Psychotropic Drug Use among Children

A Comparison of ADHD Drug Use in the Nordic Countries and the Effect of ADHD Drug Treatment on Academic Progress

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Thesis for the Degree of Philosophiae Doctor

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Geðlyfjanotkun meðal barna

Samanburður á notkun ADHD lyfja á Norðurlöndunum og áhrif lyfjameðferðar við ADHD á námsárangur

Helga Zoëga

Ritgerð til doktorsgráðu

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Ágrip

Enn vantar vísindalegan grunn um útbreiðslu geðlyfjanotkunar, meðferðaröryggi og áhrif ýmissa geðlyfja fyrir börn, þrátt fyrir aukna þekkingu um notkun og virkni geðlyfja fyrir börn síðastliðinn áratug. Athyglisbrestur og ofvirkni (ADHD) er taugaþroskaröskun sem 5-10% barna á skólaaldri glíma við. Örvandi lyfjameðferð er útbreitt meðferðarform fyrir börn með ADHD í Bandaríkjunum og í auknum mæli í Evrópulöndum. Vaxandi notkun ADHD lyfja er umdeild í ljósi mögulegrar of- og misnotkunar og vegna óvissu um langtímaáhrif lyfja. Enn er lítið vitað um langtímaáhrif örvandi lyfjameðferðar og þekkingu vantar um áhrif meðferðar á námsárangur barna með ADHD.

Niðurstöður okkar byggja á einstökum rannsóknaraðstæðum á Íslandi, sem felast í fágætu tækifæri til samtengingar gagna á landsvísu um lyfjanotkun og námsárangur barna á samræmdum prófum, ásamt lýðgrunduðum lyfjagagnagrunnum á öllum Norðurlöndunum. Markmið okkar var að (I) lýsa mynstri geðlyfjanotkunar meðal allra barna á Íslandi, (II) bera saman tíðni notkunar ADHD lyfja á Norðurlöndunum og (III) kanna tengsl námsárangurs og örvandi lyfjameðferðar hjá börnum með ADHD.

Í fyrstu rannsókn okkar lýstum við mynstri geðlyfjanotkunar meðal íslenskra barna. Niðurstöður sýndu að á árunum 2003 til 2007 var algengi geðlyfjanotkunar meðal íslenskra barna hlutfallslega hátt (48,7 á hver 1000 börn 2007). Algengust var notkun örvandi lyfja (28,4 á hver 1000 börn 2007) og þunglyndislyfja (23,4 á hver 1000 börn 2007). Bæði algengi og nýgengi þunglyndislyfjanotkunar lækkaði marktækt á rannsóknartímabilinu en algengi notkunar örvandi lyfja og geðrofslyfja jókst. Meðal þeirra 21.986 geðlyfja sem voru útleyst fyrir börn árið 2007 var rúmlega fjórðungur (25,4%) án ábendingar fyrir börn.

Í annarri rannsókn okkar bárum við saman notkun ADHD lyfja (örvandi lyf og atomoxetín) árið 2007 meðal nærri 25 milljóna íbúa Norðurlandanna. Marktækur munur fannst á lyfjanotkun milli landanna fimm. Lægst var algengið í Finnlandi (1,2 á hverja 1000 íbúa) en hæst á Íslandi (12,5 á hverja 1000 íbúa). Árið 2007 voru íslensk börn (7-15 ára) nærri fimm sinnum líklegri en sænsk börn til að fá útleyst ADHD lyf. Algengi notkunar var rúmlega fjórfalt hærra hjá norrænum drengjum (7-15 ára) en norrænum stúlkum. Meðal fullorðinna (21 árs og eldri) var notkun lyfjanna nær jöfn. Metýlfenídat var mest notaða ADHD lyfið í hverju landi og náði yfir rúmlega 80% notkunar árið 2007. Jafnframt var það eina lyfið með markaðsleyfi og endurgreitt á öllum fimm Norðurlöndum.

Þriðja rannsókn okkar var um tengsl upphafs örvandi lyfjameðferðar og námsframvindu hjá 9 til 12 ára börnum. Rannsóknin náði til barna sem höfðu tekið samræmd próf í stærðfræði og íslensku bæði í 4. og 7. bekk, alls 11.872 börn. Námsárangur barna úr almennu þýði stóð í stað milli 4. og 7. bekkjarprófa á meðan árangur barna sem fékk lyfjameðferð við ADHD versnaði almennt. Áhættan á versnun í námi var aukin meðal barna sem hófu lyfjameðferð seint (25-36 mánuðum eftir 4. bekkjarpróf) samanborið við þau börn sem hófu lyfjameðferð fyrr (≤12 mánuðum eftir 4. bekkjarpróf). Áhættuhlutfallið var 1,7 í stærðfræði og 1,1 í íslensku. Stelpum sem hófu lyfjameðferð seint var hættara við versnun í stærðfræði (áhættuhlutfall 2,7) en strákum (áhættuhlutfall 1,4).

Niðurstöður okkar, sem byggja á lýðgrunduðum upplýsingum úr miðlægum gagnagrunnum á Norðurlöndunum, benda til þess (I) að notkun geðlyfja, einkum örvandi- og þunglyndislyfja, sé algeng meðal íslenskra barna og (II) að töluverður munur sé á algengi örvandi lyfjanotkunar við ADHD milli Norðurlandanna. Ennfremur benda niðurstöður til þess (III) að börnum með ADHD sem hefja lyfjameðferð seint sé hættara við að hraka í námi en þeim sem hefja meðferð fyrr, sér í lagi í stærðfræði.

Lykilorð:

geðlyfjanokun, örvandi lyfjameðferð, ADHD, námsárangur, miðlæg gögn á landsvísu, lýðgrunduð rannsókn

Abstract

Attention-deficit hyperactivity disorder (ADHD) is a neurodevelopmental disorder affecting 5-10% of school-aged children. Drug treatment for ADHD with stimulants is now widely used as a therapeutic option in the US and increasingly in Europe. Nevertheless, the increasing use of ADHD drugs is debated, chiefly because of concerns of over-use, addiction and uncertainty of the long-term outcomes of treatment. Although research in pediatric psychopharmacology has expanded during the past decade, utilization studies have typically rested on limited data sources. Thus, the evidence base for prevalence of use and treatment safety, as well as long-term risks and effectiveness of many psychotropic agents for children remains fragmented. The long-term effects of stimulant treatment are largely unknown and evidence about their effect on academic progress among children with ADHD is limited.

Our studies are based on the unique setting in Iceland, the nationwide prescription drug registries now available in all Nordic countries and the rare opportunity of record linkage to national scholastic examinations in Iceland. We aimed to investigate patterns of psychotropic drugs use among the total pediatric population in Iceland, to compare ADHD drug use among all Nordic countries and, finally, to address whether children's academic progress is affected by the initiation of stimulant treatment for ADHD.

In Study I we found a markedly high prevalence between 2003 and 2007 of psychotropic drug use among children in Iceland (48.7 per 1000 in 2007). Stimulants and antidepressants were the two most commonly used psychotropic drugs in 2007, respectively with a prevalence of 28.4 and 23.4 per 1000 children. A statistically significant trend of declining prevalence and incidence of antidepressant use occurred during the study period, while prevalence increased for use of stimulants and antipsychotics. Out of 21,986 psychotropic drugs dispensed in 2007, 25.4% were used off-label for children.

In Study II we compared national use in 2007 of ADHD drugs (stimulants and atomoxetine) between all five Nordic countries, covering in total almost 25 million individuals. We found a significant difference in the extent of utilization between the countries. The prevalence of use varied from a low 1.2 per 1000 inhabitants in Finland, to a high 12.5 per 1000 in Iceland. Children aged 7 to 15 years were in 2007 almost five times more likely in Iceland, than in Sweden to have been dispensed an ADHD drug. Prevalence among Nordic boys (age 7-15) was 4.3-fold the prevalence among Nordic girls, while among adults (age 21+) women were almost as likely as men to use ADHD drugs. In all five Nordic

countries methylphenidate was the most commonly used ADHD drug, accounting for over 80% of the use in 2007. It was also the only ADHD drug with a valid marketing authorization and reimbursed in every Nordic county.

In study III we investigated the extent to which academic progress among 9- to 12-year old children is related to initiation of stimulant treatment, covering 11,872 children who took standardized tests in mathematics and language arts. In contrast with non-medicated children in the general population, children starting stimulant treatment between 4th and 7th grade tests presented with an overall academic decline. Compared with those starting stimulant treatment earlier (≤12 months after 4th grade test), children with later treatment start (25-36 months after 4th grade test) were 1.7-fold more likely to decline academically in mathematics and 1.1-fold more likely to decline in language arts. The adjusted risk ratio of mathematics decline with later treatment was higher among girls (RR, 2.7), than boys (RR, 1.4).

In conclusion, based on nationwide registry data from the Nordic countries our results indicate (I) a markedly high use of psychotropic drugs, especially of stimulants and antidepressants, among children in Iceland and (II) a considerable variation in use of ADHD stimulant drugs in the Nordic countries. Furthermore, our results indicate (III) that later start of stimulant drug treatment for ADHD is associated with academic decline, particularly in mathematics.

Keywords:

psychotropic drug use, stimulant drug treatment, ADHD, academic progress, nationwide registry data, population-based

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List of Abbreviations

ADHD, Attention-Deficit/ Hyperactivity Disorder

ADHD-C, Attention-Deficit/ Hyperactivity Disorder, Combined Type

ADHD-PHI, Attention-Deficit/ Hyperactivity Disorder, Predominantly Hyperactive Impulsive Type

ADHD-PI, Attention-Deficit/ Hyperactivity Disorder, Predominantly Inattentive Type

ATC, Anatomical Therapeutic Chemical Drug Classification System

CI, Confidence Interval

DDD, Defined Daily Doses

DSM IV, Diagnostic and Statistical Manual of Mental Disorders, fourth edition

e.g., exempli gratia

EMA, European Medicines Agency

et al.**,** et alii

etc., etcetera

GDP, Gross Domestic Product

ICD-10**,** International Classification of Diseases, revision 10

i.e., id est

MTA, Multimodal Treatment Study of Children with ADHD

no., number

OECD, Organization for Economic Co-operation and Development

PDCO, Pediatric Committee within European Medicines Agency

Prev., Prevalence

Prev. ratio, Prevalence ratio

RD, Risk Difference

RR**,** Risk Ratio

SNRI, Serotonin-Norepinephrine Reuptake Inhibitor

SPC, Summary of Product Characteristics

SSRI, Selective Serotonin Reuptake Inhibitor

TCA, Tricyclic Antidepressants

US, United States

UK, United Kingdom

vs., versus

WHO, World Health Organization

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This thesis is based on the following original publications, which are referred to in the text by their Roman numerals (I-III):

I. ***Psychotropic Drug Use among Icelandic Children: a Nationwide Population-Based Study.*** Zoëga H, Baldursson G, Hrafnkelsson B, Almarsdóttir AB, Valdimarsdóttir U, Halldórsson M. J Child Adolesc Psychopharmacol. 2009 Dec;19(6):757-64.

II. ***Use of ADHD Drugs in the Nordic Countries: a Population-Based Comparison Study.*** Zoëga H, Furu K, Halldórsson M, Thomsen PH, Sourander A, Martikainen JE. Acta Psychiatr Scand. 2011 May;123(5):360-367.doi: 10.1111/j.1600-0447.2010.01607.x. Epub 2010 Sep 23.

III. ***Stimulant Drug Treatment for ADHD and Academic Progress among Children***. Zoëga H, Rothman KJ, Huybrechts KF, Ólafsson Ö, Baldursson G, Almarsdóttir AB, Jónsdóttir S, Halldórsson M, Hernández-Diaz S, Valdimarsdóttir U. Submitted.

In addition, some unpublished data may be presented.

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Declaration of Contribution

The doctoral student, Helga Zoëga, planned the research work for studies I-III, applied for the appropriate ethical and research approvals, ran the statistical analyses for each study, drafted the manuscripts and wrote this thesis – with sound guidance of her supervisors, the doctoral committee and in close co-operation with the co-authors of each study.

1 Introduction

Transnational increase in psychotropic drug use among children has given rise to both recognition and concern of the effectiveness and safety of treatment. A public debate on pediatric drug use, especially of stimulants, antidepressants and antipsychotics, has ensued. Although the evidence-base for drug treatment of children with mental health problems has widened in recent years, there still remains a gap regarding their safety and effectiveness, especially in a long-term perspective. The fact that many psychotropic drugs are used off-label for children under 18 years of age underlines the importance of further research on pediatric psychotropic drug use and treatment.

We propose to examine how psychotropic drugs are prescribed and used among children in Iceland, compare the use of stimulant drugs for attention-deficit/hyperactivity disorder (ADHD) among all Nordic countries and elucidate whether stimulant treatment affects academic progress among children with ADHD.

1.1 Pharmacoepidemiology

Pharmacoepidemiology is the study of the use and effects of drugs in large numbers of people (2006b). It merges the fields of clinical pharmacology and epidemiology by applying the tools and methods of epidemiology to assess use and effects of drugs in confined places, time periods and populations. Large health care databases are often used to address research questions within pharmacoepidemiology.

The prescription of drugs is one of the most common interventions in health care. Treatment possibilities with drugs have advanced substantially over the past decades, due to continuous pharmaceutical development leading to the marketing of new drugs in the various disease areas. These advancements in treatment have brought about an increased need for pharmacoepidemiological studies to track how drugs are used in real life settings. With pharmacoepidemiology the beneficial, as well as potentially hazardous effects of drug treatment can be addressed. The year 2011, marks the 50th year since the “thalidomide disaster”, subsequent to the marketing of thalidomide. The drug was marketed as a mild hypnotic drug and shortly later a dramatic rise occurred in the frequency of a rare birth defect, phocomelia, i.e. the absence of limbs or parts of limbs (Strom, 2006b). With the tools of epidemiology this previously rare birth defect was traced to maternal use of the drug during pregnancy, i.e. in utero exposure to thalidomide. This disastrous finding confirmed the importance of pharmacoepidemiology and lead to regulatory improvements in drug safety

and to the establishment of national drug monitoring institutions around the world.

Although, the study of pharmacoepidemiology may be applied when performing clinical trials before drugs are marketed, it is mainly applied after drugs have been introduced to the market – often referred to as the post-marketing period. Randomized clinical trials are essential during the pre-marketing stage to evaluate the efficacy and safety of drugs. Such trials are limited in both size and time and most often they are performed on a relatively healthy and homogeneous group of individuals. When studying the effect of drugs, a major limitation of randomized clinical trials is their short time duration (both exposure time and follow-up time) and the homogeneous selection of participants. Rarely are important sub-groups such as individuals with co-morbid conditions, the elderly, pregnant women or children, included in randomized clinical trials (Strom, 2006b).

Non-experimental observational studies have the advantage over pre-marketing experimental trials in that they are able to follow-up on actual drug use over extended periods of time in large populations, much more diverse than those of pre-marketing trials. The study of pharmacoepidemiology can contribute information about safety and effectiveness that is not obtainable with pre-marketing clinical trials. This may include rare treatment outcomes, effects of long-term drug treatment and delayed effects of drug exposure. Computerization of medical health information has dramatically boosted the number of published register-based pharmacoepidemiologic studies over the past two decades (Bergman, 1992) (Strom, 2006a).

Pharmacoepidemiology may be descriptive or analytical. Descriptive studies often entail examination of drug utilization on a population level; how the drugs are distributed in a population, which drugs are used, in what quantity, by whom and how? Our Studies I and II are both examples of descriptive drug utilization studies. In analytical pharmacoepidemiology, associations of drug exposure and outcomes are studied, most often on the individual level. Randomization of individuals receiving drug treatment is not a viable option in these studies. Therefore, confounding and various sources of bias may become a major issue – especially confounding by indication. Methods to refrain from and assess the degree of these methodological complexities are thus essential and caution is imperative when causal assumptions are made about the observed associations. Our Study III is an example of an analytical approach in pharmacoepidemiology.

1.1.1 Nationwide Prescription Registers and Data Linkages in the Nordic Countries

The Nordic countries have a long history of registry-based epidemiological research. Ever since the early 1960s, researchers have contributed important scientific knowledge to the field of health, based on information from the various Nordic health registers. Reporting to the national registers is mandatory in each country and regulated nationally, resulting in very high completeness and data coverage. The parliaments in the Nordic countries have, on behalf of their populations, given informed consent to be included in the national registers (Rosen, 2002).

Among the first individual-based and centralized prescription drug databases were established in the Nordic countries and covered regions of Sweden and Denmark. The prescription register in Jamtland, Sweden, has been in operation since 1970. Similarly, the Odense University Pharmacoepidemiological Database and the Prescription Database of Northern Jutland were established over 20 years ago (Gaist et al., 1997; Hallas, 2001). Some pioneering studies in pediatric pharmacoepidemiology stem from these regional databases (Madsen et al., 2001; Thrane & Sorensen, 1999; Wessling et al., 1991). These Nordic regional databases are important, not only for their contribution to new knowledge in pharmacoepidemiology, but also because with them the need and potential of nationwide prescription drug registers became clear (Bergman, 1992; Wessling et al., 1991).

Today, through their nationwide prescription registers, the Nordic countries have a unique opportunity to follow drug utilization and potential treatment effects in the population. Each of the five countries now runs a centralized database with individual level information on dispensed prescription drugs to the total national population. Both reimbursed and non-reimbursed drugs are included in except the Finnish register, which only includes reimbursed drugs. These nationwide prescription databases hold continuous information on each filled prescription in outpatient care, e.g. data on dispensed item, substance, brand name, formulation, volume, date of dispensing, together with patient demographic information. The compiled data date back to 1994 in Finland, 1995 in Denmark, 2003 in Iceland, 2004 in Norway and 2005 in Sweden (Furu, 2008; Furu et al., 2010; Wettermark et al., 2007).

The prescription registers store all data under encrypted personal identification numbers of patients, unique to each citizen living in a Nordic country, allowing for data-linkages to other registers with data on outcomes and other factors important when studying medicine use. Among these registers are

in-patient registers, outpatient registers of health care centers, cancer registers, birth registers, cause-of-death registers and registers with socioeconomic and demographic characteristics. When studying rare drugs, rare patient groups, rare diseases or outcomes, large populations are essential. Pooling data from all the Nordic countries means that individual and valid data may be obtained for as many as 25 million people – making it possible to conduct some of the largest population-based pharmacoepidemiological studies in the world. Nordic prescription registers, are an excellent source of information for ascertainment of drug exposure, allowing for timely and detailed assessment of drugs used in large, representative populations under usual care conditions. The registers do, however, not include the indications why drugs are prescribed nor the prescribed daily dosage, which is a drawback in terms of pharmacoepidemiologic study validity.

Yet, with the prescription registers the Nordic countries have a world-unique opportunity to carry out population-based and cross-national comparative research in pharmacoepidemiology. By providing information on how drugs are used in practice, public health may be enhanced with identification of inappropriate use of drugs, which can in turn be prevented with interventions targeted at prescribers and patients. Furthermore, research based on the Nordic prescription registers is likely to contribute to increased knowledge on new and unknown effects of drugs and promote safer and more effective treatment. Currently, several research groups work actively with data from the prescription registers and have, in the relatively short time since their establishment, added important knowledge to the field of pharmacoepidemiology.

1.1.2 The Icelandic Medicines Registry

The Icelandic Medicines Registry is a centralized database containing national level data on near all dispensed prescription drugs to the outpatient population in Iceland since January 1st 2003. It holds individual level information, both on patients and prescribing physicians stored under encrypted personal identification numbers. Included are both reimbursed and non-reimbursed dispensed drugs, as well as drugs without valid marketing authorizations.

The Icelandic Medicines Registry was established in 2005 and is governed according to the Medicinal Products Act (with amendments) no. 93/1994. The register is operated by the Directorate of Health for purposes of general surveillance of national drug use and the prescribing of habit-forming and narcotic drugs. Each year approximately 2.3 million prescription drug fills are registered into the Medicines Registry. Initially, the Registry could by law only hold person-identifiable information for a period of three years. But in 2008 for

the purpose of research, the storage time was extended to a period of 30 years, similar to the storage time of the other Nordic prescription registers. In Iceland, due to regulations and other incentives motivating pharmacies to collect and send data of pharmacy records electronically to the centralized health insurance for reimbursement and on to the Medicines Registry, its accuracy and completeness is high. During the years 2003 to 2008 it covered between 93.7% and 99.9% of dispensed prescription drugs (Directorate of Health Iceland, 2003-2009; Icelandic Health Insurance Administration, 2003-2009).

Experience of the Medicines Registry, as a research tool, has just started to accumulate. Our studies are among the very first to be conducted with data from this relatively new Icelandic nationwide data source.

1.1.3 **Drug Classification System – ATC/DDD**

All drugs in the Nordic prescription registers are classified according to the World Health Organization Anatomical Therapeutic Chemical/Defined Daily Dose (ATC/DDD) classification (WHO, 2008). We relied on this classification system in our studies (I-III). The ATC/DDD system serves as a tool of standardization in drug utilization research. It facilitates the presentation of drug statistics and comparisons of drug utilization on a national and international level. The classification system is furthermore useful when evaluating trends in utilization and its associations to events facilitates greatly pharmacoepidemiological research.

The ATC/DDD system was originated by Norwegian researchers and has been in use since the early 1970's, first mainly in Europe and later internationally. In the 1990's the ATC/DDD system was coupled with WHO's initiatives to achieve rational use of drugs and universal access to needed drugs, particularly in the developing countries. The system on its first level classifies drugs into fourteen major groups, according to the organ or system on which the drugs act. Each of the first level classes contains four sub-levels (2^{nd} to 5^{th} level) where drugs are classified according to their chemical, pharmacological and therapeutic properties. For each new therapeutic agent, the WHO Centre for Drug Statistics Methodology decides decides the appropriate DDD, defined as the assumed average maintenance dose per day of the drug for its main indication in adults. The DDD is a technical unit and does not reflect actual prescribed dosages. Every year WHO updates a publicly available list of all drugs and their corresponding DDDs, where alternations are kept to a minimum for purposes of standardization. For more detailed information about ATC and DDD classification please see online Guidelines for ATC classification and DDD

assignment, issued by WHO Collaborating Centre for Drug Statistics Methodology: http://www.whocc.no/atc_ddd_index/

The drugs we studied all pertain to ATC-group N. Here N stands for Nervous System, as these drugs primarily act upon the central nervous system. Within the N category we studied drugs used for treatment of mental disorders, i.e. the N05 category (psycholeptics), including N05A (antipsychotics), N05B (anxiolytics), N05C (hypnotics and sedatives) (N05C), and within the N06 category (psychoanaleptics), including N06A (antidepressants) and N06B (psychostimulants/agents used for ADHD). A description of the ATC-categorization of the psychotropic drugs we used in our research may be found in Table 1, along with a more detailed list of the ATC-sub-levels within the drug group Nervous System (N) in Appendix a.

1.2 Psychotropic Drugs

Psychoactive drugs in treatment of mental disorders have been a common therapeutic option in psychiatry since the mid 20th century. During the latter half of the last century psychopharmacological research developed profoundly. Stimulants are among the oldest, most researched and widely used drugs in psychiatry. They were first used in clinical practice for behavioral disorders in children in 1937 and became a mainstream drug for those purposes in the 1960's (Conner, 2005). Other agents acting on the central nervous system and commonly prescribed in modern psychiatry include; antidepressants, used to treat clinical depression and anxiety, antipsychotics, traditionally used for psychotic disorders, such as schizophrenia, and anxiolytics, most notably used in treatment of anxiety disorders.

In our studies, we defined psychotropic drugs according to the ATC drug classification system as those acting upon the central nervous system and pertaining to the N group. Table 1 shows which categories of psychotropic drugs, subgroups and specific drugs we focused on in Studies I-III.

Table 1. Main Psychotropic Drugs Examined in Studies I-III and their ATC-Classification[a]

Psycholeptics (N05)		**Psychoanaleptics (N06)**	
Antipsychotics (N05A)	*Anxiolytics, hypnotics and sedatives (N05B, N05C)*	*Antidepressants (N06A)*	*Psychostimulants, agents used for ADHD (N06B)*
typical atypical	b. excluding hydroxyzine (N05BB01)	non-selective monoamine reuptake inhibitors, also TCAs (N06AA)	amphetamine (N06BA01)
		selective serotonin reuptake inhibitors, SSRIs (N06AB)	methylphenidate (N06BA04) cting cting
		serotonin-norepinephrine reuptake inhibitors, SNRIs (N06AX)	modafinil (N06BA07)
		other antidepressants (N06AF, N06AG)	atomoxetine (N06BA09)

a. ATC, World Health Organization Anatomical Therapeutic Chemical (ATC) classification of drugs.

b. Although classified as an anxiolytic (N05B) in the WHO ATC classification system, hydroxyzine (N05BB01) also has a main indication for allergic reactions (Icelandic Medicines Agency 2008) and is primarily used as such for children in Iceland.

