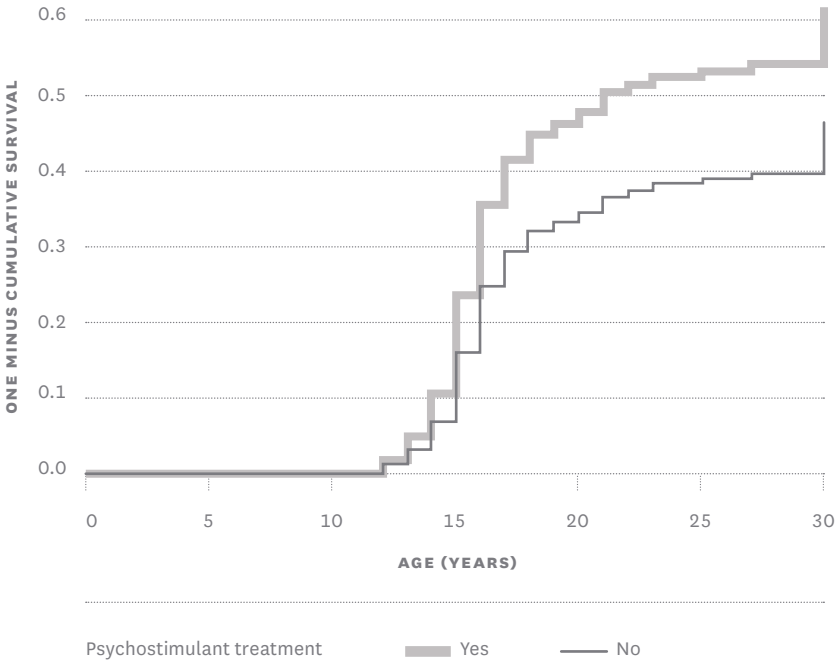


Figure 3 Cumulative incidence to life time cannabis use of ADHD patients by use of stimulant medication ever as reported by age of first use of drugs (in years)



However, independent of a history of stimulant use, analyses of associations of covariates and life time or daily drug use showed that those who suffered at T1 of a comorbid externalizing disorder showed increased risk for life time drug use in general (cannabis and/or party drugs and/or hard drugs) (N = 199) (HR 1.6 [95% CI 1.2-2.3]), and for life time cannabis use (HR 1.7 [95% CI 1.2-2.5]). As for daily use, comorbid externalizing disorders at T1 increased the risk of daily use at adulthood (HR 2.0, [95% CI 1.2-3.3]).

In females, risk was statistically decreased for life time drug use in general (cannabis and/or party drugs and/or hard drugs, (HR 0.4, [95% CI 0.2-0.7]) and for life time cannabis use (HR 0.4, [95% CI 0.2-0.7]), independent of stimulant use. Further analyses showed a diagnosis of ADHD at an older age increases the risk of life time hard drug use at follow up (HR 1.1, [95% CI 1.0-1.2]).

Discussion

In our prospective cohort study of subjects diagnosed with ADHD as a child or adolescent we showed that a history of stimulant treatment ever in life is associated with an increased risk of 1.8 times for life time drug use in general (cannabis, party- and hard drugs), and that the increased risk was particularly associated (1.6 times) for life time cannabis use. This result is not in line with findings from previous follow up studies from childhood into adolescence or early adulthood which showed an absence of influence of stimulants on drug use [16, 32, 35-39, 42-45]. Comparison with other prospective cohort studies is difficult given the diversity of definitions of drug use and inclusion criteria of subjects, underestimation of co morbid oppositional or conduct disorders, differences in mean age at follow up or differences in dosage and duration of stimulant use. An explanation of the difference in findings might be that the group of adults treated with stimulants were characterised by a more severe for of ADHD or comorbid problems compared to the group without stimulants, which is suggested by use of stimulants and the higher frequency of psychological treatment in this group.

If this were true, it might account for the differences in drug use between the two groups. Lambert found that a higher severity of symptoms in subjects with ADHD increased the risk for dependence on substances with stimulating properties in adulthood (i.e. tobacco, cocaine, and stimulants) [33]. Molina and Pelham stated that severity of childhood inattention symptoms predicts substance use outcomes, even after controlling for disruptive symptoms in childhood [55]. Unfortunately, information on severity was not present in the current study since DSM classification does not differentiate between less or more severe forms of ADHD. It is hypothesised that cannabis can be used as "self medication" to "treat" ADHD symptoms, due to its sedative and relaxing effect [58,59]. So the use of cannabis and the use of stimulants might both be a sign of more serious problems. This self-treatment is facilitated by the tolerant drug policy towards cannabis, and by the low costs and easy availability of cannabis in coffeeshops in the Netherlands. For example, during the month before interviewing, the use of cannabis in 12-18 year olds was 7.7% and for XTC 0.9%, which rates are both higher than in other countries in 2011 in the Netherlands [60]. Of note, in the same group the use of cocaine was 0.8% and of opiates less than 0.2% (heroin), which is comparable to other countries, while the use of amphetamines, showing an occurrence of 0.6%, was lower than elsewhere [60]. For 15-64 year olds,

the use of cannabis (7.0%), cocaine (1.2%) was comparable with the use in other countries in 2009 the year before. Use of XTC (1.4%) was higher and of opiates (heroin) (0.1%) and amphetamine (0.4%) was lower.

Further, we conclude that a comorbid externalizing disorder was a powerful predictor of life time drug use in general (cannabis, party- and hard drugs) and life time and daily cannabis use in adulthood in subjects diagnosed with ADHD at young age, independent of a history of stimulant use. This finding was also reported by Lynskey, Flory, Molina, Wilens, Bussing and Lee [14, 19, 32, 53-55]. Demoralization and feelings of failure are suggested to explain why comorbid externalizing disorders increase substance use and abuse [3, 19, 37].

Our results showed that females diagnosed with ADHD in childhood or adolescence are less vulnerable for life time drug use in general and life time cannabis use at follow up, which is independent of stimulant treatment. Prevalence data of the general population show that boys tend to use more alcohol and drugs than girls, so, this finding is concordant with findings in the general population [61,62].

A former hypothesis was that an early start age of stimulant treatment and therefore an early detection of ADHD in childhood or adolescence might decrease the risk for substance use in adulthood [16, 37, 45]. We found no significant moderation effect however by age of ADHD diagnosis of the effect of stimulant medication history on any of the types of life time or daily drugs use. (i.e. life time or daily cannabis use, life time party- or hard drug use) in the present study.

In our study, almost 25% of the adults diagnosed with ADHD as a child or adolescent had a history of stimulant use ever. This percentage seems nowadays rather low, but could be explained by the fact that during the early period of this study psychiatrists did not prescribe stimulants as often as currently. An alternative or additional explanation is that there might be an underestimation of medication use of the responders. Between 7.3% (1992-1996), 41.5% (1997-1999) and around 60% (1996-2005) of children with ADHD are treated with ADHD drugs in studies of clinical samples [63-65]. These differences can reflect prescription preferences in different countries, among population or mental health institutes or reflect change of view on psychotropics use during the years.

We used a self report follow up questionnaire in our study. We can not be sure whether subjects remembered details of their pharmacological treatment or other issues, so the results of our study should be interpreted with care. Second, it was not possible with our data to analyze whether specific symptoms of ADHD like inattentiveness could predict increased risk for life time or daily drug use in adulthood. Molina stated that severity of childhood inattention symptoms predicted substance use outcomes, even after controlling for disruptive symptoms in childhood [55].

Despite these limitations, we feel confident to conclude that a history of stimulant treatment ever in life, especially in males, increased the risk for life time drug use in general but is especially associated with the risk for life time cannabis use. Although one can not rule out that stimulant use is associated with the level of impairment, these findings draw attention to the fact that by treating the ADHD symptoms in childhood or adolescence, the risk for life time drug use later in life might be increased.
We emphasise that stimulant treatment improves clinical outcome later in life for example in reducing risk of developing depressive or anxiety disorders or disruptive behavior [52]. However, clinicians should be aware of the potential negative effects on drug use as well. The current results have at least two important implications for clinicians. First, patients as well as their family should be informed of the heightened risk for drug use in patients with ADHD and the possible influence of treatment with stimulants, especially in boys. Second, clinicians should carefully consider the potential benefits and harms for each individual patient. For instance, in case patients have family members known for drug dependence, alternative treatments such as non-stimulant or psychological treatment could be considered.

Of note, comorbid externalizing disorders increased the risk for life time drug use in general and life time and daily cannabis use in adulthood, independent of stimulant use ever. The data suggest that diagnosis of ADHD early in life might decrease the risk for life time hard drug use in adulthood, so, this should be a focus of future research. Future research should further focus on other moderators of life time or daily substance use such as type of ADHD medication (stimulant vs non-stimulant treatment), on differences in gender, on the effect of special preventive interventions on substance use during treatment of ADHD, and on identification of symptom clusters of ADHD that could possibly predict increased risk for substance use and abuse and/or compared to different kind of drugs.

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4

General discussion

When looking at Attention Deficit Hyperactivity Disorder (ADHD) as a collection of behaviour symptoms, one must conclude that these symptoms have been recognized since a long time. Signs of the known symptoms of disorders or deviant behaviour can be found in ancient (medical) documents, paintings, novels and movies. For example, the famous Dutch painter Jan Steen (1626-1679) has made vivid paintings of households. The Dutch proverb "it looks like the household of Jan Steen" (in Dutch: "Dit lijkt wel het huishouden van Jan Steen") refers to any busy, not well organised, chaotic situation. In the biography of the Dutch naval hero Michiel Adriaansz. de Ruyter (1607-1676) one can recognise hyperactive, thrill seeking and impulsive behaviour. The story of "Fidgety Philip" written by childrens' author Hoffmann (1809-1894) is telling us about a restless boy, who "flutters, rocks, fidgets and clatters at table". Dutch childrens' books and movies such as "Pietje Bell" and "Kruimeltje" and the world famous stories of A.A. Milne's Winnie the Pooh and his friend Tigger are showing us too uncontrollable impulsive and hyperactive behaviour. The Scottish physician sir Alexander Crichton (1763-1856) wrote one of the oldest manuscripts about a mental state comparable with ADD "An inquiry into the nature and origin of mental derangement", stating, "the incapacity of attending with a necessary degree of constancy to any object, almost always arises from an unnatural or morbid sensibility of the nerves, by which means this faculty is incessantly withdrawn from one impression to another. It may be either born with a person, or it may be the effect of accidental diseases." (1).

Presuming that the urge to describe these symptoms has been felt for a long time, one can state that it is probably as old as mankind to cluster symptoms into classifications or diagnosis and to try to unravel mechanisms of diseases and to search for treatment options to alter the prognosis. It was not until the beginning of the 20th century, as written in this thesis' Introduction, that by accident a pharmacological treatment of clustered behavioural symptoms, now classified as ADHD, was found.

Research conducted during the last decades shows that psychopharmacological treatment of ADHD in combination with other forms of therapy can be very effective. However, research also shows that there are also patients who do not respond well to medication, that they suffer from side effects or dislike medication possibly leading to non-adherence. The last few years public debate has raised the question whether ADHD really "exists", whether it is over- or underdiagnosed or whether it is treated too

often with medication instead of psychosocial, dietary, school or psychotherapeutic interventions.

In this thesis about ADHD medication we focused on two main themes. The first theme was to describe patterns of use of ADHD medication in the Netherlands in relation to the introduction of extended release ADHD medication and patient characteristics such as age, gender and ethnic background. We have found that the overall incidence of use of ADHD medication has increased over time, mainly among 6-11 year old boys. After introduction of the extended-release ADHD medication most subjects still started with immediate-release methylphenidate, but in a few years' time the use of extended-release ADHD medication increased considerably. Especially adolescents were likely to be initiated on extended-release methylphenidate. The discontinuation rate of incident ADHD medication use was high within a year after initiation, especially among female subjects and adults. The discontinuation rate of incident ADHD medication decreased over time because of increased switching to another ADHD medicine or addition of another ADHD medicine to the first prescribed, following the availability of extended release ADHD medication.
The proportion of Moroccan and Turkish patients with ADHD never using ADHD medication during the study period and the proportion of them that discontinued ADHD medication whitin five years was higher, although not associated with socio-economic status, compared to native Dutch and Surinam patients with ADHD.

The second theme was to investigate short and long term outcomes of use of ADHD medication as for the risk of injuries and the association with illicit drug use.
We found a twofold increased overall incidence of hospital admissions for injuries in the ADHD medication cohort compared to the control cohort, not using ADHD medication. Further we found that the incidence rate for injuries during exposure to ADHD medication was lower than before exposure to ADHD medication (though not statistically significant). However, the overall risk in the ADHD medication cohort was higher than in the control cohort. At last, we concluded, in contrast to international studies, that a history of stimulant treatment increased the risk for life time illicit drug use, particularly cannabis, in adults diagnosed with ADHD at childhood or adolescence.

In this general discussion two themes will be further elaborated upon:
→ we need a differentiated view of factors influencing the increase of first prescriptions and persistent use of ADHD medication.
→ challenges and barriers in long-term follow up research in children and adolescents with ADHD.

We will further discuss these issues and describe in addition some clinical implications of our findings and some perspectives for future research.

Factors influencing the increase of ADHD medication use and variability in persistence

We found an increase in prescriptions for incident and persistent use of ADHD medication over the years, as described in Chapters 2.1 and 2.2. In the diagnostic-therapeutic pathway from signaling a problem to getting a prescription for ADHD medication and the actual use thereof by the patient a lot of factors are of influence. We reflect upon several of these factors below.

Signaling symptoms of ADHD

(Grand)parents, playgroup- or schoolteachers are usually the first to notice behavioural symptoms that could be an indication for ADHD [2].
The probability that they label the observed behavioural symptoms as a problem is depending on their experience, their knowledge and their prejudice. Recently, awareness "that there could be something wrong" is rising with the increased attention for behavioural, emotional and learning problems in children in public health, at schools and in the media. More parents appear already to be able to identify hyperactive behaviour and attention problems in preschoolers [3,4]. For the clinician it is important to obtain information about the behaviour problems in different settings and from different raters in order to be able to weigh this information. The information of parents about ADHD symptoms does not often correlate high with the teachers' or physical educators' view, which is explained by Wolraich [5], Tripp [6], Hartman [7], Murray [8], Sayal [9] and Efstratopoulou [10]. So, one reason that there is an increase

in ADHD diagnosis and prescriptions might be that there is more common knowledge about the symptoms of ADHD at different ages.

Labelling behavioural symptoms as a problem

Symptoms will be labeled as problematic behaviour if the development and wellbeing of the child itself, brothers or sisters, parents, classmates and teachers are jeopardized.