1.2.1 Psychotropic Drugs and Children

The use of psychotropic drugs in treatment of children is a subject of continuous debate in developed countries. Although research in pediatric psychopharmacology has expanded during the past two decades, studies have typically rested on limited data sources (Vitiello, 2007). Thus, the evidence base for prevalence of use and treatment safety for children, as well as the effectiveness and long-term risks of many psychotropic agents, remains fragmented. Due to the nature of clinical trials and sensitive matter of testing minors, the efficacy and safety of psychotropic drugs have first and foremost been tested within the adult population. Hence, a large proportion of

psychotropic drugs prescribed to children and adolescents is not indicated for use in minors. Off-label prescribing of psychotropic drugs is an ethical dilemma in reality; when the choice stands between treating the child with drugs not formally tested or approved for pediatric use, or denying the child available treatment, which has in practice been shown to improve mental health or well-being. Often clinical trials on the efficacy and safety of the drugs are not done on children until after experience has accumulated in clinical practice. This underscores the importance of observational studies to map the prescription and utilization patterns of psychotropic drugs among children. Furthermore, it answers questions of the effectiveness and long-term outcomes of treatment – questions that are rarely answered with randomized trials.

Recent drug utilization studies have revealed pronounced variability in the use of psychotropic drugs between pediatric populations, both across and within countries (Vitiello, 2008). Prevalence of use within the United States has been reported to be the highest, whereas figures from Europe are generally lower but rising. Many of these findings rest on information from self-reported surveys, insurance or reimbursement data, or community and localized pharmacy-dispensing data. These data sources are often restricted to specific social or regional groups or, in the case of self-reports, the memory retrieval of individuals, which may hamper solid conclusions (Asheim et al., 2007; Castle et al., 2007; Clavenna et al., 2007; Faber et al., 2005; Fegert et al., 2006; Olfson et al., 2002; Zito et al., 2003; Zito et al., 1997; Zito et al., 2007; Zuvekas et al., 2006). In addition to methodological issues of this type, the international variability in the use of psychotropic drugs for children may reflect differences in diagnostic systems, clinical guidelines, cost and reimbursement of health care, drug regulations and reimbursement and cultural attitudes towards mental disorders and treatment. It is important to understand which social, cultural and personal factors may underlie the decision to treat children with psychotropic drugs.

Very few studies of psychotropic drug use among children in Iceland exist (Baldursson et al., 2000; Zoega et al., 2007). Previous studies of the Icelandic adult population indicate a considerable rise in use of many psychotropic drugs, especially antidepressants over the past three decades (Helgason et al., 1997; Helgason et al., 2004). Publicly available data indicate that the overall sale of most psychotropic drugs is higher in Iceland per capita (DDDs per 1000 inhabitants per day) than in the neighboring countries (Icelandic Medicines Agency). Recently, we carried out a study of psychotropic drug use among the elderly population in 2006 and found that, compared with Danes, Icelanders (70-74 years) were 1.5 to 2.5 times more likely to have been prescribed a psychotropic drug (Samuelsson et al., 2009).

1.2.1.1 Antidepressants

Antidepressants are now used in the treatment of an increasingly wide array of medical syndromes including depression, anxiety disorders, obsessive compulsive disorder, eating disorders, nocturnal enuresis, chronic pain, Tourette's syndrome. In some countries, such as Iceland, tricyclic antidepressants (TCAs) were also used in treatment of ADHD, in years when use of stimulants was more limited (Baldursson et al., 2000). Newer antidepressants, so-called selective serotonin re-uptake inhibitors (SSRI), are considered an improvement over older antidepressant drugs as they have less extensive side-effects and are less likely to be harmful if taken in an overdose (National Institute of Mental Health). Treatment with SSRIs for children became a subject of controversy with the publishing of studies in 2003-2004 linking their use to suicidal thoughts and behavior in youth (Jureidini et al., 2004; Vitiello & Swedo, 2004; Whittington et al., 2004). The relation between suicide and antidepressants is complex and study results are not conclusive. While some more recent results indicate a relation with suicide attempts (Olfson et al., 2006b), other studies indicate that the benefits of antidepressant drugs may outweigh their risks to children and adolescents with major depression and anxiety disorders (Bridge et al., 2007), or no significant increase in suicide risk among youth following initiation of treatment with newer antidepressants (Simon et al., 2006).

1.2.1.2 Antipsychotics

Although not as widely used as antidepressants, in the past decade antipsychotic drugs have become more common in treatment for children with mental disorders. Amongst the pediatric disorders antipsychotics are used for are: severe behavioral disorders, acute and chronic schizophrenic psychosis, Tourette syndrome and autism. Antipsychotics may lead to metabolic side effects in children and the long-term effects of use are largely unknown. Only a few antipsychotic drugs have authorized indications for use in young children, although over the recent years their marketing authorizations and licensing have widened, especially within the United States. Research indicates that the newer atypical antipsychotic drugs may not be more effective than an older conventional antipsychotic in treating child and adolescent schizophrenia (Kumra et al., 2008; Sikich, 2008; Sikich et al., 2008).

1.2.1.3 Anxiolytics, Hypnotics and Sedatives

Few studies have reported data on the use of hypnotics and anxiolytics in the pediatric population (Koelch et al., 2009; Martin et al., 2003; Olfson et al., 2002; Schirm et al., 2001; Sevilla-Dedieu & Kovess-Masfety, 2008; Zito et al., 2008). The existing ones indicate low prevalence of use among children, although, some geographic variation, such as higher use among French and Dutch children, compared with children in other European countries and in the US (Koelch et al., 2009; Sevilla-Dedieu & Kovess-Masfety, 2008; Zito et al., 2008).

Among established indications of anxiolytics, hypnotics and sedatives for children are seizures, epilepsy, and sedation prior to minor surgery, allergic skin reactions and, in some cases, restlessness or sleep disorders (Icelandic Medicines Agency; Koelch et al., 2009; Sevilla-Dedieu & Kovess-Masfety, 2008). The drug hydroxyzine is an anxiolytic but in many cases used for allergic reactions, for example itching in children (Icelandic Medicines Agency). Melatonin is a hypnotic indicated for sleep disorders in adults, but not with established indications in treatment of children, although pediatric use had been reported among children with ADHD and chronic sleep disorders (Icelandic Medicines Agency; Koelch et al., 2009; Van der Heijden et al., 2007).

1.2.1.4 Stimulants

Opposed to most other psychotropic drugs, stimulants have primarily been used in treatment for the pediatric population rather than the adult population. Stimulant drugs were amongst the first psychotropic drugs to be used in clinical practice and have been extensively researched since the 1960's, when the first double-blind randomized clinical trial of dextroamphetamine and methylphenidate was completed (Conner, 2005; Conners, 2002). Not until recently did clinical use of stimulants for adults become actual. Currently, the established indications for stimulants include ADHD symptoms in children from age six, adolescents and adults. In general stimulants are well tolerated, but common side effects include decreased appetite, insomnia, headache and stomachache (Conner, 2005).

Stimulant treatment has indeed consistently been shown to be effective in improving the core symptoms of ADHD among in children, notably inattention, hyperactivity and impulsivity (Greenhill et al., 1999; MTA Cooperative Group, 1999a) and essentially there is no doubt of their short-term efficacy in that respect. Nevertheless, treatment with stimulants and their increasing use is debated, chiefly because of concerns of over-use, addiction and uncertainty of the long-term outcomes of treatment (Jensen et al., 1999). Research on the

effect of stimulants on functioning in children's daily life, such as academic performance; have yielded inconclusive results (Brown et al., 2005; Connor, 2005; MTA Cooperative Group, 2004b; Vitiello, 2001). In spite of being amongst the most widely researched drug group, the long-term risks and benefits of stimulant drug treatment use remain unclear (Molina et al., 2009). Studies of the long-term outcomes for treated children in naturalistic settings are scarce. Unresolved safety issues and unintended side effects, such as cardiovascular risk and sudden death (Gould et al., 2009; Nissen, 2006), have illuminated the controversy of their use.

1.2.2 Time Trends in Psychotropic Drug Use among Children

A wide array of studies has documented increased use of psychotropic drugs in the pediatric population over the past two decades, especially in Western countries. The increases in use have been most profound for stimulant drugs and antidepressants, primarily SSRI's and antipsychotics. Most studies of psychotropic drug use among children and adolescents originate from North America, later followed by studies from European countries. Following are brief descriptions of time trends in use of the main psychotropic drug groups used to treat psychiatric disorders for children and adolescents.

1.2.2.1 Antidepressants

The growth of antidepressant treatment for children and adolescents in the United States and in Europe during the 1990's and early 2000's has been documented in numerous datasets (Clavenna et al., 2007; Hsia & Maclennan, 2009; Hunkeler et al., 2005; Rushton & Whitmire, 2001; Schirm et al., 2001; Shireman et al., 2002; Vitiello et al., 2006; Zito et al., 2002). During that time, in treating mental health problems a common trend in many countries included expanded use of SSRIs (N06BA) and SNRIs (N06AX), while use of older tricyclic antidepressants (TCAs, N06AA) became less prevalent.

In the United States, antidepressants are, along with stimulant drugs, reported to be the psychotropic drugs most commonly prescribed for children and adolescents. The estimated national prevalence of antidepressant drug use among children in the United States was 18 per 1000 children in 2002, up from 13 per 1000 in 1997 (Vitiello et al., 2006). Before that, Zito et al. (2002) had found a 19 fold increase in the usage of SSRIs among US youths younger than 20 years of age between the years 1988 and 1994.

Prevalence of antidepressants among European children has been reported to be considerably lower than that of the United States. Nonetheless, the trend of rising antidepressant use in the United States was followed by increased use

in many European countries. In the United Kingdom, Murray et al. (2004) found that the prevalence of antidepressant use among children (0- 18 years) increased 1.7 fold between 1992 and 2001. They demonstrated that while prevalence of SSRI use had increased by a factor of 10, from 0.5 to 4.6 per 1000 children, prevalence of TCA use decreased by 30% from 3.6 to 2.5 per 1000 children. Schirm et al. (2001) reported that antidepressant prevalence among 0- 19 year olds in the Netherlands increased from 3.8 in 1995 to 4.4 per 1000 in 1999. In 2003 to 2004, the prevalence of antidepressant use among children in various European countries was as follows: 2.3 per 1000 children in Italy, 3.7 per 1000 children in Germany, 4.0 per 1000 in France opposed to the U.S prevalence of 18 per 1000 children in 2002 (Clavenna et al., 2007; Fegert et al., 2006; Sevilla-Dedieu & Kovess-Masfety, 2008; Vitiello et al., 2006).

A slight decline in use of SSRIs among children occurred in many countries (Dean et al., 2007; Gibbons et al., 2007; Murray et al., 2005; Nemeroff et al., 2007; Olfson et al., 2008; Volkers et al., 2007), following public health warnings issued by European and U.S. regulators in 2003 and 2004, media campaigns against usage of SSRIs in treatment of childhood depression and debate of uncertainty regarding long-term effects of use (Directorate of Health Iceland, 2004; FDA, 2003; Jureidini et al., 2004; Ramchandani, 2004; Vitiello & Swedo, 2004; Whittington et al., 2004).

In Iceland data prior to 2001 on psychotropic prescriptions for the youngest age groups are scarce. Baldursson et al. (2000) demonstrated that in 1998 to 1999 among 102 children referred to the ADHD outpatient clinic in Iceland, most were started on TCA antidepressants rather than stimulants. Helgason et al. have reported that prior to 1993 very few children under the age of 15 years were prescribed antidepressants- estimating that in 1993 0.8% of total antidepressant prescriptions had been issued to children under 15 years of age (Helgason et al., 2004). Studies on antidepressant drug prevalence in Iceland have first and foremost focused on the adult population, documenting in the past 20 years an extensive growth in antidepressant prescribing. During the period 1989 to 2000 the total quantity of antidepressants sales increased by 388% (Helgason et al., 2004). In the past two decades, Iceland has consistently been reported as having the highest rate of antidepressant drug sales per capita among its neighboring Nordic countries (Iceland Social Insurance, 2004). No studies prior to our Study I exist on the trends of antidepressant use among Icelandic children.

1.2.2.2 Antipsychotics

As with other psychotropic drugs, studies of time trends in the pediatric use of antipsychotic drugs are primarily from the United States (Constantine & Tandon, 2008; Cooper et al., 2006; Cooper et al., 2004; Olfson et al., 2006a; Patel et al., 2005b). Although not as widely utilized as antidepressants, antipsychotics are more commonly used than before and for a wider array of psychiatric disorders in children. Olfson et al. (2006a) demonstrated a sharp national increase (six-fold) in antipsychotic treatment among US children between 1993 and 2002. Similarly, in the United Kingdom, Rani et al. (2008) found a doubling of antipsychotic prevalence between 1992 and 2005 among UK children in primary care. From 1997 to 2005, prevalence increased from 3.0 to 6.8 per 1000 Dutch children, according to Kalverdijk et al. (2008).

The documented increase in use among children is mainly of second generation antipsychotic drugs, the so-called atypical antipsychotics, such as risperidone (N05AX08), aripiprazole (N05AX12) and quetiapine (N05AH04), marketed in the 1990's and early 2000's, while use of typical antipsychotics has declined (Burns et al., 2006; Findling & McNamara, 2004; Patel et al., 2005a; Patel et al., 2005b). Rani et al. (2008) point out that the prescription of atypical antipsychotic drugs has increased despite the lack of conclusive evidence showing their superiority over older conventional antipsychotics.

Reports of time trends of antipsychotic use among children in other European countries are scarce. Annual prevalence ratios for antipsychotic use have been reported from Italy (in 2004), 0.5 per 1000 children, and 1.0 per 1000 children in France (in 2003) (Clavenna et al., 2007; Sevilla-Dedieu & Kovess-Masfety, 2008). Publicly available data from Nordic prescription registers show that the 2007 prevalence in Norway and Denmark was well below 1.0 per 1000 among 0- to 10- year-old children, 3.7 per 1000 among 10- to 19-year-old Norwegians, and 3.0 per 1000 among 10- to 14-year-old Danes ("Danish Medicines Registry; Norwegian Prescription Database,").

Prior to our study, patterns of antipsychotic use in the Icelandic pediatric population have not been documented.

1.2.2.3 Stimulants and Atomoxetine

Global use of ADHD drugs rose threefold from 1993 through 2003, according to Scheffler et al. (2007), whereas adjusting for inflation global spending rose nine-fold. Use of stimulant drugs to treat ADHD in children has repeatedly been reported to be higher in North America than elsewhere. The rise in use of stimulants was most pronounced during the 1990s for children in the United

States. Safer et al. (1996) approximated a 2.5- fold increase in the number of US children receiving stimulant treatment during the first half of the 1990s, estimating the national prevalence to have been 28 per 1000 children in 1995. The steep rise increase in stimulant use seems to have leveled somewhat off in the United States during the early 2000's (Scheffler et al., 2007; Zuvekas et al., 2006). Depending on populations, the US prevalence was 29 to 45 per 1000 children in the years 2000 to 2005 (Castle et al., 2007; Zito et al., 2008; Zuvekas et al., 2006).

The reported prevalence of stimulant drug use in Europe is considerably lower than the documented use in the United States. Nevertheless, in the past decade a definite rise in use has also been detected among European nations. Similar to the US trend, Schirm et al. (2001) demonstrated 2.5-fold increase of use among Dutch children between 1995 and 1999, from 1.5 to 7.4 per 1000 children. In 2002, the prevalence was still rising among children in the Netherlands, reported 12 per 1000 children that year (Faber et al., 2005). Stimulant prescriptions rose significantly for UK children according to Hsia & Maclennan (2009) a 96-fold increase, from 0.03 per 1000 in 1992 to 2.9 per 1000 in 2001. Knellwolf et al. (2008) demonstrated that stimulant use had increased by 63.5% among French children (6-18 years); 1.1 in 2003, 1.5 in 2004 and 1.8 per 1000 children in 2005. Among German children prevalence of stimulant use was estimated 7.1 per 1000 for the year 2000 (Zito et al., 2008) .

Comparing European and US prevalence figures from similar time frames, use of stimulants drugs to treat children is approximately 10 times more common in the United States. The few existing stimulant drug utilization studies originating from the Nordic countries indicate that, as elsewhere, use of stimulant drugs for ADHD has also increased there over the past decade (Asheim et al., 2007; Lundström et al., 2006; Zoega et al., 2007).

1.2.2.4 Stimulant Use among Children in Iceland

Before launching the current PhD project we conducted a nationwide study on methylphenidate (stimulant) use among children (0-17) in Iceland between the years 1989 and 2006, using data from Directorate of Health surveillance system on prescribed methylphenidate (1989-2000) and the Icelandic Medicines Registry (2003-2006) (Zoega et al., 2007). During that period we found a pronounced increase in use of methylphenidate to treat children with ADHD in Iceland, from 0.2 to 25.1 per 1000 children (Figure 1).

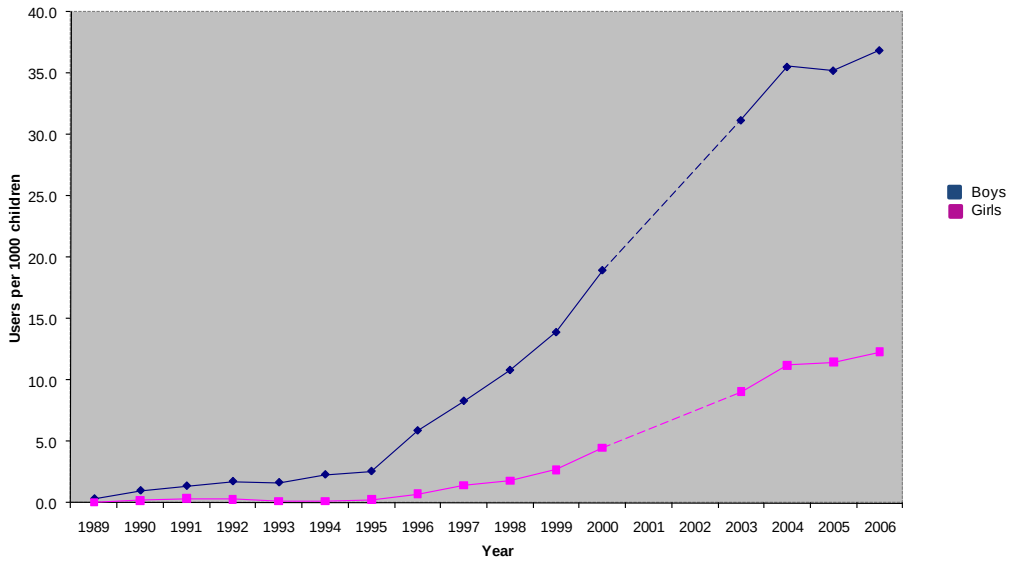


Figure 1. Rising use of methylphenidate among children (0-17 years) in Iceland from 1989 to 2006 (Zoëga et al.)

Coinciding with a trend found in many other Western countries (Scheffler et al., 2007), we detected a definite decrease in use of short-acting methylphenidate from 2003 (18.7 per 1000) to 2006 (6.8 per 1000), while prevalence of long-acting medication increased from 14.4 to 24.6 per 1000 children (Figure 2). This trend is associated with the marketing of new long acting methylphenidate formulations to treat ADHD, such as Concerta®, Ritalin Uno®, and the new non-stimulant atomoxetine (Strattera®). These long-acting drugs have a practical advantage over the older short-acting formulas, like Ritalin®, as they often can be dosed nonce daily, rather than every few hours.

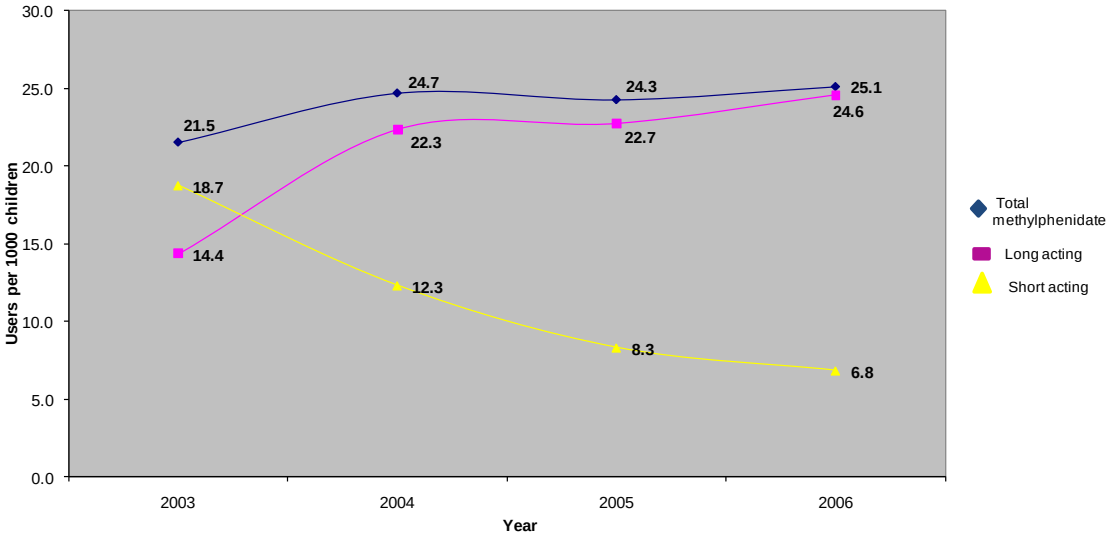


Figure 2. Increasing Use of Long-Acting Methylphenidate and Decreasing Use of Short-Acting Methylphenidate among Children in Iceland (Zoëga et al.)

Overall use was three times more common among boys than girls in Iceland (Figure 3). Prevalence in the year 2006 was highest at age 10, 77.4 per 1000 among boys and 24.3 per 1000 among girls. We detected a regional variation in use. In 2006, pediatricians were the most common prescribers of methylphenidate to children in Iceland, accounting for 41% of prescriptions.

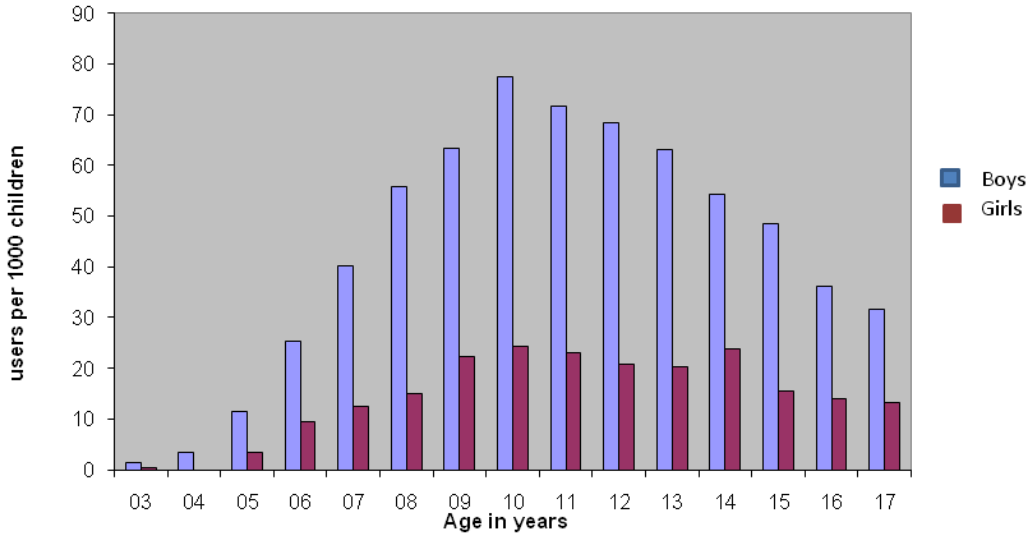


Figure 3. Age and Sex Distribution of Methylphenidate Use among Children in Iceland 2007 (Zoëga et al.)

With this study we concluded that use of methylphenidate among children in Iceland increased greatly during the study period and that compared to utilization rates in Europe, prevalence of methylphenidate use among children in Iceland was very high.

1.3 Attention-Deficit/Hyperactivity Disorder (ADHD)

Attention-deficit/hyperactivity disorder is a common neurodevelopmental disorder affecting approximately 5- 10% of school aged children in Europe and the United States (Centers for Disease Control and Prevention, 2005; Polanczyk et al., 2007). Traditionally only diagnosed among children, the disorder has in the past decade also increasingly been diagnosed in adults. Prevalence of ADHD has been shown to be relatively stable across the world, estimated 4- 6% among children of all ages and 2- 4% among adults, with research suggesting that variability of this prevalence may be explained by differences in diagnostic criteria and methodological characteristics of studies, rather than geographical location (Faraone et al., 2003; Fayyad et al., 2007; Kessler et al., 2006; Polanczyk et al., 2007).

The disorder is, as the name of it indicates, characterized by behavioral symptoms of inattention, hyperactivity and impulsivity. The disabling effects of these core symptoms vary with patients; their age and gender. Roughly though,

the symptomatology has been categorized into three major sub-groups; predominantly hyperactivity/impulsivity, ADHD-PHI, predominantly symptoms of inattention, ADHD-PI and combined symptoms of hyperactivity/impulsivity and inattention, defined as ADHD-C (Barkley, 2005b, 2005e). Under certain circumstances or in social situations symptoms may display more clearly in children, for example during school lessons where the child is expected to sit still and concentrate amongst a group of other children, as opposed to playing alone.