Labeling behaviour as a serious developmental problem has an advantage in the Netherlands. Parents can ask for a so called Personal Budget ("Persoons Gebonden Budget") for which they can buy their own extra support at home, once the problems of their child are recognized according to the DSM criteria with a classification. Schools can get extra money ("Leerlinggebonden budget") for training teachers to cope with children with serious behavioural problems, again, only if the child is diagnosed with a psychiatric disorder according to the DSM criteria. The indication for this intensive support must be renewed every two year. So, since the system is explicitely asking for DSM classifications to access the adequate help, more effort is put into systematic diagnostic protocols for children with ADHD symptoms in order to be able to give them the right support and interventions. This could be a probable cause of the increase of ADHD diagnosis and prescriptions in the Netherlands.

Further, educational principles have been changing over the past few years. Due to new insights about learning environment and adequate learning strategies there is an increasing appeal on working together and planning your work on your own. Children with (a vulnerability for) ADHD (symptoms) will probably be more challenged in this system than other children and more easily drop out of this system. This might be another factor that influences the incidence of ADHD diagnosis and prescriptions [(11)].

Seeking help

Before consulting the general practitioner or youth health care medical practitioner, parents must have made a consideration whether they should or should not seek help. Personal experience (knowledge, prejudices, believes) and mass media can influence their decision.

Professionals can use diagnostic guidelines when to refer children and they are, even as parents, influenced by their personal experience, by mass media and by professional training and literature about ADHD [(12)].

Sciutto [12] presumed that "interpretation of information from each of these sources is potentially subject to cognitive biases". This explaines why the incidence of diagnosis can be different in different periods, due to new insights, common opinion and even by hypes that result in 'over focus' and that can influence and even bias professionals.

During the first decade of the 21st century the Dutch national government has increasingly introduced the ideas of an open market and supported new free market initiatives. As a result the number of mental health care centres and offices of psychologists has expanded. Since supply and demand are keeping each other in balance, it is possible that this mechanism lowered the barriers for parents and patients for seeking help, getting a diagnosis and treatment for ADHD.

Diagnosing ADHD

The criteria for ADHD have changed, especially widened, from the DSM II to the DSM 5 during the last decades (see Introduction). Therefore, an increase in prevalence of ADHD could be expected, although with some DSM versions ADHD patients/subtypes could also be missed, because certain symptoms were not included in the criteria for ADHD [12,13].

There is a lot of debate whether the prevalence of ADHD has really increased because research on prevalence has been performed with different methods of assessment, by different raters and in different populations [12,13]. Prevalences in studies using parent or teacher reports are usually higher and do often not include all DSM criteria compared to those using clinical reports. Bruchmuller [11] showed that almost 20% of the clinicians diagnosed ADHD without fulfilling all criteria, so they overdiagnosed ADHD. Also, variability in use of assessment procedures and experience may cause diagnostic inaccuracy. Overlap of symptoms of ADHD with other disorders such as depression, anxiety, oppositional defiant disorder or conduct disorder, without a correct assessment, may increase the number of incorrect diagnosis of ADHD [12].

Further, research on gender differences showed that girls with lower levels of behaviour problems and a higher level of inattention and concentration, internalizing and social problems, are probably underdiagnosed. Assessment scales are often based on male norm groups, so girls with ADHD could easily been misdiagnosed [12]. Although we did not perform a study on prevalence or assessment of ADHD, it is striking that the percentage of Moroccan and Turkish girls with ADHD, included in

our study on ethnic differences, is lower compared to native Dutch and Surinam girls (Chapter 2.3). This suggests an even higher risk for underdiagnosing ADHD symptoms in Moroccan and Turkish girls, although Dutch studies showed that the prevalence of psychiatric disorders among youth of different ethnic origin is equally divided [14-23].

Our studies (Chapter 2.1, 2.2, 2.3) do not address the question whether the prevalence of ADHD is rising, because they were designed to study the incidence of prescriptions of ADHD medication over the years. However, factors that influence the recognition of ADHD symptoms as described above may influence prescription rates of ADHD medication as well.

Treatment proposal

As mentioned in the introduction of this thesis, the treatment of ADHD is focused on biological, environmental and psychosocial levels of functioning. Over the last years, the treatment options, besides medication, have widened. Not every treatment option is found to be equally effective. In an extended meta-analysis of randomized controlled trials of nonpharmacological interventions, Sonagu-Barke [24] concluded that only free fatty acid supplementation had a small effect in reducing primary symptoms of ADHD. Results of a recent review show "moderate to high level evidence" that, after 14 months of use, medication combined with behavioural interventions or medication alone have a positive result on the core ADHD symptoms and on academic performance [25]. The mean effect size of stimulants is between 0.6 and 1.8, depending on the rater, which is very high compared to the effect of other psychotropics or to somatic medication [26]. The high effect size combined with a very quick and often impressive effect of reduction of ADHD symptoms may stimulate the physician to propose medication. The increase in prescriptions of ADHD medication could also reflect a higher acceptation rate of psychopharmacological treatment as a treatment option, which is also more evidence based. In clinical practice, it is noticed that, due to public opinion, some parents only wish for medication for their child and do not want to reflect on other possible factors that may influence the ADHD symptoms. Factors such as the possible effect of suboptimal interaction between the child's and their own or the teachers behaviour. Further, sometimes parents feel obliged by teachers to start with ADHD medication. Without medication their child will be banished from school as told by the teachers.

Use of medication

The impact of results of studies on increase of use of ADHD medication use must be carefully analyzed and compared because of differences in included age categories, included populations (general/clinical) or differences in definitions of medication use. Increase in medication use in a general population can expect to be lower than in a clinical population with ADHD. Use can be defined as the number of prescriptions, independently if it is or is not for a unique subject, or as the number of subjects getting medication prescribed, calculated for as prevalent or incident use or as duration of use [27-33].

We found a 6.5 fold increase in incidence of ADHD medication use between 2001 and 2006 (Chapter 2.1). Incidence increased most in 6-12 year old boys, but also in females, young children and adults. The large increase in incidence of stimulant prescription as found in other (inter)national studies was confirmed by our study and was also associated with gender (male) and age (6-12 year olds) ([29-31, 34-44]. The rapid growth in treatment with stimulants among girls is probably caused by better recognition of ADHD -mainly ADD- symptoms in girls by parents, teachers and health care professionals, which results in higher diagnostic rates [45]. Although rising prescriptions of ADHD drugs to very young children are of public concern in the US, we found in our study (Chapter 2.1) that the increase in incidence was lowest among children <6 years [42]. Prior to the start of stimulants in these young children, we found a high percentage of (off-label) prescriptions of typical antipsychotics, suggesting a need for a psychopharmacological intervention due to severe behavioural symptoms in these youngsters. Increase in prescription rates in adults may be influenced by better recognition and referral by a greater awareness among themselves and health care professionals, as well as the development of diagnostic tools, medication guidelines and treatment opportunities [46-48].

We found (Chapter 2.2) less discontinuation of incident ADHD medication use in the 3 study periods that reflect 3 consecutive time periods of one to one and a half years (from fewer than 60% to less than 45% after 1 year) because of increased switching (immediate release to extended release methylphenidate) and addition of ADHD medication following the availability of extended release methylphenidate and atomoxetine. The discontinuation frequency in our study is within the same range as found in other studies, although studies in adults report even higher discontinuation rates [44,49-53]. Only Coghill [53] reported a higher

continuation rate, namely that 77% of the parents of children (6-18 years) diagnosed with ADHD reported in an online questionnaire that the length of treatment was more than one year.

In clinical practice, patients need to be able to choose between subgroups of ADHD medication. Not all patients respond very well to immediate release medication. It is very hard for a child, adolescent or parent (who can have ADHD as well) to remember taking short acting medication twice or three times a day. Forgetfulness is one of the symptoms of ADHD! It is known that compliance and duration of use is increasing with the introduction of extended release medication and that patients with more severe ADHD symptoms switch more rapidly to extended release medication [54-56].