Boys are three to four times more likely than girls to be diagnosed with ADHD, based on studies of community samples, but in clinically referred samples the gender difference is as high as five- to nine-fold (Barkley, 2005e; Gaub & Carlson, 1997; Gershon, 2002). ADHD is most often diagnosed among school aged children, around age 7-10 years, but in recent years diagnoses in very young children of pre-school age have become more frequent (Greenhill et al., 2008). While, in general, the symptoms of hyperactivity and inattention are equally common for boys, girls predominantly present symptoms of inattention (Gaub & Carlson, 1997; Gershon, 2002). As children grow older symptoms tend to decline, especially symptoms of hyperactivity/impulsivity (Barkley, 2005e; Faraone et al., 2006). Recent research shows, however, substantial diagnostic continuity into young adulthood (Biederman, 2005; Fayyad et al., 2007; Steinhausen, 2009; Wolraich et al., 2005). Follow-up studies of children with the disorder have found that 15% still have the full diagnosis at 25 years and that a further 50% are in partial remission as young adults (Asherson et al., 2007; Faraone et al., 2006), adding up to two-thirds of diagnosed children with continued symptoms into adulthood. In relation to this, first time diagnoses of ADHD among adults have increased in recent years. Studies show that, unlike the gender ratio of childhood diagnosis, adult women are as likely as adult men to be diagnosed with ADHD (Asherson et al., 2007; McCarthy et al., 2009).

Co-morbidity is common among those suffering from ADHD and may include anxiety, depression, conduct- or oppositional defiant disorder and learning disabilities. The estimated occurrence of co-morbid psychiatric disorders among children with ADHD varies widely by the studied samples. Clinically referred samples more commonly present psychiatric co-morbidity (up to 80%), than community based samples (up to 44%) (Barkley, 2005b).

Although the etiology of ADHD remains somewhat unclear, the evidence points to neurobiological and genetic factors as the major contributors to the disorder (Biederman et al., 1992; Caspi et al., 2008; Faraone et al., 2005; Larsson et al., 2004), additional to some distinct environmental factors such as fetal exposure to maternal smoking and alcohol consumption, pregnancy and birth complications and severe fetal stress (Banerjee et al., 2007; Barkley, 2005c; Mick et al., 2002; Whitaker et al., 1997).

1.3.1 **Diagnosis of ADHD**

The validity of ADHD diagnosis has been a source of debate in many countries for years, giving rise to worries of possible over-diagnosing of the disorder, leading to over-treatment and misuse of drugs used to in treatment. Similar to many other psychiatric illnesses, the diagnosis is based on non-biological measures. Although, advances in developing diagnostic criteria for the disorder have occurred over the decades resulting in more specific and precise measures of the disorder's symptomatology, a diagnostic gold standard for the diagnosis does not exist (Barkley, 2005d; Gordon, 2005).

The condition is currently diagnosed either with the criteria of the International Classification of Diseases, 10th Edition (ICD-10) for hyperkinetic disorders (F90.0-F98.8) or as attention-deficit/hyperactivity disorder with the tools of the Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition (DSM-IV) (American Psychiatric Association, 2000; World Health Organization, 1994). The diagnostic criteria of the latter system are viewed to be being less stringent (Faraone et al., 2003; Lee et al., 2008).

The diagnostic process for children involves psychological ratings scales, reports from both parents and teachers and direct observation. The ratings of specific diagnostic criteria are not always in agreement between parents and teachers (Jonsdottir, 2006; Sherman et al., 1997; Wolraich et al., 2004), which is to be expected as the symptoms of ADHD are to some extent situational (Barkley, 2005e). In Iceland, the diagnosis of ADHD among children is primarily done by psychologists with special knowledge of ADHD, child and adolescent psychiatrists, pediatricians with a specialty in neurology, often in co-operation with general practitioners in primary care and school based psychologists or social workers.

Diagnosis of adults relies mainly on interviews and rating scales calibrated to adults, where current and childhood functioning are self-reported. Historical information is often also retrieved from spouse and/or a family member or a friend. Adults diagnosed may often be parents to children who have previously been diagnosed with ADHD. Despite the broadening acceptance of adult ADHD in the past decade, the diagnostic procedures for adults are still more controversial and less validated than for children (Asherson et al.; Faraone et al., 2000; Moncrieff & Timimi; Murphy, 2005).

In 2007, the Directorate of Health in Iceland published clinical guidelines for the diagnosis and treatment of ADHD in children and adults (Baldursson et al., 2007). These guidelines are now up for renewal. According to drug regulations in Iceland, a valid diagnosis made by the above mentioned specialists is a

prerequisite for the reimbursement of stimulant (and atomoxetine) drug treatment. These regulations were reinforced and modified at the beginning of 2011 (Icelandic Health Insurance).

1.3.2 **Treatment of ADHD**

ADHD is a heterogeneous syndrome with considerable co-morbidity. Response to treatment may therefore be somewhat idiosyncratic (Smith, 2007). Although not all diagnosed children benefit equally from treatment, untreated ADHD can lead to poor self-esteem, academic under-achievement, strained peer and family relationships, increases in accidental injuries and substance abuse (Barkley, 2005a). On a group level an estimated 70 to 75% of children respond well to stimulant drug treatment for ADHD and find improvement in the core symptoms of the disorder (Conner, 2005; Greenhill et al., 1999). Psychosocial treatments for ADHD encompass a broad set of interventions, including behavior therapy, academic interventions and parent training. These options have been suggested in treatment of less severe cases and as an aid alongside stimulant treatment. The evidence base for effectiveness of non-pharmacological treatment is less convincing than for stimulants, suggesting only mild benefits, especially if used as the sole mode of treatment.

In any case, it is important to assess response to both pharmacological and non-pharmacological treatment modes on a case-by-case basis and repeatedly. A beneficial response to treatment is not guaranteed for all and response to treatment may change over time. Currently, clinical guidelines and many clinicians emphasize a “combination approach” in treatment, i.e. the use of more than one treatment options at once (Anastopoulos, 2005; Baldursson et al., 2007; Kutcher et al., 2004; Young & Amarasinghe, 2010). This involves taking into account all aspects of the child’s daily life, including counseling for the parents and teachers. However, the extent to which combined treatments are superior to medication alone remains controversial (Smith, 2005).

1.3.2.1 Pharmacological Treatment

Stimulant drugs are suggested as the first-line pharmacological treatment mode for ADHD (Baldursson et al., 2007; Banaschewski et al., 2006; Kutcher et al., 2004). Short-acting stimulant preparations, such as Ritalin®, Equasym® and Amfetamin®, have an action duration for up to a few hours and require multiple daily doses (two to four). The more recently marketed, the long-acting, or extended-release formulations, f. ex. Concerta® and Ritalin Uno®, provide longer durations of action. They require fewer daily doses and may eliminate the need for children to take them during school hours. Due to their prolonged

action, issues of adherence and abuse are less frequent with long-acting stimulants (Wolraich et al., 2005). In spite of their convenience they cannot entirely replace short-acting drugs, which are often used as the initial treatment for reasons of cost and flexibility of dosing (Banaschewski et al., 2006).

Atomoxetine, Strattera®, is a non-stimulant agent approved in 2003 for use in children and adolescents with ADHD. It is a specific noradrenergic reuptake inhibitor indicated for children who do not tolerate, or respond well to, stimulants and for those with associated co-morbidities of ADHD, including substance abuse (Dell'Agnello et al., 2009; Hammerness et al., 2009; Michelson et al., 2002; Michelson et al., 2001; Newcorn et al., 2005; Vaughan et al., 2009). In our studies (I- III) we grouped atomoxetine and stimulants together as “ADHD drugs”.

Antidepressants have also been used in treatment of ADHD. They are considered second-line drugs for the disorder and are mostly used off-label, since few have authorized indications for treatment of ADHD. Tricyclic antidepressants may be effective in controlling behavioral problems and improving cognitive impairments associated with ADHD but they are less effective than the majority of stimulants, particularly for cognitive impairments (Spencer et al., 1996). Use of these drugs has decreased over the past 10 to 15 years due to their serious adverse reactions and increased access to various stimulant drugs.

In the past decade, combined psychotropic treatment, e.g. of stimulants and antipsychotics or SSRI’s, has become more frequent for children with ADHD (dosReis et al., 2005; Faber et al., 2005; Safer et al., 2003), especially those also dealing with the associated co-morbidities. Although they act upon the central nervous system, stimulant or other pharmacological treatments do not cure ADHD (Conner, 2005).

1.3.2.2 Non-Pharmacological Treatment

Psychosocial and behavioral treatments have been suggested as an option for children not severely impaired by the symptoms of ADHD. Clinical guidelines promote their use in combination with stimulant drug treatment, especially for children with co-morbid disorders such as oppositional defiant disorder, depression and anxiety. Non-pharmacological treatments in the form of cognitive behavioral therapy, parent training, social skills training, psychotherapy and academic assistance may relieve the psychological and day-to-day burdens often associated with the symptoms and impairments of ADHD. Dietary interventions, or restricted diets, may be considered as a method to relieve

symptoms for children with ADHD. Recent study results have however been ambiguous on the role of diet in the etiology and treatment of ADHD (Pelsser et al., 2011). Opposed to pharmacological treatment, the non-pharmacological therapy options do generally not act directly upon the central nervous system.

Among the non-pharmacological treatment modes, parent training interventions have the greatest evidence base (Anastopoulos, 2005). They have been proven to be effective for ADHD-related behavioral problems in children (Anastopoulos, 2005; Chronis et al., 2004; Young & Amarasinghe, 2010). These interventions may reduce parent-child conflicts, child deviance and to some extent symptoms of ADHD. The evidence base of most other non-pharmacological options is not strong enough to recommend them as the sole or primary option for routine use in clinical practice. In Iceland access to psychosocial treatment methods and specialized school services is rather limited. Not until January 1st 2008 did any public reimbursement for outpatient psychological services in pediatrics exists ("Regulation no. 1266/2007," 2007).

1.3.2.3 The Multimodal Treatment Study of Children with ADHD (MTA)

The so-called MTA study is to date the most comprehensive examination of the effectiveness of various treatment strategies for children diagnosed with ADHD (MTA Cooperative Group, 1999a). In this study researchers randomized 579 children ages 7 to 9.9 years to one of four different treatment strategies for a period of 14 months. Researchers then compared the effectiveness of the different treatments using a wide array of outcomes. The four treatment strategies involved:

1. Intensive medication management with short-acting methylphenidate
2. Multimodal behavioral treatment
3. Combination treatment of 1 and 2
4. Community care, i.e. treatment in the community involving any options as parents preferred, (children randomized to this treatment group served as a type of base-reference as randomization to no treatment at all for was an un-ethical option).

The initial randomization was carried out in the late 1990s (MTA Cooperative Group, 1999a). Since the end of the 14-month treatment phase, the majority of the children have been followed-up in an observational manner for up to eight years on a variety of outcome measure. The MTA study is viewed as a landmark study within the field, contributing greatly to scientific knowledge of treatment options and their outcomes for children with ADHD. Its results and data

interpretation are, however, not free from controversy (BBC, 2010; Swanson et al., 2011).

Among the major findings of the MTA study were that intensive medication management (1) was clearly superior to the other treatment strategies (2-4) in relieving the core symptoms of ADHD. Children receiving behavioral treatment only (2), did not show improvements over those in community care (4). Outcome measures concerning areas of children's functioning, such as oppositional behavior, peer- and parent-child relations and academic achievement, medication management (1) and combination treatment (3) did not differ significantly. But depending on how the data were analyzed a modest but statistically significant advantage could be found for combination treatment (Conners et al., 2001). This suggests that for most children with ADHD, adding behavioral intervention on top of well-conducted medication management is not likely to yield substantial gains. The initial study outcomes did not vary significantly by gender (MTA Cooperative Group, 1999b).

Furthermore, comparing children with and without co-morbid anxiety disorder, all treatment strategies (1-3), including behavioral treatment alone (2), outperformed community treatment (4) for the children with anxiety (MTA Cooperative Group, 1999b) – suggesting that children with co-occurring anxiety might receive additional treatment benefit when behavioral treatment and stimulant treatment are combined.

Subsequent naturalistic follow-up of children two to three years after the initial randomization indicated that the superiority of intensive medication management (1) in treating ADHD symptoms diminished over time. However, continued and consistent use of medication was associated with maintenance of effectiveness. Outcomes of social skills and parent-child relations suggested meaningful advantages of combination treatment in the longer-run, compared with the other treatment modes (MTA Cooperative Group, 2004a, 2004b; Smith, 2005).

The follow-up of MTA children at three, six and eight years after the initial treatment randomization showed that most children initially assigned to medication management (1) discontinued drug treatment at some time point. At eight years of follow-up 33% of the initially medicated children were still receiving persistent stimulant drug treatment (Molina et al., 2009).

Results on academic outcomes for children in the MTA study during the naturalistic follow-up period are introduced in chapters 1.3.3 and 1.4.

1.3.3 **ADHD and Academic Performance**

Academic performance and achievement can be an area of profound difficulty for children with ADHD. Most students with ADHD typically underperform in school, which is believed to be the result of their inattentive, impulsive and restless behavior (Barkley, 2005a). Numerous studies have documented associations between ADHD and poor school performance (Barbaresi et al., 2007a; Barkley et al., 1991; Biederman et al., 1996; Faraone et al., 1993; Loe & Feldman, 2007; Polderman et al., 2010). The adverse impact of ADHD on academic performance is progressive, including early academic underachievement, grade retention and, ultimately, school dropout (Barbaresi et al., 2007a; Barkley, 2005a; Wolraich et al., 2005). This progressive decline in academic performance and achievement is likely to be associated with the increasing demands in school as children grow older in relation to their cognitive abilities, organization and independence.

The DSM-IV divides the cognitive symptoms of ADHD by its main domains, i.e. the inattention and hyperactivity/impulsivity. Currently, there are nine symptoms specified for inattention (poor in attending to details, sustaining attention, listening, organizing and finishing tasks, exerting mental effort, ignoring extraneous stimuli and remembering things/activities) and three for impulsivity (blurting out answers, cannot wait and interrupting others), which are grouped with six motor symptoms of hyperactivity (often fidgeting, leaving seat in the classroom, running about, not able to play quietly, 'on the go', and talking excessively) (American Psychiatric Association, 2000; Swanson et al., 2011).

Children with ADHD have been shown to score significantly lower on reading and arithmetic achievement tests, they are more likely to repeat a grade and be suspended or expelled from school, compared with normal controls. According to Barkley's summarization of previous study results, children with ADHD typically score 10 to 30 points lower on academic achievement tests in reading, spelling and math than children without ADHD (Barkley, 2005a). For example, Barkley and Fischer et al. found in a prospective 8-year follow-up of clinically referred children that, compared with non-ADHD controls, they had standard scores 0.5 to 1 standard deviations lower on measures of academic achievement in reading, spelling, and math (Barkley et al., 1990; Fischer et al., 1990).

More recently, Barbaresi et al. (2007a) demonstrated in a population-based study that, median reading achievement scores at age 12.8 years (expressed as a US national percentile) were significantly different for children with ADHD (45 points) and without ADHD (73 points). Furthermore, they showed that, compared

with non-ADHD controls, children with ADHD were more frequently absent from school, three times more likely to be retained a grade and almost three times more likely to drop out before high school graduation. These differences in school performance and achievement were similar for both boys and girls.

Also recently, Molina et al. (2009) demonstrated in a 6- to 8-year follow-up of the MTA study-participants, that, standardized achievement test scores, teacher ratings of academic performance and grades earned in high school were significantly lower for the children with ADHD than among a local normative comparison group of same aged children. Similarly to the results of Barbaresi et al., Molina et al. found that the MTA children had a twofold higher rate of grade retention than the normal controls.

In sum, the academic underachievement and sub-optimal school performance of children with ADHD has been quite well documented.

1.4 Stimulant Drug Treatment and Academic Performance

The use of stimulant drugs in treatment of children with ADHD is one of the most widespread pharmacological interventions in child and adolescent psychiatry and behavioral pediatrics (Swanson et al., 2011). In light of this, the relatively high prevalence of the ADHD (5- 10%) and its pervasive effects on academic performance, it is imperative to understand the cognitive effects, both in short- and long-term, of stimulant drug treatment. Educational achievement is an important predictor of future socioeconomic status that, in turn, is an important determinant of well-being and health in adulthood (Huisman et al., 2005a; Huisman et al., 2005b), further underscoring the importance of knowing to which extent stimulant treatment affects academic performance among children with ADHD.

Controlled trials have reported acutely improved cognitive performance following short durations of treatment (Bedard et al., 2007; Gorman et al., 2006; James et al., 2001; Pietrzak et al., 2006; Swanson et al., 2011). Such short-term cognitive enhancements seem to be more prominent for tasks without an executive function component (complex reaction time, spatial recognition memory reaction time, and delayed matching-to-sample) than for tasks with an executive function component (inhibition, working memory, strategy formation, planning, and set-shifting) (Swanson et al., 2011). Stimulant drugs have been shown to improve academic productivity, such as the quality of note-taking, scores on quizzes and worksheets, amount of written-language output and homework completion (Evans et al., 2001). Some clinical trials have indicated

that stimulant treatment is generally not associated with improved reading abilities (Forness et al., 1991; Forness et al., 1992; Loe & Feldman, 2007)

Long-term randomized clinical trials of stimulants' effects on academic performance are unethical and impractical. Therefore, a systematic assessment of children naturalistically treated may be the best way to study the association between treatment with stimulants and long-term academic outcomes**.** Studies of this type are, however, scarce. They have yielded inconclusive results and are hindered by methodological short-comings. Small sample sizes, short follow-up time and inappropriate use, or absence, of control groups have hampered conclusive interpretations - as have self- or parental reports of medication use. Furthermore, attrition of study subjects is a methodological issue in these follow-up studies as subjects lost to follow-up may include those with worse academic outcomes (Loe & Feldman, 2007).

Nevertheless, well designed long-term follow-up studies on representative study samples are needed to fill the existing knowledge gap and understand the underlying mechanism between stimulant treatment and academic performance among children with ADHD.

Existing studies, with follow-ups from 6-13 years, have indicated improved performance in mathematics (Molina et al., 2009; Scheffler et al., 2009), but inconsistent results for reading improvement (Barbaresi et al., 2007b; Scheffler et al., 2009). Gender-specific effects have not been reported. Very recently, Scheffler et al. (2009) found that parent-reported drug treatment was associated with higher mathematic achievement test scores within a US sample of 594 elementary school children with ADHD, but higher reading scores were dependent upon longer treatment durations. These gains were, however, not sufficient to eliminate the test score gaps between children with ADHD and normal children. Barbaresi et al. (2007b) demonstrated that stimulant treatment of children with ADHD was associated with improved reading achievement, decreased school absenteeism and decreased grade retention within a population-based sample of 349 ADHD diagnosed children.

In the naturalistic follow-up of MTA children, Molina et al. interestingly found that mathematics scores were the only functional outcome positively associated with past-year, parent-reported medication use during follow-up of at years 3, 6 and 8 after enrollment, suggesting a beneficial effect of continued medication treatment that may be unique to mathematic achievement (Molina et al., 2009). Earlier results from the MTA study indicated that medication management benefited academic achievement and performance only slightly (MTA Cooperative Group, 1999a). In a two-year sub-study conducted on 103 of the

MTA study-participants, Hechtman et al. (2004) found no advantage of combined treatment over stimulant medication alone on any academic measures.

1.5 Health Care and Education in Iceland

In 2007, Iceland had a population of 307 672, including 79 469 children (0- 17 years) (Statistics Iceland). Relative to health care in the neighboring countries and worldwide, the health care system in Iceland is good; with 3.7 physicians per 1000 inhabitants, including a total of 188 active general practitioners, 59 pediatricians (with various sub-specialties), 67 psychiatrists and 8 child and adolescent psychiatrists (Directorate of Health Iceland, 2008; OECD, 2007). Total percentage of gross domestic product (GDP) devoted to health care spending is relatively high, 9.2% in 2007, at similar range of the expenditure in other Nordic countries (OECD, 2010b; Statistics Iceland, 2008). The Icelandic health service is primarily financed by the central government. Patients pay a small part of the cost for drugs and out-patient visits (Halldorsson, 2003).

During our study period, 2003 to 2008, access to specialists in Iceland was relatively good and unrestricted. Referrals from general practitioners to see specialists in psychiatry, for example, were not required. However, due to the small number of specialists in child and adolescent psychiatry and pediatric neurology, waiting lists may have been a source of restriction. Reimbursement schemes for behavioral or psychological treatment for children in outpatient care did not exist in Iceland until the beginning of 2008 ("Regulation no. 1266/2007," 2007). Psychotropic drugs were reimbursable during the entire study period.

When comparing patterns of drug use in the Nordic countries it is essential to account for both the similarities and disparities between the national health care systems, national reimbursement systems and availability of drugs on the market. The Nordic countries share a common ideology of equal access to health care for all. Although the Nordic health systems and policies are not identical (Vallgarda, 2007), they are founded upon a similar basis. All countries have tax based public health insurances covering health care, including reimbursed drugs for the total population. The actual structures and organization of health care may vary by country, as may the national reimbursement schemes, e.g. methods for drug pricing, which drugs are included to reimbursed schemes and reimbursement ratios. In general though, prescriptions are filled for a maximum of three months (Furu et al., 2010).

Educational attainment has grown in Iceland over the past decades. Currently, the proportion of Icelanders with upper secondary and tertiary

education is at similar range to the OECD average (OECD, 2010a). In 2007, total annual expenditure per student to educational institutions was above the OECD average, with a proportionally higher amount spent on the primary educational level than on secondary and tertiary levels (OECD, 2010a). By tradition, primary education is almost entirely publicly funded. The educational system is based on equal opportunity and access to schooling irrespective of sex, residency, social and cultural background, special needs or handicap. By law children aged 6- to 16-years are required to attend school, from 1st throughout 10th grade. The size of schools at the compulsory level varies widely. During the time of our studies approximately half of the schools in the country had over 100 students. All compulsory schools follow national curriculum guidelines based on laws and regulations. In recent years Icelandic children have scored above average, although not among the top, in proficiency tests (PISA) given to 15 year-old students in the OECD countries (OECD, 2010a).

Additionally to regular assessments throughout the compulsory school years, Icelandic students take nationally coordinated examinations in grades 4, 7 and 10 (Icelandic Educational Testing Institute). The subjects examined are mathematics and language arts. The measured mathematic components are arithmetic, geometry and measurements, numbers and basic mathematical understanding. The Icelandic language art test is composed of spelling, reading and listening comprehension, grammar and writing. We used results from the examinations taken in 4th and 7th grade, in Study III, to asses of academic progress among children treated with drugs for ADHD (Study III).

1.6 Study Motivation

To date, there are no studies on psychotropic drug utilization patterns and prescribing trends for children and adolescents in Iceland. This may partly be explained by prior lack of data. Now, however, the Icelandic Medicines Registry provides a unique opportunity to examine national patterns of pediatric psychotropic drug use. There is a great public health need for a drug utilization study of this kind in order to enhance rational drug use in Icelandic society.

Furthermore, no studies comparing utilization patterns of ADHD drugs among the total Nordic population exist. In light of ADHD being among the most common childhood disorders and its serious burden on those affected, their families and society, promotion of optimal treatment is of major public health importance. We hope that by comparing drug use for ADHD between geographical regions may enhance health policies leading to increased overall treatment success. The establishment of nationwide prescription registers in all

five Nordic countries makes it possible to do a comparative study within a population of nearly 25 million individuals.

With almost 100% complete national registration of prescription drug utilization and mandatory standardized scholastic tests for all children at age 9 and 12, Iceland offers a unique setting to study academic performance among children medicated for ADHD. Studies on longer-term academic effects in naturalistic settings are scarce and have yielded inconclusive results.

The validity of the overall PhD project rests on the use of nationwide data in its three studies (I- III), providing a unique opportunity to report on national patterns of pediatric psychotropic drug use in Iceland, and its neighboring countries, and the ability to evaluate and generalize on the effect of stimulant drug treatment for ADHD on academic performance among children.

In light of the above, we anticipate that our study results will be of public health importance. In addition to serving as a basis for further study in the field, the results may enhance evidence based decision making of public and private agencies involved in child health, well-being and education.

2 Aims

Our overarching research aim was to use the unique setting and resources in Iceland to examine to what extent psychotropic drugs are used among children in Iceland, to compare that with use in our neighboring Nordic countries and finally to answer whether children benefited academically from treatment with stimulant drugs for ADHD (stimulants).

2.1 Study I - Psychotropic Drug Use among Children in Iceland

The objective of Study I was to investigate psychotropic drug use among children in Iceland during the years 2003 to 2007. More specifically we aimed to determine annual prevalence (current users) and incidence (new users) of stimulant (and atomoxetine) (N06BA), antidepressant (N06A), antipsychotic (N05A), anxiolytic (N05B), hypnotic and sedative (N05C) use for these years with regard sex and age of the child, as well as unlicensed and off-label use of these drugs. We furthermore aimed to ascertain the medical specialty of prescribers most likely to initiate treatment with these psychotropic drugs for children.

2.2 Study II - ADHD Drug Use in the Nordic Countries

The objective of Study II was to explore national accessibility of drugs for ADHD, i.e. stimulants and atomoxetine (N06BA), and determine the 2007 prevalence of their use among children, adolescents and adults in the five Nordic countries; Denmark, Finland, Iceland, Norway and Sweden. We aimed to study drug treatment patterns rather than the epidemiologic patterns of ADHD.

2.3 Study III - ADHD Drug Treatment and Academic Progress among Children

In Study III the aim was to assess academic performance and progress among children treated with drugs for ADHD, i.e. stimulants and atomoxetine (N06BA) on a nationwide level. We sought to compare academic performance among the medicated population with the non-medicated general population and, more importantly, to compare academic performance within the medicated children according to their different timing of drug treatment start, e.g. children with early vs. late treatment start.

More specifically, the research hypothesis for Study III was that delayed initiation of drug treatment for ADHD would adversely affect academic progress in mathematics and language arts among 9- to 12-year old children.