Ethnic background does influence the incident use and continuation or discontinuation of ADHD medication use (Chapter 2.3). Native Dutch and Turkish patients tend to start with ADHD medication before the ADHD diagnosis date at Altrecht, which can be an indication of differences in referral patterns and access to care. Native Dutch and Surinam ADHD patients have a higher continuation rate than Moroccan and Turkish patients with ADHD. Discontinuation rate is higher in Moroccan and Turkish patients, from whom a higher percentage never starts using ADHD medication during the study period. Feelings of shame, fear for stigmata, prejudices to mental disorders or treatment, negative experiences with professional agencies and language or cultural discrepancies are believed to explain this [57-61]. Our finding is consistent with other studies on differences in ethnic groups on prescription rates. In African-American, Latin-American, non-Hispanic black or Azian American children and adolescents, the percentage that is getting initial ADHD medication prescribed is lower than in Caucasian Americans and it was showed that the prevalence of ADHD medication prescriptions in Turkish and Moroccan populations was lower compared to Dutch natives in a Dutch study as well [44,62-72]. Surprisingly, despite this higher risk for mental disorders, prescription rates of medication for high prevalent disorders, appear to be lower in immigrant groups. Risk of discontinuation of ADHD medication within five years significantly differed and was 2.4 times higher in Moroccan and 1.6 times higher in Turkish patients compared to natives. This finding is consistent with findings in the USA from Winterstein [44] who found a higher percentage of Caucasian subjects continuing the use of stimulants compared to Hispanics or African Americans. In our study discontinuation is not explained by socio-economic status (SES) so we conclude that it is related to ethnic background.

Other factors influencing the continuation and discontinuation rate are: the organization of follow up care for evaluation of ADHD medication use, if the physician is working in a rural or urban region or with a younger or older population, privacy problems swallowing medication at school or stigmatization by classmates (especially in adolescents), influence of parents on their children (lower in adolescence), the financial situation of a family (if they can afford the high costs of (mostly not insured) extended release ADHD medication) or disturbing side effects or no effects at all [73,74].

Follow up research

Faraone showed in a meta-analysis that in nearly two-thirds of children with ADHD impairing ADHD symptoms remained in adulthood [75]. Follow up research is needed to provide information about the natural course, risk and prognosis of ADHD and results and safety of treatment. Research conducted during the previoud decades showed that psychopharmacological treatment of ADHD in combination with other forms of therapy can be very effective. However, research results also showed that a number of patients do not respond well to medication, suffer from side- or unexpected effects and dislike medication possibly leading to non-adherence.

In our study, we have found a doubled overall incidence of hospital admissions for injuries in the ADHD medication cohort (Chapter 3.1). Further, we found that the incidence rate for injuries during exposure to ADHD medication was lower, though not statistically significant. Still, the overall risk in the ADHD medication cohort was higher than in the control cohort. At last, in adults diagnosed with ADHD at childhood, we concluded that a history of stimulant treatment ever increases the risk for life time illicit drug use, particularly cannabis. This result does not confirm acknowledged international studies on the same subject (see Chapter 3.2).

In our studies (Chapters 3.1 and 3.2) we met several problems in conducting follow up research. Here under we will reflect on the challenges and barriers.

Changes over time

In our study on the association of stimulant treatment and drug use (Chapter 3.2), we lost trace of the adult subjects, who were diagnosed with ADHD as a child or adolescent. It took a lot of effort searching these subjects, whom from we did not know if they were still alive, where they lived, if they were still treated for any psychiatric disorder and if they would and could be approached for follow up research. In the Netherlands, as in many other countries, there is a gap between child- and adolescent psychiatry and adult psychiatry as it is as in paediatric and adult care for other somatic disorders. Patient files are not naturally transferred to the departments of adult psychiatry and most of the time patients have to change from hospital. Their medical record has to change as well from the system in which it is stored. In the Netherlands electronically stored patient information has been common but only since a few years. Further, different systems for transferring medical information are being used.

The change of diagnostic criteria of disorders like ADHD over time is another complication in follow up research. This makes comparison of the study population or outcome not always easy. For example in ADHD, the DSM III described 2 subtypes, the DSM IV and IV-TR described 3 subtypes whereas DSM II and III-R did not describe subtypes at all. The role of hyperactivity in the different DSM versions was more or less prominent. In our studies on trends in incidence (Chapter 2.1), using patterns of ADHD medication (Chapter 2.2) and association between ADHD medication use and injuries (Chapter 3.1) we only analysed subjects with ADHD medication use. There are no indications that ADHD medication is less effective in any of the core symptoms of ADHD such as hyperactivity, impulsivity, distractibility or concentration problems [2,76,77].

In the study described in Chapter 2.3 about differences in ADHD medication use in patients with ADHD from different ethnic backgrounds, we included diagnosed patients between 1999 and 2010. By that time, the DSM IV and IV-TR were used in the Netherlands. There were no differences between the DSM IV and IV-TR criteria. Only in our study (Chapter 3.2) on the association between stimulant treatment and illicit drug use in adults, diagnosed as a child or adolescent with ADHD, we had to face the problem that DSM III, III-R, IV or IV-TR criteria were used for classification of ADHD. We tackled this by postulating that all core symptoms of ADHD (hyperactivity, impulsivity, and distractibility and concentration problems) were represented in the different classifications.

Treated and untreated patients

Although it might be important to compare treated patients to untreated patients, it is obviously unethical in long-term follow up research to randomly assign patients with ADHD to treatment and non-treatment conditions. It is not allowed to restrain patients from a proven treatment for a long time. Often, patients with ADHD solve this "problem" -comparing treatment and non-treatment conditions by themselves, because they simply avoid treatment. However, untreated patients could not be traced in the present and, in our study used, databases in the Netherlands like from the Dutch Foundation for Pharmaceutical Statistics or PHARMO Record Linkage System. Identifying and finding untreated ADHD patients is very hard, but they are needed to compare the natural course, effects of interventions, risk factors and long term outcomes.

Chapter 3.1 reports on the association between ADHD medication use and injuries. We "solved" the problem by comparing subjects using and not using ADHD medication. In this study, we had no information about the underlying disorder, wherefore ADHD medication was prescribed. Several former studies concluded that prescription of stimulants is a valid indicator for the diagnosis of ADHD [78-80]. However, ADHD medication can also be prescribed for other medical conditions or in patients with autism spectrum or other neurodevelopmental disorders [81-83]. This approach (Chapter 3.1) may have resulted in some misclassification of ADHD in both ways: under- or overestimation of the effect. The outcomes and risk of injuries that we have found could be underestimated. The ADHD medication cohort could contain subjects who did not have ADHD, but were treated with stimulants. The reference cohort could contain subjects, not diagnosed with ADHD, while suffering from ADHD or suffering from ADHD but not treated with medication. Still, we feel confident to conclude that ADHD drug use may diminish the increased injury risk during exposure to ADHD medication, but the overall risk in the ADHD medication cohort was higher than in the control cohort.

Outcome measures

It can be hard to define outcome measures and to be sure that your measures are targeting correctly. In our study on injuries (Chapter 3.1), outcome events assessed were only the ones that required hospital admission. Injuries treated in the emergency room, by the general practitioner or by parents themselves were not assessed, possibly resulting in an underestimation of the true incidence of injuries. However, we chose a very clear definition of injury with this criterion.