3 Materials and Methods

3.1 Data Sources

3.1.1 Icelandic Medicines Registry

We used information from the Icelandic Medicines Registry in all of our studies (I-III). The Registry contains individual level data on near all dispensed prescription drugs to the total outpatient population in Iceland from January 1st 2003 and onwards.

Completeness of the Icelandic Medicines Registry ranged from 93.7 to 99.9% of all dispensed outpatient pharmacy records for the years 2003 to 2008. The percentage of outpatient prescriptions not included in the Registry prior to the year 2006, were mainly due to missing information on prescriptions handled by automated dosage dispensing mostly used for elderly or disabled people, i.e. when the pharmacy distributes the patient's drugs in unit dose packages. Since January 1st 2006, this information has been complete. The registry contains information on both reimbursed and non-reimbursed prescription drugs, as well as prescribed drugs that have not received a formal marketing authorization in Iceland.

Although validation studies have been not published yet for the Icelandic Medicines Registry, its data are continuously cross-checked with reimbursement information from the Icelandic Health Insurance (Sjúkratryggingastofnun), where drug reimbursement is determined, thus ensuring the good level of completeness.

The Icelandic Medicines Registry does not hold information on the indication for drug treatment. Accordingly, Studies I-II were studies of drug utilization patterns, rather than disease epidemiology. For Study III we made assumptions on the diagnosis of ADHD based on drug regulations and clinical guidelines in Iceland.

For our studies (I-III) we retrieved information for each dispensed prescription to a child in the study, we received information on name of drug, number of defined daily doses (DDDs), ATC code, date and pharmacy where the prescription was filled.

3.1.2 Other Nordic Prescription Registers

The Nordic prescription registers hold data on all prescribed drugs dispensed to patients in ambulatory care. They include data on dispensed item, substance, brand name and formulation together with date of dispensing, patients' identity

number, gender and age. All prescription registers contain data on drugs both with and without marketing authorization. Reimbursed and non-reimbursed prescription drug purchases are registered in all databases except the Finnish, in which only reimbursed drug purchases are registered. All drugs in the registers are classified according to the WHO's ATC classification system.

The completeness of the Nordic prescription databases is high (Furu et al., 2010), containing over 95% of all pharmacy records in outpatient care. In general, prescriptions are filled for a maximum of three months in the Nordic countries (Furu et al., 2010).

3.1.3 Database of National Scholastic Examinations

Standardized tests in mathematics and language arts are nationally coordinated academic assessments mandatory for all children in 4th grade (9-year olds) and 7th grade (12-year olds) within the Icelandic school system. These standardized tests are ideal for within-individual comparisons as they measure very similar age adjusted components in both grades. The measured mathematic components are arithmetic (50% in 4^{th} grade, 62.5% in 7^{th} grade), geometry and measurements (25 % in 4^{th} and 7^{th} grade), numbers and basic understanding (25%in 4^{th} grade, 12.5% in 7^{th} grade). The Icelandic language art test is composed of spelling (15% in 4^{th} and 7^{th} grade), reading and listening comprehension (50% in 4^{th} grade, 40% in 7^{th} grade), grammar (25% in 4^{th} grade, 35% in 7^{th} grade) and writing (10% in 4^{th} and 7^{th} grade). We obtained the test scores, test dates, school and school region for each child who took tests between 2003 and 2008. Approximately 3% of each birth cohort is exempt from the tests each year, mainly owing to illness on the test day or to disability. Migration from or to Iceland between tests, or unspecified absence, are other reasons that one of the test scores may not be available.

3.1.4 National Population Registry

From the National Population Registry we obtained demographic information of the study population in each study. In Study I we used information on the number of children by sex and age group living in Iceland at the end of each year between 2003 and 2007. For Study II we obtained the total number of individuals living in the country at the end of 2007, stratified by age and sex. Furthermore for Study II, we used similar information from the population registers in Denmark, Finland, Norway and Sweden. In Study III we obtained demographic data on every child living in Iceland during the study period 2003 to

2008, including year, month and place of birth, sex and residency. The National Population Registry has complete information for these variables.

3.2 Design and Methods

The design and methods of our research follow here described separately for each of the three studies.

3.2.1 Study I - Setting and Population

This was a nationwide population-based drug utilization study, covering the total pediatric population, ages (0- 17 years), in Iceland from January 1st, 2003 to December 31st, 2007. During the study period the annual number of children living in Iceland was according to the National Population Registry; 78,157 in 2003; 78,542 in 2004; 78,935 in 2005; 79,450 in 2006 and 79,469 in 2007. Information on dispensing of psychotropic drugs was obtained from the Icelandic Medicines Registry.

3.2.2 Study I - Measures and Statistical Analysis

We defined psychotropic drugs as those pertaining to ATC-groups *psycholeptics* (N05) and *psychoanaleptics* (N06) including the following subgroups: antipsychotics, anxiolytics, hypnotics and sedatives (N05B, N05C), antidepressants (N06A), stimulants and atomoxetine (N06BA) (WHO, 2008).

The main outcome measures for Study I were:

- prevalence of use by year and psychotropic drug group
- incidence (new users) of drug use by year, psychotropic drug group, age, sex and medical specialty of prescriber
- prevalence of concomitant (concurrent) psychotropic drug use
- prevalence of off-label and unlicensed use

Prevalence and incidence proportions were calculated as the number of children who had been dispensed at least one prescription per 1000 children in the population (prevalence proportion), or were dispensed their first prescription (incidence proportion), for a psychotropic drug during the relevant calendar year. To determine the incidence proportion in 2004, we used the year 2003 as a run-in period. We defined concomitant drug use as the dispensing of two or more different psychotropic chemical substances to a child on the same day at least once within the calendar year. We determined the extent of off-label (age inappropriate) and unlicensed drug use dividing the prescribed drugs into categories suggested by Schirm et al. (2003). To test for linear time trends in

prevalence and incidence proportions, we performed log-likelihood ratio tests assuming a betabinomial distribution for the counts, and modeled the proportion parameters with and without linear time trends.

We used Excel (Microsoft Office Excel 2003) to calculate incidence and prevalence proportions and MATLAB 7.6 to perform time trend analyses.

3.2.3 **Study II - Setting and Population**

This was a population-based drug utilization study covering the total population living in Denmark, Finland, Iceland, Norway and Sweden. The total Nordic population at the end of the year 2007 amounted to 24,947,169 individuals, according to the national population registers. Information on dispensing of ADHD drugs from January 1st, 2007 to December 31st, 2007 was obtained from the nationwide prescription registers available in each country. In Study II, we used data on dispensed drugs to the outpatient population; hence those who were dispensed drugs only within a hospital or a nursing facility did not appear in the analyses.

3.2.4 **Study II - Measures and Statistical Analysis**

We defined ADHD drugs as those pertaining to ATC-group of *centrally acting sympathomimetics* (N06BA) used to treat ADHD (WHO, 2008). Chemical substances included in Study II were amfetamine (N06BA01), dexamfetamine (N06BA02), methylphenidate (N06BA04), modafinil (N06BA07) and atomoxetine (N06BA09). Other chemical substances within the studied ATC-group N06BA; metamfetamine (N06BA03), pemoline (N06BA05), fencamfamin (N06BA06), fenozolone (N06BA08), fenetylline (N06BA10) and dexmethylphenidate (N06BA11) were not available or used for outpatient care in the Nordic countries at the time of the study.

The main outcome measures for Study II were:

- Marketing authorization and reimbursement status of ADHD drugs in each country.
- One-year prevalence of dispensed drugs to outpatients by chemical substance, patients' country of residence, sex and age group.
- Prevalence ratios (Prev. ratio) of drug use by country and sex and corresponding 95% confidence intervals (CI).

Prevalence of ADHD drug use was defined as the number of individuals who were dispensed at least one prescription during the year 2007 per 1000 inhabitants in the population. We stratified prevalence by chemical substance,

patients' country of residence, gender and age group. To describe use among children, we used the age category 7- 15 years to coincide with the age range at which ADHD is most prevalent. To show the variation of use between countries, we used the Mantel- Haenszel method to estimate age-adjusted prevalence ratios (Prev.Ratio, country ratios) of use for each country and the corresponding 95% confidence intervals (95% CI) (Greenland, 2008), with prevalence of ADHD drug use in Sweden as a reference category. We used Excel spread sheets (Microsoft Office Excel 2007) to examine all data and run analysis.

3.2.5 **Study III - Setting and Population**

We followed all 13,617 children born in 1994, 1995 and 1996 and registered in the Icelandic school system (Figure 4). From January 1st, 2003 to December 31st, 2008 we followed this cohort with respect to psychotropic drug prescription fills and standardized test results in mathematics and language arts. Using the personal identification number, we performed record linkage of data from the National Population Registry to the Icelandic Medicines Registry and the Database of National Scholastic Examinations. The final study population comprised all test-participating children who took a standardized test in both 4th (age 9) and 7th grade (age 12), (n=11,872). Available for analysis were those with both outcomes in mathematics (n=11,619) and in language arts (n=11,542).

The Icelandic Medicines Registry does not hold information on the indication for drug treatment; therefore the study lacks concrete data on the diagnosis of ADHD, subtype and co-morbidities. In Iceland, however, an ADHD diagnosis must be verified by a pediatric-, psychiatric- or neurological specialist to initiate a reimbursed drug treatment. . Thus, it is reasonable to assume that essentially all medicated children fulfilled the DSM-IV criteria for ADHD before treatment.

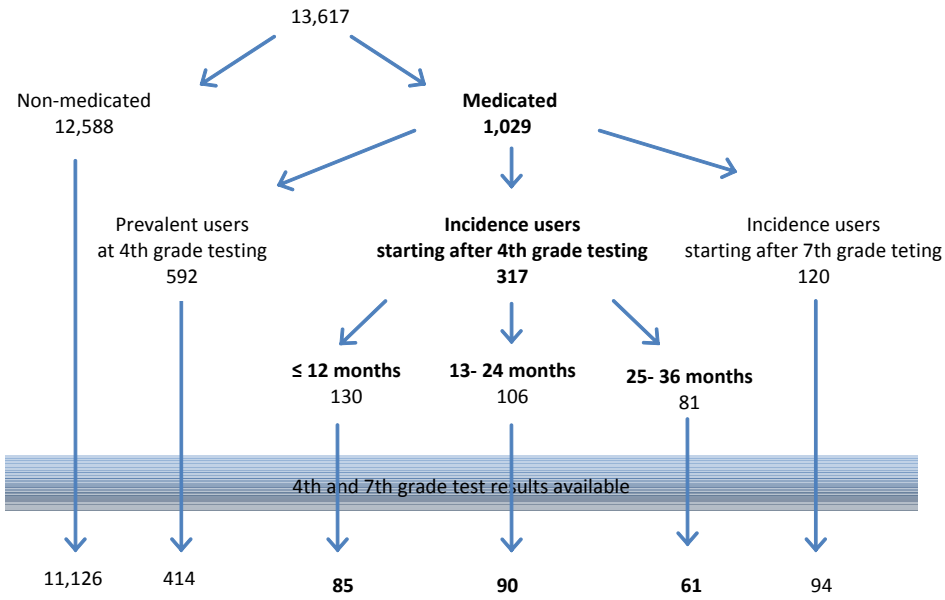


Figure 4. Origin of Study Population (Study III)

a. Prevalent users are children already treated before the 4th grade tests.

b. Incidence users are children who began treatment after the 4th grade tests.

3.2.6 Study III - Measures and Statistical Analysis

3.2.6.1 ADHD Drug Exposure

We defined ADHD drugs as drugs pertaining to the ATC-group of *centrally acting sympathomimetics (N06BA)*.(WHO, 2008) Chemical substances included were amphetamine (N06BA01), methylphenidate (N06BA04) and atomoxetine (N06BA09). Modafinil (N06BA07) was excluded because it was only indicated for narcolepsy in adults at the time of the study (Icelandic Medicines Agency) and not prescribed to children in Iceland at the time. Other chemical substances within the ATC category N06BA were not available in Iceland during the study period. All the included drugs had ADHD as its main indication, according to

clinical guidelines and drug package inserts (Baldursson et al., 2007; Icelandic Medicines Agency).

The start of treatment for each child was defined by the date of the first dispensing of a prescription for an ADHD drug (stimulant or atomoxetine) within the study period. We required a period of at least 11 months during which no prescriptions for an ADHD drug were filled, to exclude children already on therapy. To diminish the risk of confounding by indication, the main analyses were restricted to children who started treatment between test dates in 4th and 7th grade. Using the children's test dates we categorized those who started treatment anytime during follow-up and between test dates in the 4th and 7th grade as starting within 12 months, 13-24 months or 25-36 months after 4th grade tests (Figure 5). We defined later treatment as treatment that started 25-36 months after the 4th grade tests. Treatment was considered to have been discontinued early if children filled less than 90 DDDs of an ADHD drug. We considered children to have been treated on their test day in 7th grade if the number of DDDs on the last prescription overlapped with the test day.

We assumed that children were treated concurrently with psychotropic drugs if a prescription was filled for another psychotropic drug within the 90-day period following the dispensing of an ADHD drug. Other psychotropic drugs were defined as all drugs pertaining to ATC-group *nervous system (*N) including antidepressants (N06A), antipsychotics (N05A), anxiolytics, hypnotics and sedatives (N05B, N05C) and other psychotropic drugs (N01, N02, N03, N04, N06C, N06D, N07).

3.2.6.2 Academic Outcomes

We converted all test scores in mathematics and language arts, originally given on a scale of 0.0-10.0, to a percentile scale (0-100) that was ranked within each test year. Our assessment of academic performance in each subject was based on these percentile rankings. Change in performance was found by subtracting the 4th grade percentile rank from the 7th grade rank for each individual. A child at the 52nd percentile in 4th grade and 50th percentile in 7th grade would thus have a performance change of -2.0 (declining performance). We defined an important academic decline to be a drop of 5.0 or more percentile points.

3.2.6.3 Covariates

We obtained demographic data on every child living in Iceland during the study period, including year, month and place of birth, sex and residency, from The National Population Registry. The Registry has complete information for these variables. Other covariates in the analyses were school region, change of

schools between 4th and 7th grade, concurrent psychotropic drug treatment, early discontinuation of treatment and ADHD drug treatment on test day in 7th grade.

3.2.6.4 Statistical Analysis

We described the medicated and non-medicated population by available demographic characteristics. We also described the characteristics of ADHD drug treatment, e.g. type of drugs used, early discontinuation, concurrent psychotropic drug treatment and treatment on test day, according to category of treatment start.

We calculated risks (%) and effect estimates (risk ratios [RR], risk differences [RD]) and corresponding 95% confidence intervals (CI) of a drop in performance separately for mathematics and language arts, crude and controlling separately for: performance level on the 4th grade test (categorized into terciles), sex, birth month (categorized as Jan-May, Jun-Aug, Sep-Dec), birth place (urban, rural outside Iceland), school region (urban, rural), change of schools, concurrent psychotropic drug treatment, treatment on test day and early discontinuation of ADHD drug treatment (90 DDDs). Stratified risks were standardized to the distribution of the total medicated test-participating population 2003-2008 (Rothman et al., 2008). In these analyses we excluded children who scored in the lowest 5th percentile on 4th grade test, as they were unable to decline in rank by at least 5.0 percentile points. To adjust simultaneously for the available covariates, we conducted a modified Poisson regression analysis (Zou, 2004).

Finally, we ran a sensitivity analysis to assess potential selection bias,(Fox, 2009) that would result if untested children had a different association between late treatment start and academic decline. Those who did not take one or the other of the two tests could have had either a greater or lesser academic decline than those who did take both tests; we have no basis for expecting a difference in one direction or the other. Therefore we considered a range of risk combinations and risk ratios (RR, 0.0 to 4.0) in our sensitivity analysis.

We used PASW Statistics (version 18) and Excel spreadsheets to run analyses.

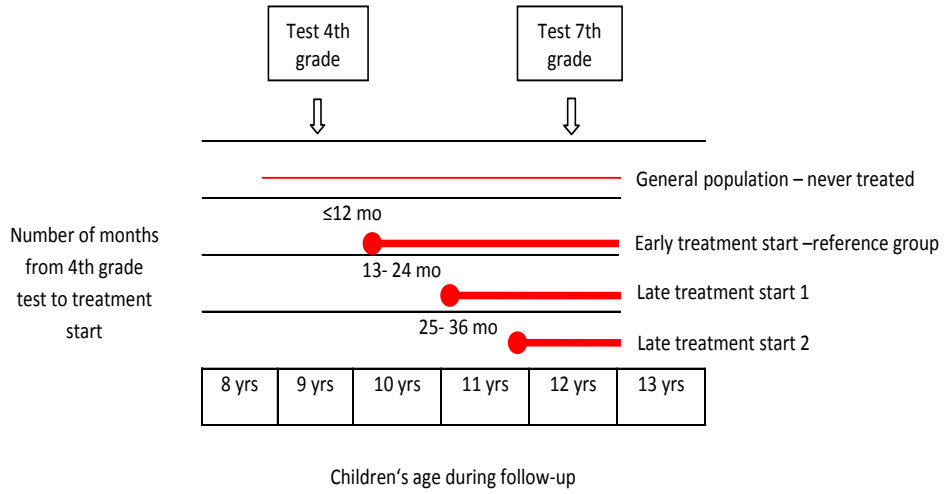


Figure 5. Study Design (Study III)

3.3 Ethics and Study Approvals

Our studies were register-based and observational. They did not involve an intervention of any sort or direct contact to patients, therefore informed consent from the studied population was not needed. All of the study material was compiled centrally by the Icelandic and Nordic state authorities for purposes additional to our research project. We did, however, receive authorization for all three studies both from the National Bioethics Committee (Vísindasiðanefnd) and the Data Protection Authority in Iceland (Persónuvernd). These approvals allude to the handling of person identifiable data and linkages between centralized databases. Data linkages were performed via personal identification numbers unique to each citizen in Iceland at the Directorate of Health, in accordance with specific procedural guidelines. We, the researchers, did not at any stage of the research process have access to these personal identification numbers or other information with direct reference to the individuals' identity, as all datasets had been cleared of this information at the Directorate of Health prior to our handling.

Ethical approvals from authorities in Denmark, Finland, Norway and Sweden were not needed to retrieve, or use, data from the prescription databases, as these countries do not require specific authorization for register-based studies

where no linkages are performed. Following are the license numbers we received from the Icelandic authorities to conduct our studies:

Study I and II. Ethical approval was obtained in 2007 from the National Bioethical Committee (license number, VSNb2007120009/ 03-7). Both studies were reported to the Data Protection Authority in Iceland (reference number, S3681) in 2007.

Study III. Ethical approvals were obtained in 2008 from the National Bioethics Committee (VSNb2008040016/03-7) and from the Data Protection Authority (license number, 2008040343/ ÞÞJ-). Reprints of the original authorizations are in Appendix b.

4 Results

4.1 Study I – Results

The overall prevalence of psychotropic drug use was 48.7 per 1000 Icelandic children in 2007. Stimulants (and atomoxetine) and antidepressants were the two most prevalent psychotropic drug groups during the study period 2003 to 2007, respectively with a prevalence of 28.4 and 23.4 per 1000 children in 2007 (Table 2). During the 5-year period, an increased prevalence was observed for stimulant (and atomoxetine) (p □0.005) and antipsychotic (p □0.01) drug use while prevalence of antidepressant use decreased significantly (p □0.0005) (Table 2). Prevalence was lowest for use of anxiolytics, hypnotics and sedatives and remained relatively stable during the study period.

The most commonly used psychotropic chemical substance used was methylphenidate, which in 2007 had a prevalence proportion of 38.3 per 1000 for boys and 12.9 per 1000 for girls. The tricyclic antidepressant amitriptyline had the second highest use prevalence.

Table 2. Prevalence of Psychotropic Drug use among Children in Iceland 2003-2007 (Study I)

Psychotropic Drug Group	Prev.[a] (n) **2003**	Prev.[a] (n) **2004**	Prev.[a] (n) **2005**	Prev.[a] (n) **2006**	Prev.[a] (n) **2007**
Any psychotropic drug group	46.0 (3595)	48.5 (3810)	47.3 (3732)	47.6 (3781)	48.7 (3872)
Antidepressants	28.3 (2210)	28.0 (2200)	25.6 (2024)	24.6 (1955)	23.4 (1860)[b]
Stimulants and atomoxetine	21.7 (1695)	25.4 (1994)	25.1 (1980)	26.7 (2121)	28.4 (2256)[b]
Antipsychotics	8.7 (678)	8.8 (694)	8.9 (702)	9.4 (745)	10.6 (839)[b]
Anxiolytics	1.7 (135)	1.7 (133)	1.5 (120)	2.0 (160)	1.8 (145)
Hypnotics and sedatives	0.8 (65)	0.8 (62)	0.8 (63)	0.7 (56)	2.6 (206)
Total study population	78,157	78,542	78,935	79,450	79,469

a. Prevalence proportions are expressed as number of children per 1000 children (0-17 years) in the population dispensed one or more prescriptions.

b. A significant linear time trend for prevalence proportions 2003 to 2007 ($p < 0.05$).

The overall psychotropic incidence was reduced from 16.3 in 2004 to 13.1 in 2007 (p □0.05). This tendency towards fewer new users was driven mainly by significantly fewer incident antidepressant users (Figure 6). A stratified analysis of incidence by drug group, sex, and age revealed that a higher proportion of boys compared to girls initiated psychotropic drug treatment, and that the number of new users increased with age. Stratification of incidence by medical specialty of prescriber demonstrated that overall psychotropic drug treatment for children was most frequently initiated by pediatricians from 2004 to 2007. This was true for all drug groups except antipsychotics, where child and adolescent psychiatrists initiated treatment slightly more frequently than pediatricians.

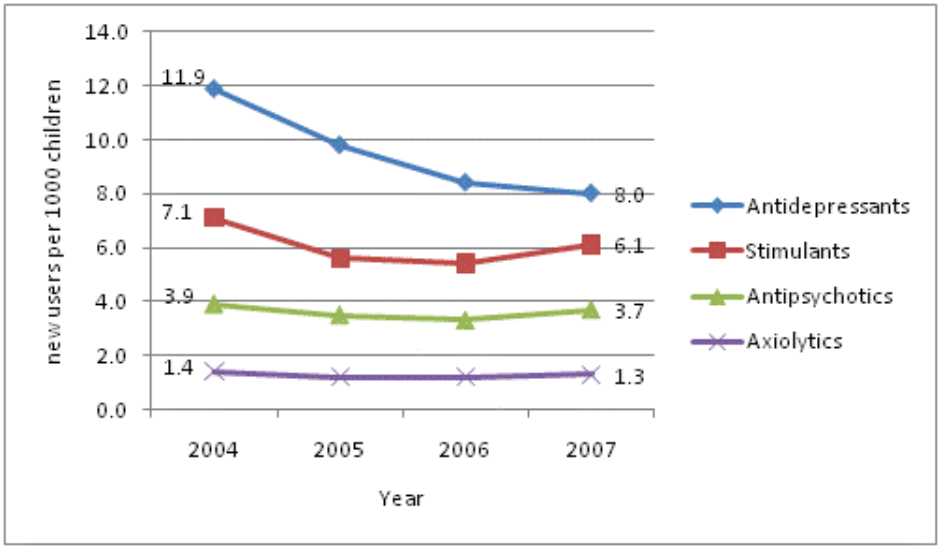


Figure 6. Incidence[a] of Psychotropic Drug Use among Children in Iceland 2004-2007 by Drug Group (Study I)

a. Incidence expressed as number of children per 1000 in the population who filled their first prescription [new users].

We found that out of 21,986 psychotropic drugs dispensed in 2007, 25.4% were used off-label (Table 3). The proportion of off-label use was 41.8%for antidepressants and 52.0% for antipsychotics. Nearly all use, 98.8%, of the most prevalent drug group, stimulants, and atomoxetine was on-label. Among psychotropic users in 2007, 17.5% (n=677) used two or more drugs concurrently, i.e. had two or more different drugs dispensed on the same day at least once within the calendar year.

Table 3. Off-Label[a] and Unlicensed[b] Psychotropic Drug Use among Children in Iceland in 2007 (Study I)

Drug Group	Total No. of Prescribed Drugs	% Off-label	% Unlicensed
Any psychotropic drug group	22,700	24.6	0.6
Antidepressants	7,606	41.8	0.0
Stimulants and atomoxetine	10,308	1.2	0.0
Antipsychotics	3,277	52.0	5.2
Anxiolytics	1,002	10.4	10.7
Hypnotics and sedatives	507	95.3	4.7

a. Drugs used outside the age terms of the product license.

b. Drugs without a product license in Iceland.

4.2 Study II – Results

The 2007 prevalence of ADHD drug use among the total Nordic population was 2.8 per 1000 inhabitants, varying from 1.2 per 1000 in Finland to 12.5 per 1000 in Iceland (Table 4). Methylphenidate was the most prevalent ADHD drug in all five Nordic countries and the only drug with both marketing authorization and reimbursable in each country.