In our study about the association between stimulant use ever and illicit drug use (Chapter 3.2), we had to rely on oral information of the subjects. To increase the reliability of the information about drugs use, collecting urine of blood samples for a very long time should be valuable, although expensive and very hard to perform as well. Outcome of our study (Chapter 3.2), that a history of stimulant treatment ever increased the risk for life time illicit drug use, particularly cannabis, in adults diagnosed with ADHD at childhood, is not in accordance with previous follow up studies from childhood into adolescence or early adulthood. Studies did not show an influence of stimulants on later drug use (no increased or altered risk), but there is some evidence that perhaps stimulants use protects from substance use later in life [84-95]. Comparison with other prospective cohort studies is difficult given the diversity of definitions of drug use and inclusion criteria of subjects, underestimation of comorbid oppositional of conduct disorders or differences in mean age at follow up. An explanation of the difference in our findings might be that the group of adults treated with stimulants were characterised by a more severe form of ADHD or comorbid problems compared to the group in our study without use of stimulants, which is suggested by use of stimulants and the higher frequency of psychological treatment in this group. Maybe the difference can also be explained by differences in public policy towards drug use between the the Netherlands and other countries. In the Netherlands drugs can be purchased with relative low costs and there is easy availability of cannabis in coffee shops in the Netherlands compared to other countries.

Use of data bases and ICT

It was not until the mid of the nineties of the 20th century, that pharmacies, health insurance companies and, much later, hospitals, designed computerised systems to systematic collect health care data. Before that time, researchers had to collect data for follow up research by collecting information from separate medical files by hand. This method was used in our UMCU study, described in Chapter 3.2.

Nowadays pharmacological data are collected by the Dutch Foundation for Pharmaceutical Statistics (Stichting Farmaceutische Kengetallen, SFK), PHARMO Record Linkage System, Psychiatric Casus Register (PCR), pharmaceutical companies and insurance companies. A problem, using these data sets for follow up, is that subjects can move and/or change from pharmacy or health care insurance company and disappear from the data set. We solved this problem by using strict criteria for inclusion in our

studies, like having a history of at least six or twelve months prior and after an index date (Chapters 2.1; 2.2; 2.3 and 3.1). Privacy of patients and ethical rules for scientific analysis became more and more important. As an illustration, we used to have postal codes and dates of birth to match cases, but nowadays this if forbidden. If we would have had access to postal codes and dates of birth we could have matched data from different datasets more easily. In our study (Chapter 3.2) about the association between stimulant treatment and illicit drug use, we had to sent all subjects questionnaires about their medication and illicit drug use instead of using computerised data about medication use during the past few years from pharmacies.

Clinical implications

- → Patients, parents and prescribers need to have a choice between different ADHD medicines. In case of non-response to a first-choice treatment, the broadened possibilities to switch to alternatives will contribute to increased treatment persistence. Our studies underline the use and need of immediate- and extended release ADHD medication and that, with the availability of extended release medication, discontinuation of medication use decreased over time, which may imply increase in compliance (Chapter 2.1 and 2.2).
- → Insurance companies must cover the costs for extended release ADHD medication, so all patients with ADHD can be offered the same psychopharmacological treatment options (Chapter 2.1, 2.2 and 2.3).
- → Special attention must be paid by clinicians to patients and parents of Moroccan and Turkish origin, because initial use of ADHD medication is low and discontinuation is high. Undertreatment can result in a higher risk of injuries and other negative outcomes in life (Chapter 2.3).
- → Patients and parents must be warned in health education about ADHD that some children and adolescents are more prone to accidents and probably need more protection in outdoor play or activities (Chapter 3.1).
- → It is important to assess the possible positive effect of ADHD medication on the risk on injuries, beside the well-known positive effect on hyperactive, impulsive and inattentive behaviour. Other treatment options such as physiotherapy should be advised as well (Chapter 3.1).

- → Clinicians should always ask for use of illicit drugs, alcohol and nicotine during their assessment and, if present, this should be discussed and treated (Chapter 3.2).
- → Patients as well as their families should be informed about the heightened risk for illicit drug use in patients with ADHD and the possible influence of treatment with stimulants, especially in boys. Clinicians should carefully educate them about conflicting results from other studies (stimulants could increase, decrease of have no effect on the risk for illicit drug use later in life) and consider the potential benefits and harms of medication use for each individual patient (Chapter 3.2).

Perspectives for future research

- → Development of more advanced databases for (follow up) research, and preferably one national database such as in Denmark of Iceland, is desirable. Data of psychiatric and somatic disorders, pharmacological prescriptions, other treatments, achieved school levels and performance, work and household should be filed. Then long-term follow up research and studies comparing treated and untreated patients, diagnosed with ADHD, could be more easily conducted (General Discussion).
- → With this desired national database, new analysis of ADHD medication use, patterns of use and objective factors influencing choices between immediate- or extended-release medications can be made from 1999-now. The effect of the introduction of other extended release methylphenidate preparats such as Medikinet CR® and Equasym XL® in 2007 could be studied. Analyses should be extended to elderly subjects of different ethnic backgrounds (Chapter 2.1, 2.2 and 2.3).
- → Subjective variables, such as the influence of (the media or pharmaceutical companies on) motivation, beliefs or prejudges of patients, parents, teachers or prescribers of all different ethnic backgrounds or changes in educational principles on initiating or discontinuing ADHD medication, should be studied (Chapter 2.1, 2.2, 2.3 and General Discussion).
- → The association of use and discontinuation of ADHD medication on school performance, comorbidity, marital and family stress, criminality in adolescence or the risk for serious accidents are

worthwhile to be looked at. Results should be implicated in clinical practice (Chapter 2.1, 2.2, 2.3, 3.1 and 3.2).

→ Future research should evaluate whether the risk for illicit drug use or injuries, not only treated in a hospital but also by an general practitioner or the parents, might be associated with differences between subgroups of ADHD medication (stimulant vs. non-stimulant treatment), with differences in gender or ethnic background, with the effect of special preventive interventions and with identification of influence of symptom clusters of ADHD (Chapter 3.1 and 3.2).

→ Little is know about differences in effects or side effects of ADHD medication in patients from different ethnic backgrounds. Possible differences and their genetically origin should be explored. Prescribers should have to pay attention in clinical practice, if differences are found, since this might have consequences for treatment (Chapter 3.1).

Final conclusions

Increase in incident use of ADHD medication is found, especially in 6-12 year old boys, but also in females, young children and adolescents. Longer use or less discontinuation within one year after ADHD medication initiation is found because of increased switching to an other ADHD medicine or addition of ADHD medication following the availability of extended release methylphenidate and atomoxetine. Ethnic background does influence the initial use and persistence of ADHD medication use: discontinuation rate within five years after the diagnosis date is higher in Moroccan and Turkish patients with ADHD, from whom a higher proportion never start using ADHD medication during the study period.

ADHD medication use may diminish the increased injury risk during exposure to ADHD medication. However, the overall risk on injuries in the ADHD medication cohort was higher than in the control cohort. In our study, a history of stimulant treatment increased the risk for life time illicit drug use, particularly for life time cannabis use, in adults diagnosed with ADHD at childhood.

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Summary

ADHD is a neurodevelopmental disorder, resulting from psychosocial, environmental, genetic and biological factors that can become visible in very early childhood, but also at school- or adult age. ADHD is characterised by inappropriate problems with attention, concentration, impulsivity and hyperactivity causing impairment in daily life. Ritalin® (methylphenidate) is one of the best known psychotropics used in children and adolescents today. This psychostimulant designed by the Italian chemist Leandro Panizon around 1944 and named after his wife Rita, unexpectedly improved behavioural problems and school performance in some children with post-pneumoencephalography headaches. This finding provided pharmacological treatment options for children with disrupting behavioural problems such as, as it is called nowadays, attention deficit hyperactivity disorder (ADHD).