Table 4. Prevalence[a] of ADHD Drug Use by Chemical Substance in Five Nordic Countries in 2007 (Study II)

		Prevalence of use by country					
	Age in years	**Denmark**	**Finland**	**Iceland**	**Norway**	**Sweden**	**Nordic Countries**
Any ADHD drug	*All ages*	2.4	1.2	12.5	4.3	2.5	2.8
	7-15	9.3	6.4	47.0	18.1	9.6	11.2
Methylphenidate	*All ages*	2.1	1.2	10.6	4.1	1.9	2.3
	7-15	9.0	6.4	42.8	16.4	8.6	10.3
Atomoxetine	*All ages*	0.2	b	1.6	0.7	0.4	0.3
	7-15	1.0	b	6.3	2.7	1.8	1.5
Modafinil	*All ages*	0.3	0.05	0.6	0.06	0.3	0.2
	7-15	0.03	0.01	-	-	0.02	0.01
Dexamfetamine	*All ages*	-	0.03	-	0.2	0.05	0.05
	7-15	-	0.02	-	0.3	0.04	0.07
Amfetamine	*All ages*	-	-	0.4	0.04	0.1	0.05
	7-15	-	-	-	0.03	0.1	0.05
Total study	*All ages*	5,447,084	5, 300, 328	307, 672	4,681,134	9,182,927	24,919,145
population	*7-15*	623,276	557,626	40,085	561,102	949,266	2,731,413

a. Prevalence is expressed as number of individuals per 1000 in the population dispensed one or more prescriptions.

b. Atomoxetine does not appear in the Finnish prescription database since the database only holds information on reimbursable drugs and this chemical substance is not reimbursed in Finland.

– . No use.

Adjusting for age, Icelanders were nearly five times more likely than Swedes to have used ADHD drugs (Prev.Ratio 4.5; 95%CI, 4.38 to 4.69) (Table 5).

Table 5. Prevalence Ratios[a] of ADHD Drug Use between the Nordic Countries in 2007[b] (Study II)

	Age in years	Prev.Ratio	95% CI
Denmark	*All ages*	0.9	(0.88; 0.92)
	7-15	0.9	(0.85;0.91)
Finland	*All ages*	0.5	(0.53; 0.55)
	7-15	0.8	(0.80; 0.86)
Iceland	*All ages*	4.5	(4.38; 4.69)
	7-15	4.9	(4.68; 5.15)
Norway	*All ages*	1.8	(1.75; 1.82)
	7-15	1.9	(1.84; 1.95)
Sweden	*All ages*	1.0	Ref.
	7-15	1.0	Ref.
Nordic	*All ages*	1.1	(1.07; 1.10)
Countries	*7-15*	1.2	(1.14; 1.20)

a. Stratum specific (age 7-15 years) and pooled prevalence ratios (Prev.Ratio) shown with corresponding 95% confidence intervals (CI).

b. Use in Sweden as reference (Prev.Ratio=1.00).

Prevalence among boys (age 7–15) was fourfold the prevalence among girls (Prev.Ratio, 4.3; 95% CI, 3.70 to 4.96). The gender ratio was diminished among adults (age 21 +), (Prev.Ratio, 1.2; 95%CI, 1.21 to 1.27) (Figure 7, Figure 8).

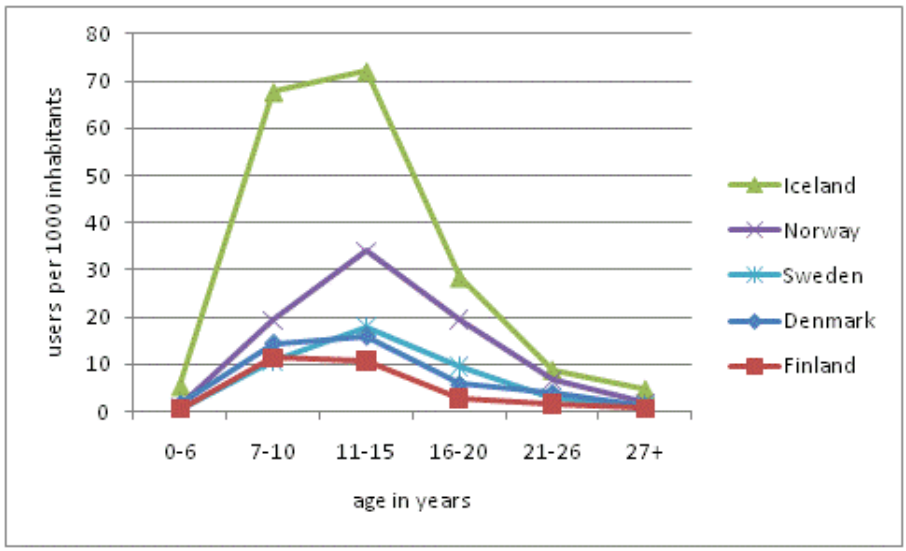


Figure 7. Prevalence of ADHD Drug Use among Nordic Males in 2007 (Study II)

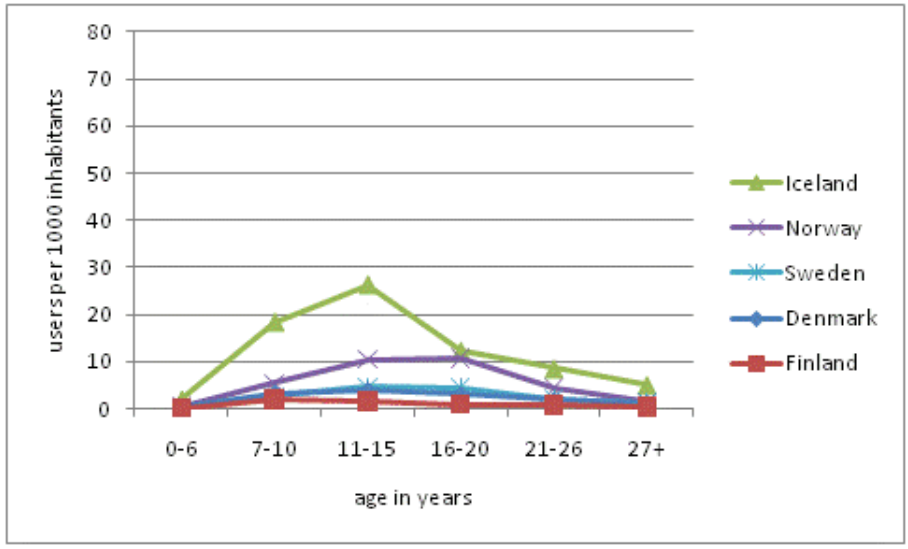


Figure 8. Prevalence of ADHD Drug Use among Nordic Females in 2007 (Study II)

4.3 Study III – Results

Of the 13,617 children registered in the Icelandic school system, 1029 children (7.6%) were treated with ADHD drugs at any time during the study period. Test participation, i.e. children taking tests in 4th and 7th grade in either mathematics or language arts, was lower for the total medicated population (72.5%) than among the non-medicated general population (88.4%) (Figure 4). Of 317 medicated children who began treatment between 4th and 7th grade test, 235 took tests; resulting in 65.4%, 84.9% and 75.3% test-participation for children starting medication ≤12 months, 13-24 months and 25-36 months respectively after the date of 4th grade tests.

Nearly all medicated test-participating children were treated with methylphenidate (97.2%), a few also with the non-stimulant atomoxetine, and just under half (46.6%) concurrently with another psychotropic drug. Among the children starting treatment after 4th grade tests these respective proportions were: 95.7% treated with methylphenidate and 33.9% treated concurrently with another psychotropic drug. Children who started treatment within 12 months after 4th grade tests received on average over double the supply (427 DDD) of ADHD drugs before tests in 7th grade, compared with those who started later (175 DDD).

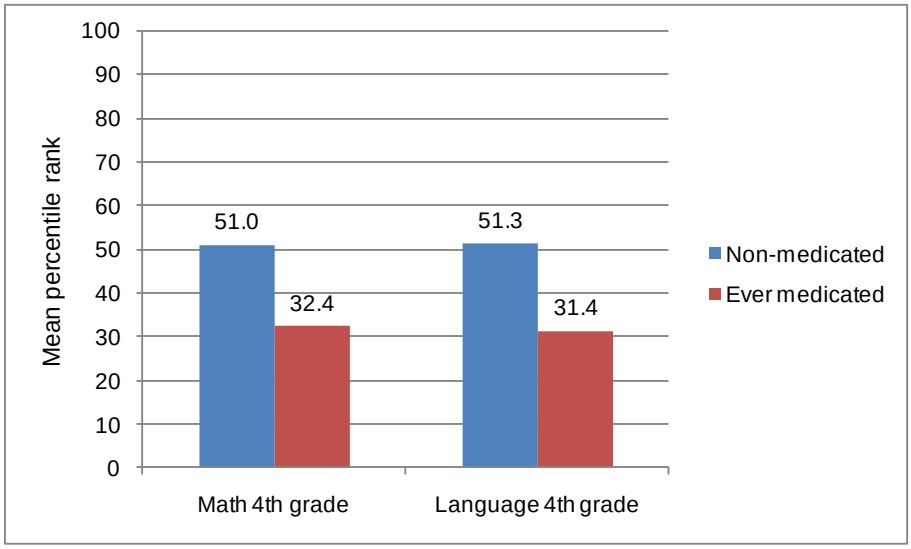


Figure 9. Academic Performance in 4th Grade among the total Medicated Population (anytime 2003-2008) and the Non-Medicated General Population (Study III)

On average children medicated with ADHD drugs anytime during follow-up 2003 to 2008 performed worse academically on standardized tests in mathematics and language arts in 4th grade compared with the non-medicated general population (Figure 9). Medicated children who started treatment between 4th and 7th grade test (n=235) had a lower mean score percentile in 4th grade than those who had started before tests (n=414).

4.3.1 Change in Academic Performance

Among children in the non-medicated general population, performance on average did not change much between tests in 4th and 7th grade; crude mean percentile score change was 0.4 (95%CI, 0.0 to 0.8) in mathematics and 0.0 (95%CI, -0.3 to 0.4) in language arts. In contrast, mean performance level declined among medicated children starting treatment between tests. The decline was concentrated among those with later treatment initiation and was much more striking for mathematics than for language arts (Table 6, Figure 10, and Figure 11).

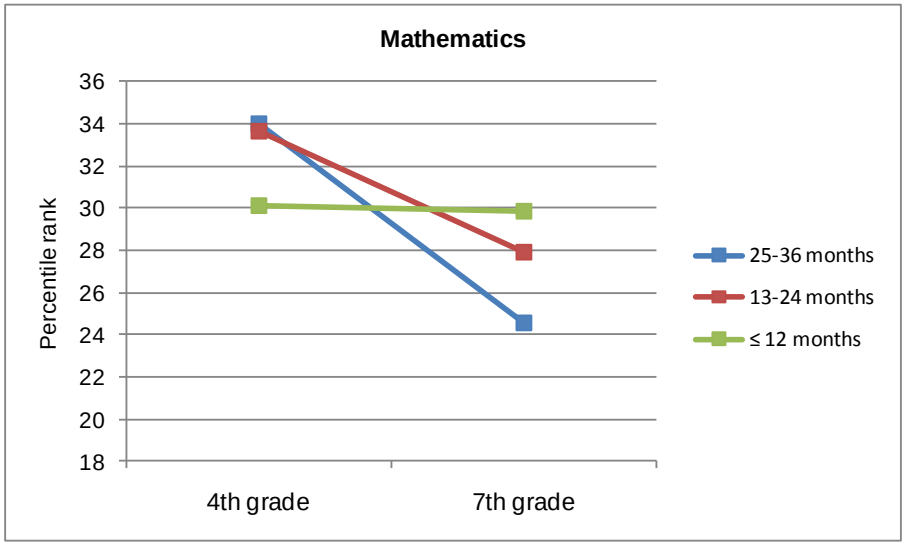


Figure 10. Change in Mathematic Performance according to Time since 4th Grade Test until ADHD Drug Treatment (Study III)

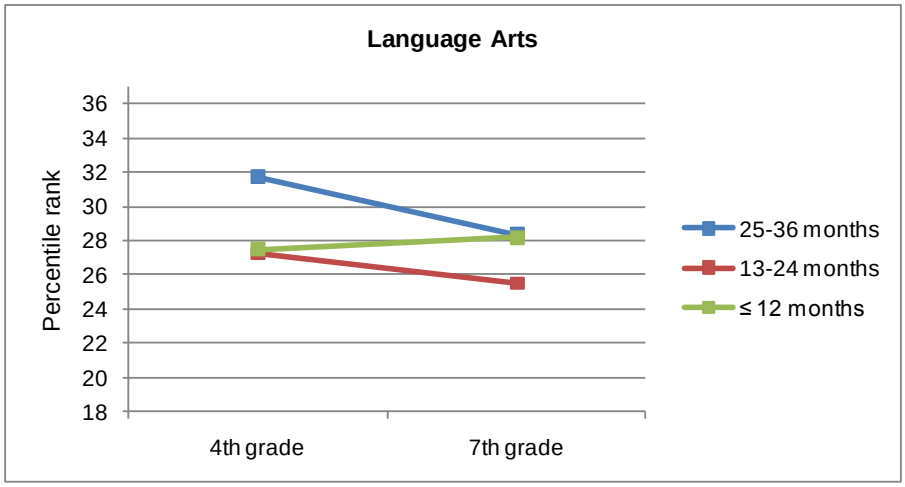


Figure 11. Change in Language Art Performance according to Time since 4th Grade Test until ADHD Drug Treatment (Study III)

In mathematics, the risk of academic decline was high among all medicated students, but especially high (crude risk ratio 1.8, 95%CI 1.3 to 2.5) for children who started treatment 25-36 months after their 4th grade test. The absolute increase in risk of decline in mathematics for the late starters on medication was 32% (95%CI, 14%- 48%) greater than the risk among those starting treatment ≤12 months after their test. For language arts, in contrast, the crude risk ratio of academic decline with later treatment was 1.1 (95%CI, 0.7 to 1.7) and the absolute increase in risk for academic decline among late starters was 4% (95%CI, -14% to 22%) (Table 6).

Table 6. Crude Risks, Risk Differences and Risk Ratios of Academic Decline according to Time since 4th Grade Test until ADHD Drug Treatment (Study III)

	Time since 4th grade test until ADHD drug treatment		
Mathematics	**≤ 12 months**	**13-24 months**	**25-36 months**
Mean percentile score change (95%CI)	-0.3 (-4.8 to 4.3)	-5.7 (-10.5 to 1.0)	-9.4 (-14.4 to -1.4)
Declined in performance ≥ 5.0 percentile	28	36	35
Total	68	76	48
Crude risk	41%	47%	73%
Risk difference (95%CI)	0.0 (ref.)	6% (10% to 22%)	32% (14% to 48%)
Risk ratio (95%CI)	1.0 (ref.)	1.2 (0.80 to 1.7)	1.8 (1.3 to 2.5)
Language Arts			
Mean percentile score change (95%CI)	0.7 (-3.4 to 4.8)	-1.7 (-5.4 to 2.0)	-3.4 (-9.2 to 2.5)
Declined in performance ≥ 5.0 percentile	25	31	21
Total	65	72	49
Crude risk	39%	43%	43%
Risk difference (95%CI)	0.0 (ref.)	5% (-12% to 21%)	4.4 (-14% to 22%)
Risk ratio (95%CI)	1.0 (ref.)	1.1 (0.75 to 1.7)	1.1 (0.71 to 1.7)

- CI, confidence interval.

The adjusted effect estimates remained similar to the crude estimates, indicating little confounding. There was some variation in the estimates across strata especially by children's performance level on their 4th grade test, sex and concurrent psychotropic drug treatment. Later treatment had a larger effect for children who scored in the lowest third (RR, 2.1) and mid third (RR, 1.9) on their 4th grade test than for those who scored in the highest third (RR, 1.1). The

absolute risk of academic decline in mathematics was higher for girls than boys (86.7% versus 66.7%), as was the risk ratio, 3.6 for girls versus 1.4 for boys (Figure 12, Figure 13). Furthermore, the effect of later treatment start was slightly stronger for children not receiving any concurrent psychotropic drug treatment than for those treated concurrently with other psychotropic drugs. Finally, the estimated effect was increased for children still being treated with ADHD drugs on their test day in 7th grade (RR, 1.9) compared with those no longer being treated on test day (RR, 1.5).

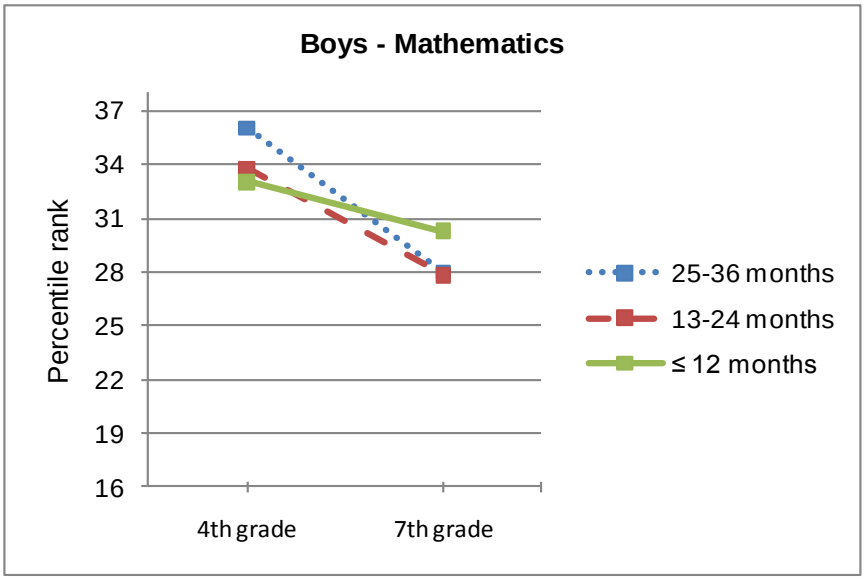


Figure 12. Change in Mathematic Performance among Boys according to Time since 4th Grade Test until ADHD Drug Treatment (Study III)

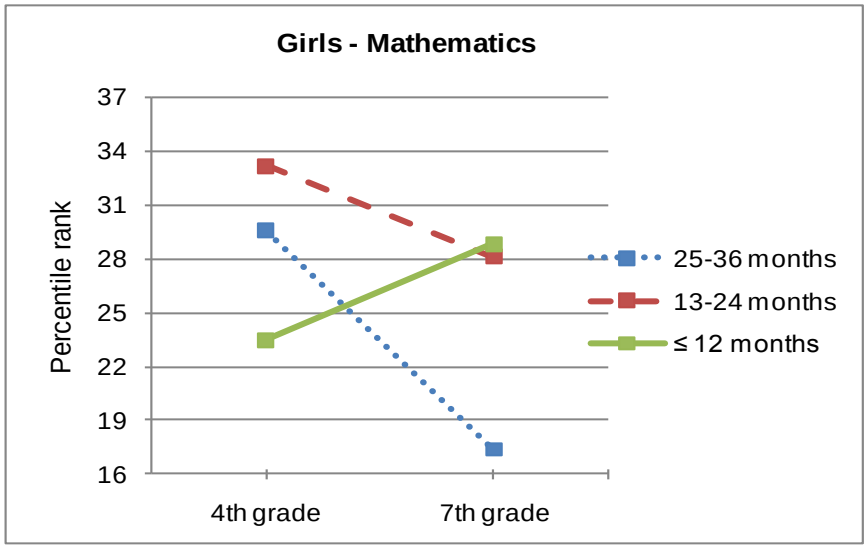


Figure 13. Change in Mathematic Performance among Girls according to Time since 4th Grade Test until ADHD Drug Treatment (Study III)

In language arts the adjusted effect estimates did not differ much from the crude estimates and indicated weak associations. The estimated effect of later treatment on decline in language arts was slightly elevated for boys (RR, 1.5), but not for girls (RR, 0.6). There was an effect among those still being treated on test day in 7th grade (RR, 1.6), but not among those no longer being treated (RR, 0.8).

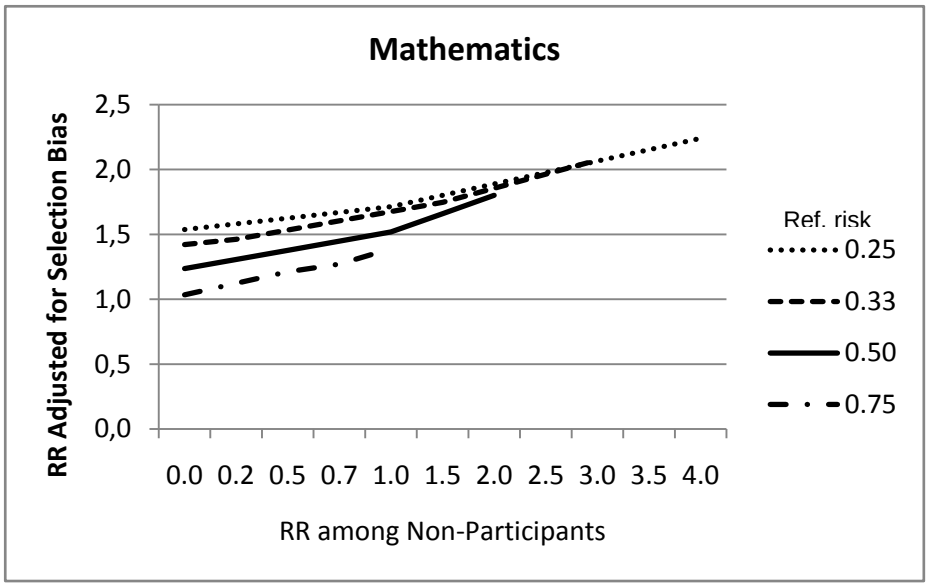
The adjusted estimates of the effect of later drug treatment on academic performance remained the same, or changed only minimally, when we stratified the data by other covariates (birth year, -month, -place, school region and change of school) , indicating only negligible confounding by these variables. Similarly, the risk ratios remained nearly the same when controlling simultaneously for all covariates in a multivariate analysis (RR, 1.7 in mathematics and RR, 1.1 in language arts).

Finally, compared with the non-medicated general population, we found that the adjusted risk of academic decline was 1.6 times greater (95%CI, 1.4 to 1.8) in mathematics and 1.3 times greater (95%CI, 1.1 to 1.6) in language arts among children starting treatment anytime between tests in 4th and 7th grade.

We ran a simple sensitivity analysis to account for potential selection bias related to the different test-participation between early and late treatment initiation after 4th grade tests. Figure 14 displays the estimated risk ratio from the main analysis adjusted for hypothetical selection bias (y-axis) given the assumed risk ratios among non-test-participants (x-axis). The depicted lines,

one for each assumed reference risk, represent adjusted risk ratios for a range of associations between later treatment and academic decline among non-test-participants children. The risk ratios from the main analysis, adjusted for selection bias, varied from 1.0 to 2.2 in mathematics and 0.6 to 1.7 in language arts, depending on the assumed combination of risk for academic decline among non-test-participating children starting treatment later versus earlier and the resulting risk ratio (RR, 0.0 to 4.0) (Figure 14). The sensitivity analysis indicates that the basic findings would look roughly the same, potentially somewhat weaker, over a broad range of assumptions about the risks and associations among children who did not take both tests.

Assuming a null-association (RR, 1.0) among non-test-participants, the adjusted risk ratios varied only slightly from the reported effect estimates among tested children (1.4 to 1.7 in mathematics; in 0.9 to 1.2 language arts).



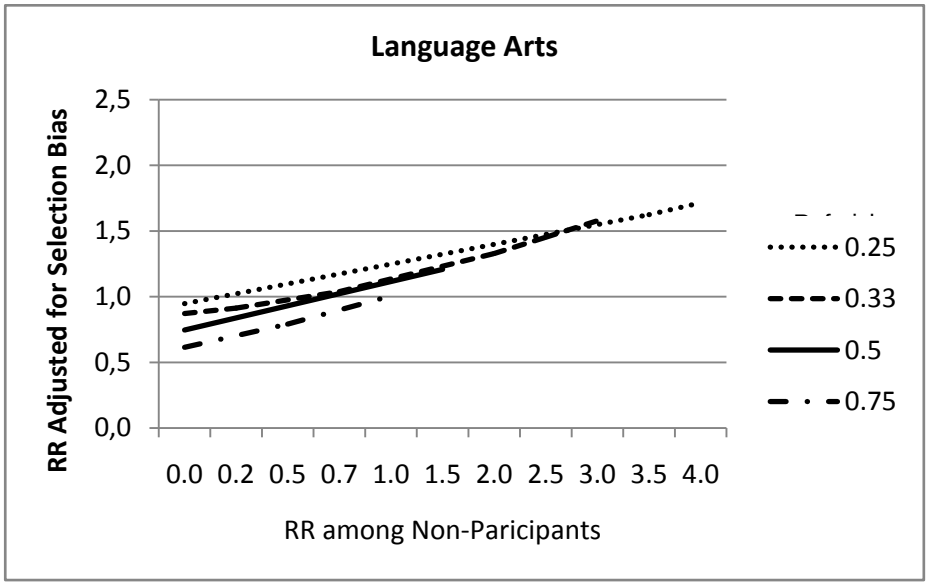


Figure 14. Graph of Sensitivity Analysis for Selection Bias (Study III)

- Assuming a range of risks of academic decline for non-test-participants.
- Ref. risk, refers to the risk of academic decline in non-test-participants who started treatment early (≤ 12 months after 4th grade tests).
- RR, refers to the risk ratio of academic decline in children who started treatment later (25-36 months after 4th grade tests) versus those who started early.

5 Discussion

5.1 Main Findings

In our studies we found that the use of psychotropic drugs to treat children is widespread in Iceland, especially use of antidepressants and stimulant drugs. In relation to the other Nordic countries, Icelanders were in 2007 four to five times more likely have filled a prescription for ADHD drugs (stimulants or atomoxetine). Furthermore, our results indicate earlier that, sustained treatment with ADHD drugs between 9- and 12-years of age is associated with a lower risk of a decline in academic performance, particularly in mathematics. Our data indicate that the apparent advantage of earlier treatment differs for boys and girls. Girls show a definite benefit only in mathematics, whereas boys show marginal benefits in both mathematics and language arts.

5.2 Studies I and II – Validity Consideration

The major strength of these descriptive drug utilization studies is the completeness of the data on which they rest. The Nordic prescription databases hold information on filled drug prescriptions of the entire national outpatient population in all five countries, demonstrating a clear and representative picture of the patterns and variations of psychotropic and stimulant drug use. Owing to regulations and other incentives motivating Nordic pharmacies to collect and send data from pharmacy records electronically to the national prescription registers, their accuracy and completeness is high (Furu et al., 2010). By measuring drug use with pharmacy records from national register data, we minimize the risk of recall bias, often associated with survey data, and selection bias associated with use of localized community data (West et al., 1995). Few previous drug utilization studies rest on individual based data covering entire national populations similar to ours. Studies I and II do, however, have limitations that must be noted.

Firstly, with regard to the external validity or generalizability of the studies, the data only covered drug use in outpatient care, not within hospitals. But since the vast majority of Icelandic children with mental health problems and individuals in the Nordic countries with ADHD are treated in ambulatory care, the results of study I and II should estimate well total use of the drugs in each country.

Secondly, also regarding external validity of our results on ADHD drug use in the Nordic countries, the Finnish prescription register lacked information on non-reimbursed drugs at the time of the study. For that reason, use of the non-

stimulant atomoxetine used to treat ADHD did not appear in our results for Finland, thus underestimating the overall ADHD drug use in the Nordic countries. But wholesale statistics from Finland indicate this to be a minor limitation, though, total consumption of atomoxetine in Finland was negligible in 2007, only 0.02 DDDs per 1000 inhabitants per day (Finland National Agency for Medicines).

Thirdly, we have no means of knowing whether the individuals who filled the prescriptions actually took the drugs. This is a well-known limitation of most drug use studies based on dispensing data and limits us in concluding on actual use or potential misuse. However, dispensing data are one step closer to actual use than data on prescribed drugs. We know that individuals actually went to the pharmacy and paid for the drugs after they had been prescribed, but not whether they or someone else consumed the drugs.

Fourthly, we did not analyze duration of drug use in our studies I and II, nor did we show incidence use or time trends of ADHD drug use in Study II, comparable to what we did in Study I. Further knowledge of how long children are treated with psychotropic drugs and how, in recent years, use of ADHD drugs may have changed in the Nordic countries would be informative and give a fuller picture of the drug utilization patterns.

Finally and very importantly, the conclusions we were able to draw from the results of Study I and II are limited by the fact that we did not have access to the underlying diagnoses, or indications, for which drugs were prescribed. Thus, the appropriateness of psychotropic drug treatment for children in Iceland and ADHD drug prescribing in the Nordic countries remains largely unanswered. This is in accordance with the main objectives of Studies I and II to describe drug utilization patterns, rather than provide an epidemiologic description of psychiatric disease or thorough assessment of treatment quality.

5.3 Study III – Validity

The results of this population-based, nationwide study indicate early and sustained treatment with ADHD drugs (stimulants or atomoxetine) between 9- and 12-years of age is associated with a lower risk of a decline in academic performance, particularly in mathematics. Our data indicate moreover that the beneficial effect from ADHD drug treatment is somewhat different across gender; girls show a definite benefit in mathematics only, while boys show marginal benefit in both mathematics and language arts.

To our knowledge this is the first study that assesses the association between timing of longer-term drug treatment for ADHD and academic progress.

Because randomization of ADHD drug treatment to children with long-term follow-up is impractical, this study, with complete ascertainment of drug exposure and standardized academic assessment at two points in time, may offer the strongest evidence to date on the effectiveness of early versus later drug treatment for ADHD on academic performance.

This said, the study has several important limitations which must be taken to account for the validity of its results. Despite statistically significant results, notably with regard to change in mathematic performance, we cannot exclude bias due to systematic or random error in our study. The latter source of error affects the precision of the effect estimates; the former error must be related both to the study exposure and outcome to disturb our results.

5.3.1 Confounding by Indication

Without randomized allocation of treatment start we cannot rule out bias due to different disease characteristics between children starting treatment late and early. These differences may introduce bias to the comparison called confounding by indication (Rothman, 2002; Strom, 2005). This type of bias is frequently encountered in pharmacoepidemiology. It arises when the underlying risk factors for disease influence treatment choices of physicians and patients, including the decision to start or stay on a drug. Confounding by indication may be pronounced in register-based studies, as they rely on data collected for reasons unrelated to the research hypothesis and may not include information on important confounders or effect modifiers (Brookhart et al.; Sturmer et al., 2007). Despite the advantages of the Nordic prescription registers, being an excellent source for ascertainment of drug exposure, and allowing for detailed assessment of used drugs in large, representative populations under usual care conditions, the lack of indications for drug prescribing is a major drawback for most research purposes in pharmacoepidemiology.

In light of this, we lack information of the underlying ADHD diagnosis, subtype, severity of the condition or potential co-morbid learning- or psychiatric disorders. In Iceland, however, an ADHD diagnosis must be verified by a pediatric-, psychiatric- or neurological specialist to initiate a reimbursed drug treatment. On that basis we assumed that all medicated children fulfilled the DSM-IV criteria for ADHD before treatment. We restricted the main analyses to children who started treatment between their tests in 4th and 7th grade, ensuring that sometime between ages 9 and 12 all study children had the indications for treatment of ADHD. In spite of our restriction to this three-year age span, confounding by indication may still arise from differences that relate to the age at initiating treatment. It could be expected that children with severe symptoms and

more persistent academic problems also begin medicating very soon after their 4th grade tests. But notwithstanding this expected bias, our results show that those who started drug treatment the earliest declined the least academically in mathematics.

With respect to potential confounding by co-morbidities, on which we also lack direct information, we attempted to capture co-existing psychiatric disorders by accounting for concurrent psychotropic drug treatment. We found that the negative effect of later treatment on academic progress was stronger among those not medicating concurrently with other psychotropic drugs. This indicates that children who are not medicated for psychiatric co-morbidities, such as anxiety or depression, are likelier to show academic benefit from starting early stimulant treatment. But as our measure is not a perfect proxy, further investigation is needed to conclude how potential co-morbid psychiatric or learning disorders as well as ADHD subtypes affect the reported associations.

To account better for confounding by indication, we could consider linking our study data to complete medical charts of the study children, which would include information on the diagnoses of ADHD, subtype and co-morbidities. This information is, however, not easily obtained in Iceland since children with ADHD are most often diagnosed and treated as outpatients and no centralized registry of such information existed at the time of our study. Another option could be to conduct a study based on specialized questionnaires containing information on the underlying disorder among the study children and the decisions to start, continue or quit drug treatment. This, in turn, could lead to different kinds of biases related to response rates and self-reports.

5.3.2 **Other Sources of Systematic Error**

Measurement Error of Exposure and Outcome

We used information from centralized registers in Iceland to ascertain exposure and outcome in our study. Since information in such data sources is prospectively collected in such data sources, recall bias can be excluded. Measurement of exposure and outcome variables in the Nordic social and health registers is generally accurate and highly valid.

Exposure to stimulant treatment was measured as dispensed drugs, which does not necessarily imply use of a drug. We do not know whether the children to whom the drugs were dispensed, actually took them between examinations. However, our data showed that over 80% of the medicated population filled more than three prescriptions for stimulants, similar to the proportion filling over 90 DDDs. We furthermore, tested our hypothesis using alternative measures to

define drug exposure, such as a minimum amount of DDDs (equivalent to approximately 12 month, 13-24 month and 36 months drug supply) between test dates in 4th and 7th grade, a minimum amount of dispensed drug prescriptions between test dates and a combination of timing of treatment start and minimum amount of DDDs (data not shown). These different measures of the exposure lead to very similar results as shown in Study III. Despite the advantages of the standardized DDD unit as a measurement in drug utilization studies, we acknowledge its lack of clinical relevance and thus refrained from displaying it overly the main analyses of Study III. The DDD a predefined technical unit (30 mg for methylphenidate, 80 mg for atomoxetine) (WHO, 2008), which does not necessarily reflect the prescribed daily doses in Iceland.

Our main comparison of exposure level pertains to timing of treatment start (late vs. early start), which should be quite accurate as the dates of drug dispensing are automatically registered to the Medicines Registry. Any misclassification of exposure would furthermore most likely be non-differential according to outcome status and should thereby not affect our effect estimates.

For the outcome we used children's results on two national standardized tests to measure change (decline) in academic performance. The standardized test in mathematics and language arts have been given to Icelandic children aged 9- and 12-years since the early 1990's and are quite well validated and calibrated for their intended purposes within the school system, i.e. to assess academic standing of students and schools (Icelandic Educational Testing Institute). For the purposes of this study, however, a concern may arise that a measure of this sort may not be sensitive enough to grasp meaningful variation in cognitive function amongst our study group of medicated children.

We set out to find differences in academic decline amongst children able to take part in the standardized tests and starting drug treatment for ADHD at different times between the tests. We tested our hypothesis that later treatment would lead to academic decline, with various methodological approaches and models regarding the outcome measure (not shown in the final paper), such as keeping it on a continuous scale, rather than dichotomizing it, converting the original test results to a normalized scale, rather than a percentile rank, and using a ten percentile point drop in performance as the cut-off for academic decline instead of a five percentile drop. These efforts all led to very similar results, supporting our study hypothesis. Irrespective of methodological approach, we found consistent differences in academic decline amongst the comparison groups, indicating that the standardized tests were not a too crude or general measurement for the purpose of our study. Furthermore, a systematic error in the outcome measure is unlikely be related to the time at which children

start stimulant treatment, thus a not a threat to the study validity. Differential test-participation between exposure groups is, on the other hand, as we discuss below, a potential threat to the study validity.

Selection Bias

Bias due to the selection of study participants and attrition is another source of systematic bias we must consider. Selection bias is a systematic error that stems from the procedures used to select subjects and from factors that influence study participation (Rothman, 2002). Our study population is limited to exam takers in both 4th and 7th grades and test-participation was, as we expected, lower among the total medicated population (72.5%) than in the general population (88.4%). Moreover, test-participation varied somewhat across early and late initiators between 4th and 7th grade tests (65.4% vs. 75.3%).

We attempted to account for this potential source of bias with a sensitivity analysis Test-participation also varied between early and late treatment initiators between the 4th and 7th grade tests. We attempted to account for this potential source of bias with a sensitivity analysis. Assuming a null-association among the non test-participants, we found that the adjusted main effect estimates did not vary greatly from those reported among test-participants. Importantly though, our main findings are unlikely to be generalizable to children too impaired by ADHD or its co-morbidities to participate in regular school activities.

Ideally we would have followed-up on all children who took 4th grade tests, irrespective of whether or not they took tests in 7th grade or not. But in our study one of the cohort entry criteria (completing a test in 7th grade) could be related to the outcome (performance on the 7th grade test). Children who did not complete the 7th grade test did not enter our cohort and not completing the test could be related to the study exposure (delayed stimulant treatment). We do, however, suspect that the lower test-participation among medicated children is due to them not taking any tests at all, rather than dropping out between 4th and 7th grade. Therefore, this could be viewed as an issue of the generalizability of our results, rather than selection or attrition bias.

In a future study design, however, it would be more appropriate to consider the cohort entry criteria as having no history of ADHD medication and having completed 4th grade test, rather than also completion of 7th grade test. In such a study exposure would then be defined as drug treatment start after 4th grade test (no medication, within 12, 13-24, 25-36 months) and one of the outcomes of

interest would be participation in 7th grade tests, along with performance on those tests and change thereof since 4th grade.

Healthy User Bias

Healthy user bias may be defined as a type of selection bias. When studying the effect of drug treatment in pharmacoepidemiology, prevalent users of a drug have by definition persisted in their drug use, similar to the concept of survivor cohorts in chronic disease epidemiology (Rothman, 2002; Schneeweiss et al., 2007). Being persistent or adherent is a characteristic more likely found in individuals with health-seeking behavior, those who tolerate the drug well or perceive some therapeutic benefit (Osterberg & Blaschke, 2005). These factors are difficult to assess with prescription data and can therefore lead to a so-called healthy user bias.

We excluded all prevalent stimulant users at baseline by limiting the main analysis to children without any drug dispensing for at least 11 months prior to tests in 4th grade, thereby accounting in part for the potential healthy user bias. An estimated of 20-30% of children do not respond well to or tolerate methylphenidate treatment (Barkley, 1990; Greenhill et al., 1999; Santosh & Taylor, 2000). In our study the proportion of children filling less than 90 DDDs of stimulants was higher among those who started treatment early after 4th grade tests (21.2%), compared with those with later treatment start after tests in 4th grade (14.4%).

We accounted for early discontinuation (i.e. persistence) of treatment by stratifying the data by those filling less or more than 90 DDDs of stimulants, as well as by treatment on whether or not treatment continued until the day of 7th grade tests. When doing so, as expected, we did indeed observe higher effect estimates for the persistent users. Indicating that, the benefit of treatment is more pronounced among persistent or adherent users.

Additional to stimulant tolerance, we expect parental involvement and family factors to play a role in treatment adherence among children in the study population. With regard to this potential bias, it is possible that children initiating treatment early also have family- or social support benefiting their academic performance and progress. This may cause the reported results to be overstated in our study. However, the within-subject comparisons, i.e. assessment of children's academic performance at two points in time, would not be affected by any time-invariant confounding factor. Therefore, family background, health conscious behavior or social support would only be confounding if these influences changed between the two examinations.

Time-Variant Confounding Factors

On the other hand, concurrent psychological therapy or educational school services received by children in the study population are obvious time-dependent influences that we must consider with regard to the internal validity of our study. Our study lacks information of these events, which may have been introduced between the two examinations, along with the stimulant drugs, and had a positive effect on academic performance. Availability of psychological services for children in Iceland is low, however, and in light of evidence indicating that combined therapy provides only modest advantages over drug treatment alone, (Abikoff et al., 2004; Hechtman et al., 2004; MTA Cooperative Group, 1999a) this limitation may not be of major concern. Bias due to other time-dependent events occurring systematically in the study population between tests is less obvious. In the following chapter we discuss further, a few mechanisms through which this type of confounding could have affected our study results.

Potential Mechanisms of Confounding

We found a positive association between delayed treatment for ADHD and academic decline in our study, which can also be interpreted as children who start treatment earlier (i.e. soon after 4th grade tests) are less likely to decline in academic performance, compared with those who start treatment later. This dynamic resembles somewhat previous research findings that suggest stimulant treatment of ADHD might reduce the risk of later alcohol or substance abuse (Conner, 2005; Wilens et al., 2003). As appropriate treatment of ADHD, including use of stimulants, may decrease the risk of substance abuse, our data indicate that it may also decrease the risk of academic decline.

This association we observed in our study is, however, not necessarily causal. As previously mentioned, a variety of factors could be related both to children starting ADHD drug treatment early and how they progress academically. Because our study design controls for all time-invariant confounding, the potential confounding need to have occurred between the standardized tests in 4th and 7th grade to affect the association. Following are a few potential alternative explanations for the observed associations, i.e. mechanisms through which time-variant confounding could have occurred in our study:

- Children who start treatment soon after the 4th grade test might have parents who follow their performance more closely and are willing to immediately take additional measures to try and improve academic

performance, such as provide more support at home, arrange for additional tutoring etc. If these parents become aware of their child's problem based on the 4th grade standardized test results and modify their behavior/support accordingly before 7th grade tests, then academic progress might be affected irrespective of ADHD stimulant drug treatment. This potential confounding mechanism needs close consideration when interpreting the results of Study III.

- ADHD frequently occurs in children with co-existing learning disabilities, such as reading disorders and language impairment (Barkley, 2005a). The presence of such learning difficulties could affect the time at which children start ADHD treatment. They could have started earlier or later depending on when the problems are noticed and how long it takes to complete the full academic/cognitive/neuropsychological testing to reach a diagnosis of learning disability. Such a co-morbid diagnosis could, in turn, affect the level of other educational support the children receive in or outside of school, which might affect children's academic progress, irrespective of the ADHD stimulant treatment.

- With regard to the subtypes of ADHD, children with hyperactive/impulsive symptoms (ADHD-PHI) might be treated earlier than those predominately with inattentive symptoms (ADHD-PI), because the hyperactive/impulsive behavior is more disruptive in the classroom. If children with the hyperactive/impulsive subtype are less impaired academically than those with inattention deficits, we might be dealing with a type of confounding by indication. Some previous studies indicate that inattention is more strongly associated with cognitive inabilities than hyperactivity is (Abikoff et al., 2002; Chhabildas et al., 2001). However, our results showing a stronger academic benefit for girls in mathematics than boys are counterintuitive to this argument. Our data indicate that the effect of treatment might be stronger for girls than boys in mathematics, even though girls predominately present with inattentiveness, while boys also frequently show symptoms of hyperactivity/impulsivity and aggressiveness (Gaub & Carlson, 1997).

- Finally, in most cases some trial and error involved in finding the optimal dose regimen with stimulants that balances efficacy and tolerability. Children starting stimulant treatment soon after 4th grade tests would have had more opportunity, in terms of time, to have found and be treated with the optimal regimen, compared with children starting later, and therefore show better academic progress. This argument does in fact, lend support to the importance of not delaying appropriate treatment for ADHD to avert academic decline.

5.3.3 Random Error

Even though our study is population-based on nationwide data, the comparison groups on which we performed the main analysis ended up being relatively small. Due to their small size and in some cases wide confidence intervals, the risk of bias due to random error is increased. To achieve more precise effect estimates we would have needed larger comparison groups. In the current study the population is limited to children born in 1994, 1995 and 1996. This is due to constraints, firstly, set by the short time since the establishment of the Icelandic Medicines Registry, which contains data from January[1st], 2003. Secondly, all study children needed to have taken the latter standardized test at age 12 before the end of 2008, when we performed data linkages. However, now that more data have accumulated in the Medicines Registry, we could consider conducting a study less prone to random error, hence more with reliable results, by increasing the size of the study population examining the association between timing of treatment start and academic progress in at least five birth cohorts (1994-1998).

5.4 General Discussion

5.4.1 Use of Psychotropic Drugs among Children in Iceland

In this nationwide population-based study we found a markedly high prevalence of psychotropic drug use in children (48.7 per 1000 in 2007) and a generally increasing prevalence of stimulants and antipsychotic drug use between 2003 and 2007. The use of antidepressants was decreased in the Icelandic pediatric population during the study period, but remains still markedly higher than reported use in other European countries.

Prevalence

Pediatric psychotropic use in Iceland, both overall and for specific subgroups, is considerably higher than what has been reported from other European countries, and thus closer to previously published use rates for children in the United States (Clavenna et al., 2007; Danish Medicines Registry; Martin & Leslie, 2003; Norwegian Prescription Database; Olfson et al., 2002; Schirm et al., 2001; Sevilla-Dedieu & Kovess-Masfety, 2008; Zito et al., 2003).

The extensive use (28.4 per 1000 children in 2007) of stimulants and atomoxetine, mainly used to treat ADHD, is in accordance with use patterns we had previously described (Zoega et al., 2007). In 2003 to 2004, stimulant use in Iceland was at least two-fold that found for French, Dutch, and Norwegian

children but slightly below the U.S. prevalence of 29 per 1000 children in 2002 (Asheim et al., 2007; Faber et al., 2005; Sevilla-Dedieu & Kovess-Masfety, 2008; Zuvekas et al., 2006).

Even more pronounced is the difference in antidepressant use between children in Iceland and European countries. In 2003 to 2004, approximately 28 per 1000 Icelandic children received antidepressant treatment, as opposed to 2.3 per 1000 children reported in Italy, 3.7 per 1000 in Germany, 4.0 per 1000 in France, and the U.S prevalence of 18 per 1000 children in 2002 (Clavenna et al., 2007; Fegert et al., 2006; Sevilla-Dedieu & Kovess-Masfety, 2008; Vitiello et al., 2006). Despite the steady decline in use among Icelandic children since 2004 - a trend also apparent in other countries - the differences between Iceland and other European countries remain notable. Given the reported side-effect profile of tricyclic antidepressants for children (Hazell et al., 2002; Hazell et al., 1995; Whittington et al., 2004), we find it disturbing that, in 2007, amitriptyline was the second most used psychotropic drug among Icelandic children. At the same time pediatric use of this tricyclic antidepressant was barely observable in Denmark and Norway ("Danish Medicines Registry; Norwegian Prescription Database,"). Amitriptyline use in Iceland warrants careful attention and further scrutiny of the reasons for its frequent prescribing.

We found a relatively high prevalence (10.6 per 1000 children in 2007) for antipsychotic use among children in Iceland and a significant rise in antipsychotic prevalence between 2003 and 2007. European prevalence estimates are many times lower than observed in this study for Icelandic children (Clavenna et al., 2007; Danish Medicines Registry; Norwegian Prescription Database; Schirm et al., 2001; Sevilla-Dedieu & Kovess-Masfety, 2008). The increase in use we found concurs with reports of a similar trend among children in the US and the UK (Olfson et al., 2006a; Rani et al., 2008). In 2007, three antipsychotics —risperidone, aripiprazole, and quetiapine—were among the 10 most used psychotropic drugs for both boys and girls in Iceland. Potential metabolic complications, such as weight gain and insulin sensitivity, coupled with the lack of research on the long-term effects of pediatric use of antipsychotics, warrant a further justification for the extensive use of these drugs in Iceland.

Incidence

We detected a time trend toward reduced incidence of psychotropic drug use between 2004 and 2007, along with a tendency toward increasing prevalence.

This may reflect a leveling off in the rising use of these drugs among children in Iceland, longer drug treatment duration, or a combination of both.

The overall decreasing incidence was primarily driven by significantly fewer children initiating antidepressant treatment. The fall in antidepressant incidence, 11.9 per 1000 children to 8.0 between 2004 and 2007, is in accordance with recent trends reported from other countries (Bramness et al., 2007; Dean et al., 2007; Gibbons et al., 2007; Murray et al., 2005; Nemeroff et al., 2007; Olfson et al., 2008; Volkers et al., 2007). This decline is likely to be associated with the 2003 and 2004 public health warnings of antidepressant use in treatment of childhood depression (Directorate of Health Iceland, 2004; FDA, 2003; Jureidini et al., 2004; Ramchandani, 2004; Vitiello & Swedo, 2004). Furthermore, the trend we found of fewer new antidepressant users among Icelandic children is, furthermore, likely to be a function of drug substitution when treating ADHD, from tricyclic antidepressants to both long-acting methylphenidate and atomoxetine. Baldursson et al. (2000) showed that tricyclic antidepressants were the most common drug choice in 1998 to 1999 for Icelandic physicians treating children referred to the National University Hospital outpatient ADHD clinic. Since that time, however, pediatric use of long-acting stimulants and atomoxetine, marketed in Iceland in 2002 and 2006, respectively, has risen markedly (Iceland Social Insurance, 2008; Zoega et al., 2007).

Off-Label Use and Prescribing Physicians

Given the still fragmented evidence base for safety and efficacy of childhood psychotropic drug use, it is not surprising to see that in 2007, one fourth of all psychotropic drug prescriptions for children in Iceland were either off-label (age inappropriate) or unlicensed. This concurs with previous studies from other countries showing similar proportions of pediatric prescriptions to be off-label (Koelch et al., 2009; Sevilla-Dedieu & Kovess-Masfety, 2008; Ufer et al., 2003; Volkers et al., 2007). The need for clinical documentation of drug use in children is substantial in Iceland, as elsewhere (Kimland et al., 2007).To minimize clinical risk for children with mental health problems, it is essential that physicians initiating and maintaining treatment be equipped with proper education and up-to-date knowledge on pharmaceutical safety.

Our results show that between 2004 and 2007 pediatricians most often initiated psychotropic treatment for children in Iceland. This concurs with the fact that child and adolescent psychiatrists are 10 times fewer than pediatricians in Iceland. We did not attempt to determine which medical specialties were most likely to maintain psychotropic drug treatment for children in this study.

Potential Explanations for Widespread Use in Iceland

The rationale for the extensive psychotropic use among Icelandic children remains unclear. Assuming that prevalence of mental health disorders is not considerably higher in Iceland than elsewhere in Europe (Gudmundsson et al., 2007; Polanczyk et al., 2007), the first possible explanation may lie in the registration of drug dispensing data in Iceland, i.e., that it better captures actual use than elsewhere. This is, however, not a probable cause when comparing use between the Nordic countries, where registration of drug-dispensing rests on very similar nationwide prescription registers. A central and well-financed health care system, which includes unrestrained access to specialist and generous public copayment of drugs, is a possible underlying factor for the widespread use. Additionally, because drug use is a direct function of prescribing habits, part of the explanation may lie in the education of Icelandic medical specialists, as well as cultural norms in the country. Further research is needed to assess the determinants of pediatric use of psychotropic drugs in Iceland and the quality and outcomes of treatment.

5.4.2 **ADHD (Stimulant) Drug Use in the Nordic Countries**

The 2007 prevalence of use in the total Nordic population varied from a low 1.2 per 1000 inhabitants in Finland to a high 12.5 per 1000 in Iceland. Compared with Swedish children aged 7- to 15-years, Icelandic children were almost five times more likely to have been dispensed an ADHD drug in 2007. Methylphenidate was the most commonly used ADHD drug in all five Nordic countries, accounting for over 80% of ADHD drug users.