This thesis about ADHD medication focused on two main themes. The first theme was the prescription patterns of ADHD medication. There was and is ample national and international evidence of the increasing use of ADHD medication. Little is known about the effect of the introduction of new long acting ADHD drugs including extended release methylphenidate (Concerta®) in 2003 and atomoxetine (Strattera®) in 2005. and in subjects older than 18 years in the Netherlands. Only twenty years ago ADHD was recognized as not only a child- or adolescent disorder but also as a adult disorder. Nowadays it is even diagnosed in the elderly. Little is known about changes in prescription of ADHD medication in adult patients.

In Chapter 2.1 of this thesis, the objective of the study was to describe changes in incidence of ADHD medication use and the prescription profiles of patients younger than 45 years starting treatment with these medicines between 2001 and 2006. We found that the overall incidence of ADHD drug use increased 6.5 fold in men as well as in women. The major proportion of all treated patients comprised of 6-11 year old boys. Most of them started with methylphenidate immediate-release. We found that in a few years' time the use of extended-release ADHD medication (Concerta® and atomoxetine (Strattera®) increased considerably despite the lack of full reimbursement of these extended-release medicines. Since we found that children and adolescents that initiated with atomoxetine were often previously treated with antipsychotics or clonidine/guanfacine. Further, we found that adults were often previously treated with SSRIs, benzodiazepines or antipsychotics. We hypothesised that psychostimulants and atomoxetine were probably used to address different treatment needs in children, adolescents and adults.

The second study in Chapter 2.2 described changes in patterns of ADHD medication use and determinants thereof among subjects younger than 45 years starting ADHD medication between 2001 and 2006 following the introduction of long acting ADHD medication including extended release methylphenidate (Concerta®) and atomoxetine (Strattera®). Most ADHD medication users were initiated on short acting methylphenidate between 2002 and 2006. We showed that discontinuation of incident ADHD medication use was high after three, six and twelve months after starting, but that discontinuation decreased over time since the availability of long acting ADHD medication. This made it possible to switch to another ADHD medicine or use more than one ADHD medicine at the same time. We found that combined ADHD medication therapy was not very common in the Netherlands.

In Chapter 2.1 and 2.2 we studied ADHD medication use and using patterns only comparing different age groups and gender. In Chapter 2.3 we hypothesised that there were differences in ADHD medication use between native patients with ADHD and with Moroccan, Turkish or Surinam backgrounds. We studied 817 patients younger than 19 years, referred to a center for mental healthcare between 1999 and 2010. We found that a higher proportion of ADHD diagnosed Moroccan and Turkish patients never used ADHD medication compared to Dutch natives. Native Dutch and Turkish patients more frequently started with ADHD medication before the ADHD diagnose date at the mental healthcare centre, which could be an indication of differences in either referral patterns and/or access to care. Almost all patients that used medication, around 80%, started with short acting methylphenidate. Discontinuation of ADHD medication within 5 years was highest in Moroccan and Turkish patients. A sensitivity analysis with a postal code matched comparison between Dutch natives and non-natives showed similar results, suggesting this effect is probably not explained by socio-economic status but by ethnicity.

In the second part of this thesis we investigated short and long-term outcomes of use of ADHD medication including the risk of injuries and the association with illicit drug use.

In Chapter 3.1 we studied an ADHD medication cohort as well as an up to six age/sex/index date sampled control cohort with no history of ADHD medication use. We found, as expected, that the overall incidence of hospital admissions for injuries was two times higher in the ADHD

medication cohort. We also found that the incidence rate for injuries during exposure to ADHD medication was lower in the exposed period compared to the period prior to ADHD medication use, although the difference was not statistical significant. However, the overall risk in the ADHD cohort was higher than in control cohort with no history of ADHD medication use. Use of ADHD medication and concomitant psychotropics increased the risk for injuries compared to only ADHD medication use. So, we tentatively conclude that ADHD medication use diminishes the increased injury risk in subjects treated with ADHD medication.

We investigated the long term benefit-risk balance of treatment of disorders like ADHD in Chapter 3.2. In this 20+ year follow up study we described the association between past stimulant treatment and life time or daily illicit drug use in adults who were diagnosed with ADHD as a child or adolescent, related to gender, IQ, psychological treatment, age of ADHD diagnosis, comorbid externalizing and internalizing disorders.
We concluded that a history of stimulant treatment increased the risk for life time illicit drug use, particularly cannabis, in adults diagnosed with ADHD at childhood. This result was in contrast to (inter)national studies on the same subject. Irrespective of stimulant use ever, a comorbid externalizing disorder diagnosed at young age (< 19 years) increased the risk for life time use of illicit drugs in general and life time and daily cannabis use in adulthood. The later in life a subject was diagnosed with ADHD, the higher the risk for life time hard-drug use at follow-up, independent of stimulant use. A limitation of this study was that we did nog have a non-ADHD cohort available to compare outcomes on illicit drug use.

In Chapter 4, the general discussion, we summarised the results of the different studies and put the results into a broader context. We discussed that we need a differentiated view of factors influencing the increase of first prescriptions and persistent use of ADHD medication. Further, we discussed the challenges and barriers in long-term follow up research in children and adolescents with ADHD. Many factors are of influence in the diagnostic-therapeutic pathway from signaling a problem to getting a prescription for ADHD medication and the actual use thereof by the patient.

We conclude that patients, parents and prescribers need to have a choice between different immediate- and extended release ADHD medicines.
In case of non-response to a first-choice treatment, the broadened

possibilities to switch to alternatives will contribute to increased treatment persistence. Special attention must be paid by clinicians to patients and parents of Moroccan and Turkish origin, because initial use of ADHD medication is low and discontinuation is high. Undertreatment may result in a higher risk of injuries and other negative outcomes in life. Patients and parents must be warned in health education about ADHD that some children and adolescents are more prone to accidents and drug use. Clinicians should inform patients as well as their families about the possible influence of treatment with stimulants on injuries and drug use.

The development of more advanced databases for (follow up) research, and preferably one national database, is desirable. Long-term follow up research and studies comparing treated and untreated patients, diagnosed with ADHD, could be more easily conducted. New analysis of ADHD medication use in patients 0-100 years old from different ethnic backgrounds on patterns of use and objective and subjective factors influencing choices between no medication use and use of immediate- or extended-release medication could be made from 1999-now. As little is known about differences in effects or side effects of ADHD medication in patients from different ethnic backgrounds, possible differences and their genetically origin should be explored.

Samenvatting

ADHD is een neurobiologische ontwikkelingsstoornis, die beïnvloed wordt door psychosociale-, omgevings-, genetische - en biologische factoren. ADHD kan zichtbaar worden vanaf peuter- of kleuter leeftijd, maar ook tijdens de adolescentie of op volwassen leeftijd. ADHD wordt gekenmerkt door problemen bij het richten en behouden van de aandacht, concentratie, impulsiviteit en hyperactiviteit, die tevens beperkingen in het dagelijks leven geven. Ritalin® (methylfenidaat) is een van de bekendste psychofarmaca die tegenwoordig bij kinderen en adolescenten wordt voorgeschreven. Rond 1944 werd dit psychostimulantium, vernoemd naar zijn vrouw Rita, ontworpen door de Italiaanse chemicus Leandro Panizon. Het bleek onverwacht gedragsproblemen te verminderen en schoolprestaties te verbeteren bij sommige kinderen met hoofdpijn ten gevolge van een pneumoencephalogram.
Deze bevinding voorzag in een farmacologische behandeling van kinderen met gedragsproblemen. Tegenwoordig worden deze problemen ook wel een aandachtstekortstoornis met hyperactiviteit (ADHD) genoemd.

In dit proefschrift over ADHD medicatie hebben we ons gericht op twee hoofdthema's.

Ten eerste hebben we ons gericht op het analyseren van voorschrijf-patronen van ADHD medicatie. Er was en is veel nationaal en internationaal bewijs over het toenemende gebruik van ADHD medicatie.
Er is weinig bekend over het effect op het gebruik na introductie van nieuwe langwerkende ADHD-medicijnen zoals methylfenidaat met verlengde afgifte (Concerta®) in 2003 en atomoxetine (Strattera®) in 2005.
Sinds ongeveer twintig jaar wordt ADHD niet alleen (h)erkend als een kinder- of jeugdpsychiatrische stoornis, maar ook als een volwassen stoornis. Tegenwoordig wordt het zelfs gediagnosticeerd bij ouderen.
Er is weinig bekend over veranderingen in het voorschrijven van ADHD medicatie bij volwassenen.

In Hoofdstuk 2.1 van dit proefschrift hebben we de verandering in de incidentie van ADHD medicatiegebruik en de voorschrijfprofielen van de patiënten jonger dan 45 tussen 2001 en 2006 in Nederland beschreven.
We vonden dat de totale incidentie van ADHD medicatie voorschriften bij mannen en bij vrouwen 6,5 keer was toegenomen. Het grootste deel van alle behandelde patiënten bestond uit jongens van 6-11 jaar. De meesten van hen begonnen met kortwerkend methylfenidaat. We vonden echter dat het gebruik van lang werkende ADHD medicatie in een paar jaar tijd aanzienlijk was toegenomen, ondanks het ontbreken van een vaak

volledige vergoeding van deze verlengde afgifte geneesmiddelen door de ziektekostenverzekering. We vonden dat kinderen en adolescenten, die startten met atomoxetine vaak eerder werden behandeld met een antipsychoticum of clonidine / guanfacine en dat volwassenen vaak eerder werden behandeld met een serotonineheropnameremmer (SSRI), een benzodiazepine of een antipsychoticum. We veronderstelden dat psychostimulantia en atomoxetine waarschijnlijk werden gebruikt om aan verschillende behandelingsbehoeften te voldoen bij kinderen en adolescenten en volwassenen.

In de tweede studie in Hoofdstuk 2.2 werden veranderingen in de patronen van ADHD medicatiegebruik en de determinanten daarvan bij personen jonger dan 45 jaar beschreven. Deze patronen werden beschreven over een periode tussen 2001-2006 na de invoering van langwerkende ADHD medicatie zoals methylfenidaat met verlengde afgifte (Concerta®) en atomoxetine (Strattera®). Tussen 2002-2006 begonnen de meeste ADHD medicatie gebruikers met kortwerkend methylfenidaat. We toonden aan dat het staken van voor het eerst gestarte ADHD medicatie hoog was na 3, 6 en 12 maanden na de start. Het staken van eerst gestarte ADHD medicatie nam af over de tijd nadat langwerkende ADHD medicatie beschikbaar kwam. Dit maakte het mogelijk om over te schakelen naar een andere ADHD medicament of om tegelijkertijd meerdere ADHD medicijnen voor te schrijven. Wij vonden overigens dat gecombineerde ADHD medicatie therapie niet erg gebruikelijk was in Nederland.

In Hoofdstuk 2.1 en 2.2 bestudeerden we ADHD medicatiegebruik en gebruikerspatronen waarbij we alleen verschillende leeftijdsgroepen en geslacht vergeleken. In Hoofdstuk 2.3 onderzochten we de hypothese dat er verschillen zouden kunnen zijn in ADHD medicatiegebruik tussen autochtone Nederlandse patiënten met ADHD en patiënten met een Marokkaanse, Turkse en Surinaamse achtergrond. We bestudeerden 817 patiënten jonger dan 19 jaar, die tussen 1999 en 2010 gediagnosticeerd waren met ADHD bij een centrum voor geestelijke gezondheidszorg. Wij vonden dat een groter deel Marokkaanse en Turkse patiënten nooit ADHD medicatie gebruikte in vergelijking met autochtone Nederlanders. Autochtone Nederlandse en Turkse patiënten begon vaker met ADHD medicatie voor de ADHD diagnose datum gesteld bij het centrum voor geestelijke gezondheidszorg. Dit zou een indicatie kunnen zijn dat er verschillen bestaan in verwijzingspatronen en/of toegang tot zorg tussen de verschillende etnische groepen. Vrijwel alle patiënten die medicatie

gebruikten, ongeveer 80%, startten met kortwerkende methylfenidaat. Staken van ADHD medicatie binnen 5 jaar was het hoogst bij Marokkaanse en Turkse patiënten. Een sensitiviteitsanalyse waarbij werd gematched op postcode gebied toonde vergelijkbare resultaten tussen Nederlandse autochtonen en allochtonen patiënten met ADHD. Dit effect wordt dus waarschijnlijk niet verklaard door de sociaal economische status maar door de afkomst.

In het tweede deel van het proefschrift werden korte- en lange termijn effecten van ADHD medicatiegebruik onderzocht, waaronder de kans op verwondingen waarvoor ziekenhuisopname en de associatie met gebruik van illegale drugs.

In Hoofdstuk 3.1 onderzochten we een ADHD medicatiecohort in vergelijking met een tot zes keer zo grote controlecohort gematched op leeftijd / geslacht / index datum zonder voorgeschiedenis van ADHD medicatiegebruik. We vonden, zoals verwacht, dat de totale incidentie van ziekenhuisopnames voor verwondingen twee keer hoger was in het ADHD medicatiecohort. We vonden ook dat de incidentie van verwondingen tijdens de blootstelling aan ADHD medicatie lager lag in de periode van ADHD medicatiegebruik ten opzichte van de periode voorafgaand aan ADHD medicatiegebruik. Het verschil was statistisch niet significant. Echter, het totale risico op verwondingen waarvoor een ziekenhuis-opname nodig was lag in de ADHD medicatiecohort hoger dan in het controlecohort, dus bij kinderen en adolescenten zonder gebruik van ADHD medicatie. Gelijktijdig gebruik van ADHD medicatie en andere psychofarmaca verhoogde het risico op verwondingen nog meer. We concludeerden dat ADHD medicatiegebruik het verhoogde risico op letsel kan verminderen bij patiënten die werden behandeld met ADHD medicatie.

Vervolgens onderzochten we de balans tussen kosten/risico en baten van de behandeling van een stoornis als ADHD in Hoofdstuk 3.2. In deze 20+ jaar follow-up studie beschreven we de associatie tussen het gebruik van een stimulantium en het gebruik van illegale drugs ooit tijdens het leven of dagelijks bij volwassenen die als kind of adolescent werden gediagnosticeerd met ADHD, gerelateerd aan geslacht, IQ, psychologische behandeling, leeftijd van de diagnose ADHD, comorbide externaliserende en internaliserende stoornissen. Wij concludeerden, in tegenstelling tot andere (inter)nationale studies, dat een geschiedenis van behandeling met een stimulantium een verhoogd risico geeft op het ooit gebruiken

van illegale drugs, vooral cannabis. Ongeacht het gebruik van een stimulantium ooit, gaf een comorbide externaliserende stoornis gediagnosticeerd op jonge leeftijd (< 19 jaar) een verhoogd risico op het ooit gebruiken van illegale drugs in het algemeen, maar ook op het ooit en dagelijks gebruik van cannabis op volwassen leeftijd. Hoe later in het leven ADHD werd gediagnosticeerd, hoe hoger het risico op het ooit gebruiken van harddrugs ten tijde van de follow-up, onafhankelijk van het gebruik van stimulantia ooit. Een beperking van deze studie was dat we geen niet-ADHD cohort hadden om uitkomsten van drugsgebruik te kunnen vergelijken.