Prevalence of ADHD and Use of Drugs

We found the overall prevalence of ADHD drug use in the Nordic area (11.2 per 1000 children, 2.8 per 1000 adults) to be considerably lower than reported use between in the United States (Castle et al., 2007; Scheffler et al., 2007; Zito et al., 2008; Zuvekas et al., 2006) . Iceland is the only Nordic country where use of ADHD drugs approximates the United States rates. Generally, the prevalence of ADHD drug use in the Nordic countries seems to be more in line with, or slightly higher than, previously published rates for children in European countries (Faber et al., 2005; Jick et al., 2004; Zito et al., 2008).

In our study, compared with use in Sweden, use of ADHD drugs was nearly fivefold in Iceland and double in Norway. Prevalence of ADHD has been shown to be relatively stable across the world, estimated 4 to 8% among children and 2 to 4% among adults (Faraone et al., 2003; Fayyad et al., 2007; Polanczyk et al., 2007). Thus, the variation we found in drug treatment between the Nordic

countries is most likely a reflection of clinical trends and health care policies, rather than a reflection of epidemiologic patterns of ADHD. This significant difference in prevalence of drug utilization between neighboring countries, with relatively homogeneous populations, similar culture and national health care systems, invokes questions.

Age and Gender Distribution

Our results on age and gender distribution of ADHD drug use in the Nordic countries coincide well with the epidemiologic patterns of ADHD. The disorder has the highest prevalence among 9 to 14 year-old children, and boys are three to four times more likely than girls to be diagnosed (Costello et al., 2003; Ford et al., 2003; Jonsdottir, 2006) . We found that drug treatment was most common among 11 to15 year-old boys and among Icelandic children the gender ratio of use was 3:1 (boys vs. girls). Our data indicated, however, that the gender ratio for Nordic children varied between countries. It was lowest in Iceland but highest among children in Finland (6:1).

Recent research shows substantial diagnostic continuity into young adulthood, as well as increases in first time diagnoses of ADHD among adults (Biederman, 2005; Fayyad et al., 2007; Steinhausen, 2009). Follow-up studies indicate that 15% of diagnosed children still meet full diagnostic criteria at 25 years and a further 50% are in partial remission as young adults (Faraone et al., 2006). In the adult population, women seem to be as likely as men be diagnosed with ADHD (McCarthy et al., 2009; Nutt et al., 2007), which is in accordance with the overall diminished gender ratio we found in ADHD drug use among the adult population, or almost a 1:1 ratio for those older than 20 years.

Potential Explanations for Varying Use among the Nordic Countries

Several factors such as accessibility of drugs, available treatment alternatives, clinical practice and national guidelines, may influence the patterns of prescribing and use of ADHD drugs in the Nordic countries. In each Nordic country, drugs can be approved for use through separate national application procedures and different reimbursement regulations are applied. Although the countries all have comprehensive drug coverage, reimbursement rates vary by country, by drug and by patient characteristics. Based on the number of marketing authorizations and reimbursement rules for substances, in 2007 accessibility seems to have been the most in Iceland but the least in Finland. Methylphenidate was the only substance validly marketed and reimbursable in all five countries in 2007.

The validity of ADHD diagnosis has been a source of debate in many countries, giving rise to worries of possible over-diagnoses and treatment. Like for many other psychiatric illnesses, the diagnosis is based on non-biological measures. At the time of our study physicians in the Nordic countries are likely to have relied on either or both the DSM-IV and ICD-10 criteria when diagnosing ADHD (or hyperkinetic disorders). Since we do not know to which extent the prescribing physicians relied upon either classification system, we cannot conclude whether these criteria are a contributing factor to the differences we found in drug use among the countries. But in addition to diagnostic criteria, drug prescribing habits are a likely function of professional training and traditions of physicians and other mental health care providers.

At the time of our study all five Nordic countries had clinical guidelines and reimbursement regulations that to some extent restricted initiation of ADHD drug treatment to specialists in psychiatry, neurology, or to physicians with special knowledge in mental and physical development of children and adolescents (Baldursson et al., 2007; Danish National Board of Health, 2000; Finnish Medical Society Duodecim/Current Care, 2008; Norwegian Directorate of Health and Social Services, 2007; Sweden Medicinal Products Agency, 2009). Access to such medical specialists may have varied by country and thereby influenced prescription rates. In contrast to customary practice in the other Nordic countries, patients in Iceland generally do not need to be referred to a specialist of this type by primary care practitioners.

Finally, it is worth mentioning that the availability of non-pharmacological interventions for ADHD, such as behavioral treatment and specialized learning support within schools, may have influenced variation in prescription of ADHD drugs. Our study did not include data on such services in each country but the access to such services may vary by country and also within each Nordic country. In Iceland, outpatient psychological services were not reimbursed during the study period and other psychosocial services were not in large supply for children.

5.4.3 Effect of Delayed Stimulant Drug Treatment for ADHD on Academic Progress

The results of this population-based, nationwide study indicate that, earlier, sustained treatment with ADHD drugs (stimulants or atomoxetine) is associated with a lower risk of a decline between ages 9 and 12 in academic performance, particularly in mathematics. Our data indicate that the apparent advantage of

earlier treatment differs for boys and girls. Girls show a definite benefit only in mathematics, whereas boys show marginal benefits in both mathematics and language arts.

In line with the previously established association between ADHD and poor academic outcomes (Barbaresi et al., 2007a; Faraone et al., 1993; Loe & Feldman, 2007; Molina et al., 2009; Polderman et al., 2010), we found that children medicated for ADHD fare worse academically, compared with their peers without ADHD, and that their performance generally declines with time, particularly in mathematics when initiation of drug treatment is delayed. Our data suggest that children in the lower two-third percentiles prior to treatment benefit from starting earlier to avoid further declines in mathematics; only few children in the top third percentile initiated stimulant treatment between exams and their decline seems independent of when treatment started. Previous studies lend support to some of our findings.

Interestingly, Molina et al. (2009) found that mathematics scores were the only functional outcome positively associated with past-year parent-reported medication use during follow-up of participants of the Multimodal Treatment Study of Children with ADHD (MTA), at years 3, 6 and 8 after enrollment, suggesting a beneficial effect of continued medication treatment that may be unique to mathematic achievement. Similarly, Scheffler et al. (2009) recently found that parent-reported drug treatment was associated with higher mathematic achievement test scores within a US sample of 594 elementary school children with ADHD, but higher reading scores were dependent upon longer treatment durations. Barbaresi et al. (2007b) demonstrated that stimulant treatment of children with ADHD was associated with improved reading achievement, decreased school absenteeism and decreased grade retention within a population-based sample of 349 ADHD diagnosed children. Finally, Marcus & Durkin (2011) just recently showed, by merging insurance claims with academic records for insured children living in urban Philadelphia, that stimulant adherence was associated with slight improvements in grade point averages among for elementary and middle school children diagnosed with ADHD.

In our data children with lower scores prior to treatment seem to benefit from starting earlier to avoid further declines in mathematics, while those in the upper scores tend to decline independently on when treatment starts. The stronger effect estimates we found for mathematics than language arts could point to underlying differences in the cognitive process and knowledge acquisition for the two areas, potentially also to selective effects of drug treatment (Bedard et al., 2007; Bedard & Tannock, 2008). Studies have indicated that language disorders (dyslexia) and mathematical disability (dyscalculia) have separate cognitive

profiles (Landerl et al., 2009). It is possible that stimulant drug treatment has more positive effects on the cognitive function underlying mathematical ability than on that underlying language ability. In a very recent study Polderman et al. (2011) concluded that more complex academic skills, requiring higher cognitive processes, such as mathematics and comprehension, were especially negatively associated with attention problems. They found a stronger negative correlation of attention problems with mathematics than with comprehension and no significant correlations with reading.

The gender differences in our data could be a result of the smaller numbers within subgroups, but they might reflect real differences in the academic benefit of stimulant treatment. Girls diagnosed with ADHD present predominantly symptoms of inattention and lower levels of hyperactivity than boys with ADHD (Gaub & Carlson, 1997; Gershon, 2002), which may play a role in how early the disorder is detected and when treatment starts. Previous studies, however, have not identified sex or ADHD subtype as modifiers of stimulant treatment outcomes (Gorman et al., 2006; Gunther et al.; MTA Cooperative Group, 1999b).

5.5 Implications and Future Studies

The Nordic Prescription Registers and their linkage possibilities to other nationwide data provide a great opportunity for further advancements in the field of pharmacoepidemiology. The Nordic registers are a unique resource in assessing the beneficial and adverse effects of drug use in large populations, under regular care-conditions and for long periods of time. It is especially important to seize this opportunity to study effects of drug treatment in the pediatric population. Not the least since randomized clinical trials are seldom conducted on children and, in the long-run, such studies lack many of the advantages of observational studies. The need for increased research concerning pediatric drug treatment is obvious. To date, a large proportion of psychotropic drugs are used off-label for children and adolescents. Since 2007, The European Medicines Agency (EMA) has put special effort, via its Pediatric Committee (PDCO), to stimulate pediatric studies and accumulation of data to support drug authorizations for use of drugs in children (European Medicines Agency). Their aim is to improve the health of children in Europe, without subjecting children to unnecessary trials, or delaying the authorization of medicinal products for use in adults.

We found that in 2007, 42% of antidepressants and 52% of antipsychotics were prescribed off-label or unlicensed to children in Iceland. This proportion was only 1.2% for stimulant drugs and atomoxetine – not surprisingly since

stimulants are among the most widely researched drugs, especially in regard to their short-term effects.

To minimize clinical risk for children with mental health problems, it is imperative that physicians who initiate and maintain psychotropic drug treatment for children are equipped with proper education and up-to-date knowledge of pharmaceutical safety. Our results show that pediatricians most often initiated psychotropic treatment for children in Iceland between the years 2004 and 2007. Scrutiny is needed to assess the rationale behind the overall widespread use of psychotropic drugs in Iceland, especially of tricyclic antidepressants and antipsychotics with known adverse side effects. Further research is needed to assess the determinants of pediatric use of psychotropic drugs, the quality and outcomes of such treatment in Iceland. This should involve examinations of the procedures applied when diagnosing mental disorders in children. More challenging, but just as important, are future studies of extraneous influences, such as cultural attitudes, education of health care workers, teacher and school motivation, parental attitudes, reimbursement schemes and further economic incentives for treating children. This not only requires application of a diverse set of quantitative methods on already available data, but also a generation of new data and the use of qualitative study approaches.

The significant difference we found in stimulant drug utilization between the neighboring Nordic countries, where people, culture and health care are rather similar, also invokes questions. Although relatively very high, the prevalence of ADHD drug use in Iceland does not exceed the estimated prevalence of the underlying disorder. Without further information of the ADHD diagnoses and individual treatment outcomes, we are precluded from concluding on the quality of ADHD treatment in Iceland and the Nordic countries. It is crucial to emphasize that stimulants are potential drugs of abuse, capable of inducing tolerance and producing problems with withdrawal when used non-medically. In the past few years, the topic of misuse has been widely discussed in Iceland, without much systematic research being conducted. The extent of misuse and diversion of stimulants prescribed for ADHD needs to be examined in all five Nordic countries. Furthermore, future longitudinal studies are crucial to elucidate how individuals with ADHD might be affected by the profound differences we found in use of ADHD stimulant drugs. We recommend that the Nordic countries put joint effort into assessing the quality of treatment and support mechanisms to enhance rational drug use and overall treatment success for ADHD.

Our third study was aimed at elucidating important questions about the effectiveness of stimulant drug treatment of children with ADHD. We asked whether starting stimulant treatment affects academic progress among children

with ADHD. Our findings suggest that, sustained treatment with ADHD drugs between ages 9 and 12 is associated with a lower risk of a decline in academic performance, particularly in mathematics. Furthermore, that the apparent advantage of earlier treatment differs for boys and girls. Girls show a definite benefit only in mathematics, whereas boys show marginal benefits in both mathematics and language arts. These findings warrant further investigation.

We suggest that the unique data sources in Iceland be further used to study the associations between stimulant drug treatment for ADHD and academic progress. The precision of our results could be increased by adding to the number of birth cohorts. It would also be interesting to follow children up for a longer period of time to see if the observed associations hold up in the longer-run. Currently, for example, it would be possible to use up to five birth cohorts (1994 to 1999) and follow the three oldest birth cohorts through their 10^{th} grade standardized tests, taken at age 15 in Iceland.

With these already existing data in Iceland stimulant treatment and academic progress can be studied among children of a wider age span. This is important since as children grow older the academic demands in school increase and are likely to require more sustained attention and cognitive ability, than during the earlier years of school. Furthermore, it is important to look more closely into the younger age groups as well. In our study population over half of the medicated children had started treatment at the age of nine. Even though the academic demands are less rigorous at early age, foundation for later life academic achievement is laid during these years, thus important to see if our findings apply to them as well.

The gender differences we found in our study are noteworthy, especially in light of previous studies suggesting that ADHD might be under-diagnosed and under-treated in girls (Ramtekkar et al., 2010). Our findings on gender differences need further verification. It is of great importance to better understand the interplay between gender, ADHD sub-type, stimulant treatment and academic performance. We anticipate that gender differences in treatment response will become a central topic of future studies.

Adherence to treatment is an extremely important issue when studying treatment effects. We suggest that future studies of the long-term effects of stimulant drugs take adherence into close consideration, as we only partially tapped into the issue with our study.

In sum, stimulant drugs remain controversial in spite of sound evidence of their efficacy in relieving the core symptoms of ADHD. Unresolved safety issues and unintended side effects have illuminated this controversy, as have concerns

about overuse and misuse of the drugs. The widespread use of these drugs in Iceland is controversial, although it does not exceed the prevalence of ADHD. With our studies we are unable to conclude about any potential over- or under-treatment in Iceland or other Nordic countries. Recently, evidence of longer-term effects of stimulants has been accumulating. Our study adds to this evidence-body, suggesting that sustained stimulant treatment for ADHD may be somewhat beneficial for academic progress in children.

6 Conclusions

- The Nordic prescription registers are an excellent foundation to build upon in pharmacoepidemiology. The registers hold near-complete information on all prescription drugs dispensed to the entire outpatient population of almost 25 million people and may be linked to other Nordic social and health registers – yielding opportunities for timely assessments of the use and effects of drugs in representative populations.

- With reference to reports from other countries, in 2003 to 2007 use of psychotropic drugs was strikingly high among children in Iceland.

- A considerable national variation in total use of ADHD drugs existed in 2007 among the Nordic countries, but patterns with respect to age, gender and drug selection were similar in all five Nordic countries.

- In 2007, compared to the other Nordic countries, Iceland had by far the most widespread use of stimulant drugs for ADHD – approximating or surpassing documented utilization rates in the United States.

- Our nationwide follow-up study suggests that early initiation of sustained drug treatment is associated with a reduced risk of declining academic performance among boys and girls with ADHD, especially in mathematics.

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Original Publications[1]

[1] Please note an editing mistake in the published **Abstract** of Study I. The following in line 7 of abstract is incorrect and should be ignored: “antidepressants increased in prevalence from 2003 to 2007”.

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Psychotropic Drug Use among Icelandic Children: A Nationwide Population-Based Study

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Abstract

Objective: The aim of this study was to investigate psychotropic drug use among children in Iceland between 2003 and 2007.
Methods: A nationwide population-based drug use study covering the total pediatric population (ages 0–17) in Iceland. Information was obtained from the National Medicines Registry to calculate prevalence of use by year and psychotropic drug group; incidence by year, psychotropic drug group, child's age and sex, and medical specialty of prescriber; the most commonly used psychotropic chemical substances, off-label and unlicensed use and concomitant psychotropic drug use.
Results: The overall prevalence of psychotropic drug use was 48.7 per 1000 Icelandic children in 2007. Stimulants and antidepressants increased in prevalence from 2003 to 2007 and were the two most prevalent psychotropic drug groups, respectively, 28.4 and 23.4 per 1000 children in 2007. A statistically significant trend of declining prevalence ($p = 0.00013$) and incidence ($p = 0.0018$) of antidepressant use occurred during the study period. Out of 21,986 psychotropic drugs dispensed in 2007, 25.4% were used off-label.
Conclusions: With reference to reports from other European countries, the results indicate extensive psychotropic drug use among children in Iceland between 2003 and 2007. Further scrutiny is needed to assess the rationale behind this widespread use.

Introduction

PSYCHOTROPIC DRUG USE OF CHILDREN in Westernized countries is a subject of continuous debate. Although research in pediatric psychopharmacology has expanded during the past decade, utilization studies have typically rested on limited data sources (Vitiello 2007). Thus, the evidence base for prevalence of use and treatment safety, as well as long-term risks and effectiveness of many psychotropic agents (on and off-label use), for children remains fragmented.

Recent drug use studies have revealed pronounced variability in the use of psychotropics between pediatric populations, both across and within countries (Vitiello 2007). Use rates within the United States have been reported to be the highest, whereas figures from Europe are generally lower but rising. Many of these findings rest on information from self-reported surveys, insurance or reimbursement data, or community and localized pharmacy-dispensing data. These data sources are often restricted to specific social or regional groups or, in the case of self-reports, the memory retrieval of individuals, which may hamper solid conclusions (Zito et al. 1997; Olfson et al. 2002; Zito et al. 2003; Faber et al. 2005; Fegert et al. 2006; Zuvekas et al. 2006; Asheim et al. 2007; Castle et al. 2007; Clavenna et al. 2007; Zito et al. 2007).

With the establishment of the nationwide Medicines Registry in 2003, Iceland has a good opportunity to conduct population-based drug use research. The database contains individual-level information on all dispensed prescription drugs. The Registry enables us to follow an entire nation over an extended period of time for the use of various psychotropic drug groups. A recent study from this data source reported a substantial rise in pediatric use of methylphenidate (MPH), i.e., from 0.2 to 25.1 per 1000 children between 1989 and 2006, indicating a use rate equal to accounts from the United States (Olfson et al. 2002; Zuvekas et al. 2006; Castle et al. 2007; Scheffler et al. 2007; Zoega et al. 2007).

In the present study, we seek to answer whether use of other psychotropic drugs is also widespread among Icelandic children. More specifically we wanted to determine annual prevalence and incidence of psychotropic drug use in Icelandic children between

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2003 and 2007 with regard to sex and age of the child, medical specialty of the prescriber, as well as unlicensed and off-label use of these drugs.

Methods

This is a population-based drug use study on pediatric psychotropic drug use in Iceland from January 1, 2003, to December 31, 2007.

Data

Data were retrieved from the nationwide Medicines Registry on prescribed drugs in Iceland. Using personal identification numbers unique for every citizen, the Medicines Registry contains individual information on dispensed prescriptions to the total outpatient population in Iceland from January 1, 2003. Completeness of the Registry is high, ranging from 99.9% of all dispensed outpatient prescriptions in 2007, 98.6% in 2006, 94.9% in 2005, and 93.7% in 2004 to 94.7% in 2003. The percentage of outpatient prescriptions not included in the Register prior to the year 2006 is mainly due to lack of information on prescriptions handled by mechanical dosage dispensing, i.e., when the pharmacy distributes each daily drug dosage to the patient in unit dose packages.

Study population and measures

The study population consisted of all children living in Iceland aged 0–17 during the study period 2003–2007. General population statistics were based on the number of inhabitants in Iceland on January 1 each year as specified by Statistics Iceland (Statistics Iceland 2008).

Psychotropic drugs were defined according to World Health Organization (WHO) categories and comprised the following subgroups of the Anatomic Therapeutic Chemical (ATC) classification system (World Health Organization 2008): Stimulants and atomoxetine (ATC group N06BA), antidepressants (ATC group N06A), antipsychotics (ATC group N05A), anxiolytics (ATC group N05B, excluding N05BB01 hydroxyzine, which is primarily used as an antihistamine for allergic reactions in children), and hypnotics and sedatives (ATC group N05C).

The prescriber's medical specialty is identifiable in the national Medicines Registry. We assigned the attained specialty of each prescriber into one of the following five categories: Child and adolescent psychiatry (1), psychiatry (2), pediatrics (3), family practice (4), and other (or no) specialty (5). Those prescribers with more than one attained specialty were ranked hierarchically according to the above order (1–5) of specialty. Hence, a prescriber with a specialty both in child and adolescent psychiatry and pediatrics was categorized as a child and adolescent psychiatrist, etc. In this study, the medical specialty of prescribers was examined in association with initiation of pediatric drug treatment (incidence proportions), not with respect to its maintenance.

We determined the extensiveness of off-label (age inappropriate) and unlicensed drug use among children in Iceland by analyzing all psychotropic drug prescriptions dispensed in the year 2007 to the study population and dividing the prescribed drugs into the following categories suggested by Schirm et al. (2003): Unlicensed (no product license in Iceland), off-label (licensed drugs used outside the age terms of the product license), and on-label (licensed drugs used according to the product license's age terms). Off-label drugs were those used by children outside the age range specified in official license information (Iceland Medicines Control Agency 2008). As indications of prescribed drugs are not available in the national Medicines Registry, we were not able to distinguish between different indications in the license information.

Concomitant drug use was defined as the dispensing of two or more different psychotropic chemical substances to a child on the same day at least once within the calendar year.

Statistical analyses

The annual prevalence and incidence proportions during the study period for each drug group and specific chemical substances were computed. Incidence proportions were stratified by children's sex and age and prescribers' medical specialty. Prevalence and incidence proportions were calculated as the number of children who had been dispensed at least one prescription per 1000 children in the population (prevalence proportion), or were dispensed their *first* prescription (incidence proportion), for a psychotropic drug during the relevant calendar year. To determine the incidence proportion in 2004, we used the year 2003 as a run-in period; hence incident users in 2004 had not had any precedent prescriptions for the particular psychotropic agent, or substance, for at least 12 consecutive months.

To test for linear time trends in prevalence and incidence proportions, we performed log-likelihood ratio tests, assuming a beta-binomial distribution for the counts, and modeled the proportion parameters with and without linear time trends. This results in a one-tailed test with a chi-squared test statistics with one degree of freedom (Lehmann and Romano 2005). We reported p values based on this test that were smaller than the significance level of $\alpha = 0.05$. Prevalence proportions of off-label and unlicensed drug use among children in Iceland were calculated for the year 2007 only. The proportion of psychotropic users in 2007 who had two or more psychotropic substances dispensed concomitantly during that year was calculated.

Extraction of data and summarizations from the national Medicines Registry, which is kept as an Oracle database, was done with SQL scripts. We used Excel (Microsoft Excel 2003) to calculate incidence and prevalence proportions and MATLAB 7.6 to perform time trend analyses.

Ethical approval for the study was obtained in 2007 from the National Bioethical Committee (license number: VSNb-2007120009/03-7) and the Data Protection Authority in Iceland (license number: S3681).

Results

Prevalence of psychotropic drug use

During the 5-year period, an increased prevalence was observed for stimulant ($p = 0.0011$) and antipsychotic ($p = 0.0052$) drug use while the prevalence of antidepressant use decreased ($p = 0.00013$) (Table 1). The decrease in prevalence of antidepressant use was mainly driven by diminished tricyclic antidepressant use, which decreased from 12.9 per 1000 children in 2003 to 10.4 per 1000 in 2007; the corresponding decrease for selective serotonin reuptake inhibitors (SSRIs) was from 14.3 to 13.4 per 1000 children. Table 2 illustrates the 10 most used psychotropics among boys and girls in Iceland in 2007. The most commonly used psychotropic drug was MPH, which in 2007 had a prevalence proportion of 38.3 per 1000 for boys and 12.9 per 1000 for girls. The tricyclic antidepressant amitriptyline had the second highest use prevalence.

Table 1. Prevalence of Psychotropic Drug Use among Children 0–17 Years Old in Iceland 2003–2007

Psychotropic drug group	*Prev.*[a] (n) *2003*	*Prev.*[a] (n) *2004*	*Prev.*[a] (n) *2005*	*Prev.*[a] (n) *2006*	*Prev.*[a] (n) *2007*
Any psychotropic drug group	46.0 (3595)	48.5 (381)	47.3 (3732)	47.6 (3781)	48.7 (3872)[b]
Antidepressants	28.3 (2210)	28.0 (2200)	25.6 (2024)	24.6 (1955)	23.4 (1860)[b]
Stimulants and atomoxetine	21.7 (1695)	25.4 (1994)	25.1 (1980)	26.7 (2121)	28.4 (2256)[b]
Antipsychotics	8.7 (678)	8.8 (694)	8.9 (702)	9.4 (745)	10.6 (839)[b]
Anxiolytics	1.7 (135)	1.7 (133)	1.5 (120)	2.0 (160)	1.8 (145)[b]
Hypnotics and sedatives	0.8 (65)	0.8 (62)	0.8 (63)	0.7 (56)	2.6 (206)
Total study population	78157	78542	78935	79450	79469

[a]Prevalence proportions are expressed as number of children per 1000 children in the population receiving one or more prescriptions.
[b]A significant linear time trend for prevalence proportions 2003 to 2007 ($p < 0.05$).
Abbreviations: Prev. = Prevalence.

Incidence of psychotropic drug use

Table 3 illustrates the annual incidence of psychotropic drugs use among Icelandic children from 2004 through 2007. The overall psychotropic incidence was reduced from 16.3 in 2004 to 13.1 in 2007 ($p = 0.037$). This tendency toward fewer new users was driven mainly by significantly fewer incident antidepressant users ($p = 0.0018$), which were 11.9 per 1000 in 2004 but 8.0 per 1000 in 2007.