In Hoofdstuk 4, de algemene discussie, hebben we de resultaten van de verschillende studies samengevat en de resultaten in een bredere context geplaatst. Hierbij bespraken we dat er gedifferentieerd gekeken moet worden naar factoren die de stijging van de voorschriften van ADHD medicatie en het continueren van gebruik kunnen verklaren. Verder hebben we beschreven dat er nog heel wat uitdagingen zijn en barrières moeten worden overwonnen om adequaat lange termijn follow-up onderzoek bij kinderen en adolescenten met ADHD te kunnen uitvoeren. Vele factoren zijn van invloed op het diagnostische therapeutische traject van het signaleren van een probleem tot het voorschrijven van een recept voor ADHD medicatie en het daadwerkelijke gebruik ervan door de patiënt.

We concluderen dat patiënten, ouders en voorschrijvers een keuze moeten kunnen maken tussen verschillende kortwerkende en langwerkende ADHD medicijnen. Bij non-respons op een middel van eerste keuze, zal de toegenomen keuzemogelijkheid voor een ander middel de compliance kunnen verhogen. Bijzondere aandacht moet door clinici worden besteed aan patiënten en ouders van Marokkaanse en Turkse afkomst omdat zij ADHD medicatie minder vaak starten en sneller en vaker staken. Onderbehandeling met ADHD medicatie kan namelijk resulteren in een verhoogd risico op blessures en kan ook andere negatieve resultaten later in het leven geven. Patiënten en ouders moeten adequate gezondheids-voorlichting over ADHD krijgen, bijvoorbeeld dat sommige kinderen en adolescenten groter risico lopen op ongelukken of drugsgebruik. Zij moeten hen zorgvuldig informeren over mogelijke effecten van behandeling met stimulantia op ongelukken en drugsgebruik.

De ontwikkeling van meer geavanceerde databases, bij voorkeur een landelijke database, voor onderzoek is wenselijk. Lange-termijn follow-up onderzoek en vergelijkende studies van behandelde en onbehandelde ADHD patiënten kunnen op die manier gemakkelijker worden uitgevoerd. Nieuwe analyses van ADHD medicatiegebruik bij patiënten van 0-100 jaar met een diverse etnische achtergrond, naar gebruikspatronen en objectieve en subjectieve factoren die keuzes beïnvloeden tussen het al dan niet starten met kort- of langwerkende medicatie kunnen worden uitgevoerd vanaf ongeveer 1999 tot nu. Omdat er weinig bekend is over verschillen in effect en bijwerkingen van ADHD medicatie bij patiënten met ADHD met een verschillende etnische achtergrond, is het zinvol mogelijke verschillen en de genetische oorsprong hiervan te onderzoeken.

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The CNS clinical pharmacoepidemiology research group

Background

Central Nervous System Clinical Pharmacoepidemiology is one of the research themes of the division of Pharmacoepidemiology & Clinical Pharmacology of the Utrecht Institute for Pharmaceutical Sciences (UIPS). The division of Pharmacoepidemiology & Clinical Pharmacology consists of a multidisciplinary team of young and internationally oriented researchers. The research program is directed at the epidemiological, therapeutic and policy aspects of drug use and their effects. The mission of the research program is to contribute to the knowledge of and decision-making in the effectiveness, safety and economics of drug usage.
In bridging the gap between the science of pharmacoepidemiology and the 'real world' of patients' drug usage and public health, the program covers a variety of methods and approaches from (molecular) epidemiology, pharmacovigilance, practice research and policy analysis. The myriad of research strategies provides an excellent environment for thoughtful learning and innovation in system therapeutics.

The Central Nervous System Clinical Pharmacoepidemiology research group focuses on the use and effects of psychotropic drugs in psychiatry and neurology, both in ambulatory care and in clinical settings. Principle investigators of this research group are Dr Eibert R Heerdink and Prof dr Toine CG Egberts. There is close collaboration with psychiatric hospitals including Altrecht and GGZ Centraal and with the University Medical Centre Utrecht.

Contact: www.uu.nl/science/pharmacoepidemiology

Theses from the CNS clinical pharmacoepidemiology research group

Dr Jochem Gregoor (2013)
Genetic Determinants of Antipsychotic Drug Response.
(Co)promotores: Prof dr ACG Egberts, Dr J van de Weide, Dr ER Heerdink

Dr Arne Risselada (2012)
Genetic determinants for metabolic abnormalities.
(Co)promotores: Prof dr ACG Egberts, Dr H Mulder, Dr ER Heerdink.

Dr Bart Kleijer (2011)
Balancing the benefits and risks of antipsychotics.
(Co)promotores: Prof dr ACG Egberts, Prof dr MW Ribbe, Dr ER Heerdink, Dr R van Marum.

Dr Wilma Knol (2011)
Antipsychotic induced parkinsonism in the elderly: assessment, causes and consequences. (Co)promotores: Prof dr AFAM Schobben, Prof dr ACG Egberts, Dr PAF Jansen, Dr R van Marum.

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(Co)promotores: Prof dr ACG Egberts, Prof dr H Vaarkamp, Dr M Smits.

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Curriculum vitae

Els van den Ban was born on the 15th of October 1967 in Rotterdam, the Netherlands. She completed Gymnasium B at the Marnix Gymnasium in Rotterdam. She enrolled in Utrecht University in 1986 studying psychology, and moved on to study medicine in 1987.

In the period between her doctoral exam and her clinical internship she was a junior research assistant in a longitudinal study of adolescents with a Multiple Complex Developmental Disorder at the Department of Child and Adolescent Psychiatry at the University Medical Centre Utrecht (UMCU). Her interest in behavioural problems motivated her to work during her clinical internship at the Forensic Department of the Amsterdam high security prison 'Bijlmerbajes' and at the Dr. F.S. Meijers Institute, Utrecht, specialized in Forensic Psychiatry and Selection.

After her graduation in 1994 she worked at the Dr. F.S. Meijers Institute, and subsequently she worked at different departments at the Department of Child and Adolescent Psychiatry at the UMCU were she started her training by professor dr. Herman van Engeland as a child- and adolescent psychiatrist. Following her professional training by professor dr. René Kahn at the Department of Psychiatry (UMCU), she became psychiatrist (1997-2001) and by 2002 she graduated as a child- and adolescent psychiatrist,

Between 2002-2007 she worked as a child- and adolescent psychiatrist and part-time as a medical manager of the child outpatient clinic (2002-2004) at the Department of Child- and Adolescent Psychiatry (UMCU). During 2007 Els started her Ph.D. project.

In 2007 Els started working as a child- and adolescent psychiatrist and medical manager of an outpatient clinic for patients with ADHD and behavioural problems at Altrecht, Mental Health Institute, Youth Department, Utrecht. She is a member of the Guideline Committee ADHD for general practitioners and youth health care, Trimbos Institute and a member of the expert committee ADHD of the Kenniscentrum Kinder- en Jeugdpsychiatrie.