Stratified incidence

A stratified analysis of incidence by drug group, sex, and age revealed that a higher proportion of boys compared to girls initiated psychotropic drug treatment, and that the number of new users increased with age (Table 3). Among the psychotropic subgroups, antidepressants had the highest incidence proportion among children aged 0–5 (1.6 per 1000 in 2007). For children aged 6–11 years, stimulants and atomoxetine had the highest incidence proportion (10.9 per 1000 in 2007), but antidepressants for children aged 12–17 (13.4 per 1000 in 2007). Stratification of incidence by medical specialty of prescriber (Table 3) demonstrated that overall psychotropic drug treatment for children was most frequently initiated by pediatricians from 2004 to 2007. This was true for all drug groups except antipsychotics, where child and adolescent psychiatrists initiated treatment slightly more frequently than pediatricians.

Off-label and concomitant psychotropic drug use

Out of 21,986 psychotropic drugs prescribed in 2007, 25.4% and 0.06% were, respectively, off-label or unlicensed (Table 4). The proportion of off-label use was 41.8% for antidepressants and 52.0% for antipsychotics. Nearly all use, 98.8%, of the most prevalent drug group, stimulants, and atomoxetine was on-label. Among psychotropic users in 2007, 17.5% ($n = 677$) used two or more drugs concomitantly, i.e., had two or more different drugs dispensed on the same day at least once within the calendar year.

Discussion

In this nationwide population-based study, with complete registration of drug dispensing, we found a markedly high prevalence of psychotropic drug use in children (48.7 per 1000 in 2007) and a generally increasing prevalence of stimulants and antipsychotic drug use between 2003 and 2007. The use of antidepressants was decreased in the Icelandic pediatric population during the study period, but remains still markedly higher than reported use in other European countries.

Pediatric psychotropic use in Iceland, both overall and for specific subgroups, is considerably higher than what has been reported from other European countries, and thus closer to previously published use rates for children in the United States (Schirm et al. 2001; Olfson et al. 2002; Martin and Leslie 2003; Zito et al. 2003; Clavenna et al. 2007; Danish Medicines Agency 2008; Norwegian

Table 2. The 10 Most Used Psychotropic Chemical Substances in 2007 among Boys and Girls in Iceland

	Boys (0–17)			*Girls (0–17)*	
Substance	*Prevalence* (n)[a]	*Number of prescribed drugs*	*Substance*	*Prevalence* (n)[a]	*Number of prescribed drugs*
Methylphenidate	38.3 (1554)	7033	Methylphenidate	12.9 (501)	2211
Amitriptyline	12.1 (490)	1290	Amitriptyline	7.2 (282)	669
Risperidone	7.3 (297)	1178	Sertraline	6.2 (243)	1108
Sertraline	5.7 (232)	1032	Fluoxetine	4.2 (163)	694
Atomoxetine	5.6 (226)	779	Escitalopram	2.6 (101)	489
Aripiprazole	4.8 (196)	667	Risperidone	2.3 (90)	311
Fluoxetine	4.5 (184)	963	Aripiprazole	2.1 (83)	261
Escitalopram	2.2 (90)	357	Atomoxetine	1.8 (72)	235
Melatonin	2.0 (82)	242	Quetiapine	1.7 (65)	185
Quetiapine	1.6 (66)	229	Melatonin	1.2 (45)	117

[a]Prevalence proportions are expressed as number of children per 1000 children in the population receiving one or more prescriptions.

TABLE 3. NEW USERS OF PSYCHOTROPIC DRUGS AMONG CHILDREN IN ICELAND 2004–2007

		Incidence[a] *2004*	*Incidence*[a] *2005*	*Incidence*[a] *2006*	*Incidence*[a] *2007*
Any psychotropic drug					
Overall		16.3 (1284)	13.8 (1088)	12.1 (958)	13.1 (1038)[b]
Sex	Boys	18.5 (744)	15.2 (612)	13.4 (545)	15.1 (612)
	Girls	14.1 (540)	12.4 (476)	10.6 (413)	10.9 (426)
Age group	0 to 5	6.6 (166)	4.1 (104)	4.0 (102)	3.7 (95)
	6 to 11	18.5 (495)	15.4 (406)	14.7 (383)	16.6 (432)
	12 to 17	23.4 (623)	21.1 (578)	16.9 (473)	18.3 (511)
Medical specialty of prescriber initiating treatment	Child & adoles. psychiatry	3.0 (233)	2.5 (196)	2.3 (184)	3.0 (240)
	Psychiatry	0.7 (53)	0.7 (59)	0.7 (55)	0.7 (53)
	Pediatrics	7.6 (599)	6.2 (490)	5.7 (456)	5.9 (472)
	Family practice	3.0 (238)	2.7 (211)	1.7 (139)	2.3 (181)
	Other/no specialty	2.0 (161)	1.7 (132)	1.6 (124)	1.1 (92)
Antidepressants					
Overall		11.9 (932)	9.8 (770)	8.4 (666)	8.0 (639)[b]
Sex	Boys	12.6 (506)	9.9 (399)	8.5 (346)	8.3 (333)
	Girls	11.1 (426)	9.6 (371)	8.2 (320)	7.8 (303)
Age group	0 to 5	3.7 (94)	2.4 (61)	2.1 (53)	1.6 (41)
	6 to 11	12.5 (334)	9.1 (240)	8.8 (230)	8.7 (225)
	12 to 17	18.9 (504)	17.2 (469)	13.7 (383)	13.4 (373)
Medical specialty of prescriber initiating treatment	Child & adoles. psychiatry	2.4 (189)	1.5 (120)	1.2 (99)	1.5 (118)
	Psychiatry	0.6 (50)	0.6 (50)	0.6 (48)	0.5 (48)
	Pediatrics	4.9 (387)	4.4 (344)	4.0 (319)	3.3 (267)
	Family practice	2.4 (185)	2.2 (172)	1.5 (119)	1.9 (153)
	Other/no specialty	1.5 (121)	1.1 (84)	1.0 (81)	0.8 (60)
Stimulants and atomoxetine					
Overall		7.1 (557)	5.6 (439)	5.4 (431)	6.1 (482)
Sex	Boys	10.0 (402)	7.9 (318)	7.6 (310)	9.0 (366)
	Girls	4.0 (155)	3.1 (121)	3.1 (121)	3.0 (116)
Age group	0 to 5	1.9 (47)	1.2 (30)	1.2 (30)	0.9 (23)
	6 to 11	11.8 (315)	9.7 (257)	9.3 (243)	10.9 (283)
	12 to 17	7.3 (195)	5.6 (152)	5.6 (158)	6.3 (176)
Medical specialty of prescriber initiating treatment	Child & adoles. psychiatry	2.4 (188)	1.8 (142)	1.9 (151)	2.2 (174)
	Psychiatry	0.1 (7)	0.1 (5)	0.2 (14)	0.2 (15)
	Pediatrics	3.9 (307)	3.1 (241)	2.9 (233)	3.3 (265)
	Family practice	0.4 (28)	0.4 (30)	0.3 (20)	0.2 (16)
	Other/no specialty	0.3 (27)	0.3 (21)	0.2 (13)	0.2 (12)
Antipsychotics					
Overall		3.9 (303)	3.5 (279)	3.3 (265)	3.7 (293)
Sex	Boys	4.8 (191)	4.3 (173)	3.8 (155)	4.5 (185)
	Girls	2.9 (112)	2.8 (106)	2.8 (110)	2.7 (108)
Age group	0 to 5	2.2 (55)	1.0 (25)	1.3 (34)	1.3 (34)
	6 to 11	4.0 (107)	4.4 (115)	4.0 (105)	4.8 (124)
	12 to 17	5.3 (141)	5.1 (139)	4.5 (126)	4.8 (135)
Medical specialty of prescriber initiating treatment	Child & adoles. psychiatry	1.1 (84)	1.0 (82)	1.2 (97)	1.7 (136)
	Psychiatry	0.4 (31)	0.4 (32)	0.3 (27)	0.4 (31)
	Pediatrics	1.7 (137)	1.5 (119)	1.3 (103)	1.1 (91)
	Family practice	0.3 (24)	0.3 (26)	0.2 (16)	0.2 (19)
	Other/no specialty	0.3 (27)	0.3 (20)	0.3 (22)	0.2 (16)
Anxiolytics					
Overall		1.4 (110)	1.2 (92)	1.2 (115)	1.3 (103)
Sex	Boys	1.4 (57)	1.1 (43)	1.3 (53)	1.3 (52)
	Girls	1.4 (53)	1.3 (49)	1.6 (62)	1.3 (51)
Age group	0 to 5	0.9 (23)	0.7 (18)	1.0 (25)	0.6 (16)
	6 to 11	1.0 (26)	0.7 (18)	0.7 (19)	0.7 (17)
	12 to 17	2.3 (61)	2.0 (56)	2.5 (71)	2.5 (70)
Medical specialty of prescriber initiating treatment	Child & adoles. psychiatry	0.1 (8)	0.1 (8)	0.1 (8)	0.1 (5)
	Psychiatry	0.1 (6)	0.1 (10)	0.1 (9)	0.0 (2)
	Pediatrics	0.3 (27)	0.2 (18)	0.4 (32)	0.3 (27)
	Family practice	0.4 (35)	0.4 (30)	0.3 (27)	0.5 (42)
	Other/no specialty	0.4 (34)	0.3 (26)	0.5 (39)	0.3 (27)

(continued)

TABLE 3. (CONTINUED)

		Incidence[a] *2004*	*Incidence*[a] *2005*	*Incidence*[a] *2006*	*Incidence*[a] *2007*
Hypnotics and sedatives					
Overall		0.7 (53)	0.7 (57)	0.6 (44)	2.5 (198)
Sex	Boys	0.6 (25)	0.6 (26)	0.5 (19)	3.0 (120)
	Girls	0.7 (28)	0.8 (31)	0.6 (25)	2.0 (78)
Age group	0 to 5	0.0 (0)	0.1 (2)	0.0 (1)	0.8 (20)
	6 to 11	0.0 (1)	0.0 (1)	0.0 (0)	2.7 (71)
	12 to 17	2.0 (52)	2.0 (54)	1.5 (43)	3.8 (107)
Medical specialty of prescriber initiating treatment	Child & adoles. psychiatry	0.1 (5)	0.1 (9)	0.0 (2)	0.8 (60)
	Psychiatry	0.1 (7)	0.1 (6)	0.1 (10)	0.1 (7)
	Pediatrics	0.1 (4)	0.1 (6)	0.1 (5)	0.9 (74)
	Family practice	0.3 (25)	0.3 (22)	0.2 (15)	0.4 (34)
	Other/no specialty	0.2 (12)	0.2 (14)	0.2 (12)	0.3 (23)

Incidence by sex, age group, and medical specialty of prescriber.
[a]Incidence proportions are expressed as number of children per 1000 children in the population receiving their first prescription for a pychotropic in the relevant year.
[b]A significant linear time trend for incidence proportions 2004–2007 ($p < 0.05$).

Institute of Public Health 2008; Sevilla-Dedieu and Kovess-Masfety 2008).

The extensive use (28.4 per 1000 children in 2007) of stimulants and atomoxetine, mainly used to treat attention-deficit/hyperactivity disorder (ADHD), is in accordance with use patterns previously described by the authors (Zoega et al. 2007). In 2003–2004, stimulant use in Iceland was at least two-fold that found for French, Dutch, and Norwegian children but slightly below the U.S. prevalence of 29 per 1000 children in 2002 (Faber et al. 2005; Zuvekas et al. 2006; Asheim et al. 2007; Sevilla-Dedieu and Kovess-Masfety 2008).

Even more pronounced is the difference in antidepressant use between children in Iceland and other European countries. In 2003–2004 approximately, 28 per 1000 Icelandic children received antidepressant treatment, as opposed to 2.3 per 1000 children reported in Italy, 3.7 per 1000 in Germany, 4.0 per 1000 in France, and the U.S prevalence of 18 per 1000 children in 2002 (Fegert et al. 2006; Vitiello et al. 2006; Clavenna et al. 2007; Sevilla-Dedieu and Kovess-Masfety 2008). Despite the steady decline in use among Icelandic children since 2004—a trend also apparent in other countries—the differences between Iceland and other European countries remain notable.

Given the reported side-effect profile of tricyclic antidepressants for children (Hazell et al. 1995; Hazell et al. 2002; Whittington et al. 2004), we find it disturbing that amitriptyline was the second most used psychotropic drug among Icelandic children in 2007 (Table 2). That year, around 10 per 1000 children in Iceland received this tricyclic, whereas pediatric use in Denmark and Norway was barely observable (Danish Medicines Agency 2008; Norwegian Institute of Public Health 2008). Amitriptyline use in Iceland warrants careful attention and further scrutiny of the reasons for its frequent prescribing.

We found a relatively high prevalence (10.6 per 1000 children in 2007) for antipsychotic use among children in Iceland and a significant rise in antipsychotic prevalence between 2003 and 2007. European prevalence estimates are many times lower than observed in this study for Icelandic children. Publicly available data from Nordic prescription registers show that the 2007 prevalence in Norway and Denmark was well below 1.0 per 1000 among 0- to 10-year-old children, 3.7 per 1000 among 10- to 19-year-old Norwegians, and 3.0 per 1000 among 10- to 14-year-old Danes (Danish Medicines Agency 2008; Norwegian Institute of Public Health 2008). Also, earlier prevalence ratios for antipsychotic use are markedly lower in Italy (in 2004), 0.53 per 1000 children; in France (in 2003), 1.0 per 1000; and in the Netherlands (in 1999), 3.4 per 1000 (Schirm et al. 2001; Clavenna et al. 2007; Sevilla-Dedieu and Kovess-Masfety 2008).

Olfson et al. (2006) found that diagnosis of bipolar disorder increased greatly among American children between 1993 and 2002. They also demonstrated a sharp national increase (six-fold) in antipsychotic treatment. Similarly, Rani et al. (2008) found a doubling of antipsychotic prevalence between 1992 and 2005 among U.K. children in primary care. In 2007, three antipsychotics —risperidone, aripiprazole, and quetiapine—were among the 10 most used psychotropic drugs for both boys and girls in Iceland (Table 2). Risperidone's summary product characteristics (SPC) indications include severe behavioral disorders and autism in young children (older than age 5) and acute and chronic schizophrenic psychoses among youths older than 15. Neither aripiprazole nor quetiapine are, on the other hand, licensed for use under age 18 (Iceland Medicines Control Agency 2008). Potential metabolic complications, such as weight gain and insulin

TABLE 4. OFF-LABEL[a] AND UNLICENSED[b] PSYCHOTROPIC DRUG USE AMONG CHILDREN (0–17) IN ICELAND IN 2007

Drug group	*Total number of prescribed drugs*	*% Off-label*	*% Unlicensed*
Any psychotropic drug group	22,700	24.6	0.6
Antidepressants	7,606	41.8	0.0
Stimulants and atomoxetine	10,308	1.2	0.0
Antipsychotics	3,277	52.0	5.2
Anxiolytics	1,002	10.4	10.7
Hypnotics and sedatives	507	95.3	4.7

[a]Drugs used outside the age terms of the product license.
[b]Drugs without a product license in Iceland.

sensitivity, coupled with the lack of research on the long-term effects of pediatric use of antipsychotics, warrant a further justification for the extensive use of these drugs in Iceland.

We detected a time trend toward reduced incidence of psychotropic drug use between 2004 and 2007, along with a tendency toward increasing prevalence. This may reflect a leveling off in the rising use of these drugs among children in Iceland, longer drug treatment duration, or a combination of both. The overall decreasing incidence was primarily driven by significantly fewer children initiating antidepressant treatment. The fall in antidepressant incidence, 11.9 per 1000 children to 8.0 between 2004 and 2007, is in accordance with recent trends reported from other countries (Murray et al. 2005; Bramness et al. 2007; Dean et al. 2007; Gibbons et al. 2007; Nemeroff et al. 2007; Volkers et al. 2007; Olfson et al. 2008). Reasons for this decline may be traced to public health warnings, issued by European and U.S. regulators in 2003 and 2004, media campaigns against the use in treatment of childhood depression, and uncertainty regarding long-term effects of use U.S. Food and Drug Administration 2003; Directorate of Health Iceland 2004; Jureidini et al. 2004; Ramchandani 2004; Vitiello et al. 2004; Whittington et al. 2004). A few recent studies have examined a proposed association between the decline of antidepressant use and increased risk of suicide among youths (Bridge et al. 2007; Gibbons et al. 2007; Olfson et al. 2008; Simon 2008; Wheeler et al. 2008), but results still remain inconclusive.

The decrease of new antidepressant users among Icelandic children is, furthermore, likely to be a function of drug substitution when treating ADHD, from tricyclic antidepressants to both long-acting MPH and atomoxetine. Baldursson et al. (2000) showed that tricyclic antidepressants (amitriptyline) were the most common drug choice in 1998–1999 for Icelandic physicians treating children referred to the National University Hospital outpatient ADHD clinic. Since that time, however, pediatric use of long-acting MPH and atomoxetine, marketed in Iceland in 2002 and 2006, respectively, has risen markedly (Zoega et al. 2007; Iceland Social Insurance 2008).

We excluded the drug hydroxyzine (N05BB01) from all analyses of this study. Although classified as an anxiolytic (N05B) in the WHO ATC classification system (World Health Organization 2008), the drug also has a main indication for allergic reactions (Iceland Medicines Control Agency 2008) and is primarily used as such for children in Iceland. The exclusion of hydroxyzine may be debated because our data did not include information on the diagnosis for which the drug was prescribed.

Given the still fragmented research base for safety and efficacy of childhood psychotropic drug use, it is not surprising to see that one fourth of all psychotropic drug prescriptions to children in Iceland in 2007 were either off-label (age inappropriate) or unlicensed. This concurs with previous studies from other countries showing similar proportions of pediatric prescriptions to be off-label (Ufer et al. 2003; Volkers et al. 2007; Sevilla-Dedieu and Kovess-Masfety 2008). To minimize clinical risk for children with mental health problems, it is essential that physicians initiating and maintaining treatment be equipped with proper education and up-to-date knowledge on pharmaceutical safety. Our results show that pediatricians most often initiated psychotropic treatment for children in Iceland between 2004 and 2007. This concurs with the fact that child and adolescent psychiatrists are 10 times fewer than pediatricians in Iceland. We did not attempt to determine which medical specialties were most likely to maintain psychotropic drug treatment for children in this study.

The rationale for the demonstrated extensiveness of psychotropic use among Icelandic children remains unclear. Assuming that prevalence of mental health disorders is not considerably higher in Iceland than elsewhere in Europe (Gudmundsson et al. 2007; Polanczyk et al. 2007), the first possible explanation may lie in the registration of drug dispensing data in Iceland, i.e., that it better captures actual use than elsewhere. This is, however, not a probable cause when comparing use between the Nordic countries, where registration of drug-dispensing rests on very similar nationwide databases. A central and well-financed health-care system, which includes unrestrained access to specialist and generous public co-payment of drugs, is a possible underlying factor for the widespread use. Additionally, because drug use is a direct function of prescribing habits, part of the explanation may lie in the education of Icelandic medical specialists, many of whom seek training and continuing education in the United States, where relatively high psychotropic use rates are also found. Further research is needed to assess the determinants of pediatric use of psychotropics in Iceland and the quality and outcomes of treatment.

Validity/limitations

Very few previous drug use studies rest on data covering an entire national pediatric population. Thus, the major strength of the present study is the completeness of the Icelandic Medicines Registry, allowing us to demonstrate a clear representative picture of the patterns of pediatric psychotropic drug use of a whole nation.

The study does have some limitations. First, the National Medicines Registry only contains data on dispensed drugs to outpatients, not within hospitals. Because in Iceland the vast majority of children with mental health problems are treated in ambulatory care, the study results should reflect total pediatric psychotropic drug use in the country. Second, we did not analyze duration of use in the present study. The simultaneous overall rise in prevalence and fall in incidence between 2003 and 2007 may, however, suggest that treatment duration is becoming longer. Third, our method to estimate concomitant drug use is conservative. Given that drugs can be used concomitantly without being dispensed on the same day, the method is likely to underestimate the actual number of children receiving concomitant treatment. Fourth, we have no means of knowing whether children actually took the dispensed drugs in question. This is a well-known limitation of most all drug use studies based on dispensing data. Finally, the Medicines Registry in Iceland does not include information on the underlying diagnosis, or indications, for which drugs are prescribed. This limits our conclusions of the appropriateness of psychotropic drug treatment for children in Iceland.

Conclusion

In comparison to reported use in other European countries, this nationwide study provides evidence for strikingly high psychotropic drug use among children in Iceland. Further scrutiny is needed to assess the rationale behind the widespread use of various psychotropics, especially subtypes of tricyclic antidepressants and antipsychotics, with known adverse side effects.

Disclosures

Authors Zoega, Baldursson, Hrafnkelsson, Almarsdottir, Valdimarsdottir, and Halldorsson have no financial ties or conflicts of interest to disclose.

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Use of ADHD drugs in the Nordic countries: a population-based comparison study

Zoëga H, Furu K, Halldórsson M, Thomsen PH, Sourander A, Martikainen JE. Use of ADHD drugs in the Nordic countries: a population-based comparison study.

Objective: To compare national use of attention-deficit/hyperactivity disorder (ADHD) drugs between five Nordic countries.
Method: A population-based drug utilisation study based on nationwide prescription databases, covering in total 24 919 145 individuals in 2007. ADHD drugs defined according to the World Health Organization Anatomic Therapeutic Chemical classification system as *centrally acting sympathomimetics* (N06BA).
Results: The 2007 prevalence of ADHD drug use among the total Nordic population was 2.76 per 1000 inhabitants, varying from 1.23 per 1000 in Finland to 12.46 per 1000 in Iceland. Adjusting for age, Icelanders were nearly five times more likely than Swedes to have used ADHD drugs (Prev.Ratio = 4.53, 95% CI: 4.38–4.69). Prevalence among boys (age 7–15) was fourfold the prevalence among girls (Prev.Ratio = 4.28, 95% CI: 3.70–4.96). The gender ratio was diminished among adults (age 21 +) (Prev.Ratio = 1.24, CI: 1.21–1.27).
Conclusion: A considerable national variation in use of ADHD drugs exists between the Nordic countries.

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Key words: pharmacoepidemiology; drug utilisation; central nervous system stimulants; prevalence; attention-deficit/hyperactivity disorder

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Significant outcomes

- The Nordic prescription databases hold near-complete information on all prescription drugs dispensed to the entire outpatient population of nearly 25 million people. This study thus demonstrates a clear and representative picture of the patterns and differences of ADHD drug use in the five countries.
- We found significant differences in total use of ADHD drugs between the neighbouring Nordic countries, where relatively homogeneous populations, similar culture and national health care systems exist.
- Drug use for ADHD is the least in Finland but most widespread in Iceland, where rates are similar to what has been reported within the United States. Methylphenidate is the most commonly used drug in all five Nordic countries.

Limitations

- The study data do not include information of the underlying diagnosis for the prescribed drugs, hence the appropriateness of ADHD drug use remains unanswered.
- The study covers only 1 year of dispensed ADHD drugs so we are unable to analyse time trends of use within the Nordic countries.
- Co-medication and treatment length among those treated with ADHD drugs are not estimated in this study.

Introduction

Use of medication to treat attention-deficit/hyperactivity disorder (ADHD) in children has increased over the past two decades (1–7). In more recent years, adults have also increasingly been treated with stimulants for the disorder, which historically was thought to only exist among children (8, 9).

The worldwide prevalence of ADHD is estimated to be 4–6% among children (10, 11), and 2–4% among adults (12, 13). Given the serious burden of ADHD on those affected, their families and societies, promotion of optimal treatment is of major public health importance (14). This is further underlined by concerns of the long-term outcomes of drug use, although the efficacy of drug treatment to relieve the core symptoms of ADHD in the short term has been established (15, 16). In addition to concern of possible overtreatment of the disorder, the validity of ADHD diagnosis has been publicly debated (17–19), but as for many other psychiatric conditions, it is based on non-biological measures.

Comparisons of drug use between geographical regions may enhance health policies leading to increased overall treatment success. The establishment of nationwide prescription databases in all five Nordic countries made it possible to do a comparative study within a population of nearly 25 million individuals (20).

Aims of the study

The objective of this study was to explore the accessibility of attention-deficit/hyperactivity disorder (ADHD) drugs and the prevalence of their use among children, adolescents and adults in the five Nordic countries; Denmark, Finland, Iceland, Norway and Sweden. This was a study of drug treatment patterns rather than the epidemiologic patterns of ADHD.

Material and methods

Setting

We examined the ADHD drug use among all people living in the five Nordic countries in 2007: Denmark (5 447 084 inhabitants), Finland (5 300 328), Iceland (307 672), Norway (4 681 134) and Sweden (9 182 927).

Study drugs

ADHD drugs were defined according to the World Health Organization Anatomic Therapeutic Chemical (ATC) classification system and comprised drugs in the category of *centrally acting sympathomimetics* (N06BA) used to treat ADHD (21). Chemical substances included in this study were amfetamine (N06BA01), dexamfetamine (N06BA02), methylphenidate (N06BA04), modafinil (N06BA07) and atomoxetine (N06BA09). Other chemical substances within the studied ATC-group N06BA; metamfetamine (N06BA03), pemoline (N06BA05), fencamfamin (N06BA06), fenozolone (N06BA08), fenetylline (N06BA10) and dexmethylphenidate (N06BA11) were not available or used for outpatient care in the Nordic countries at the time of the study.

Data sources

The number of inhabitants in each country at the end of 2007, used as a dominator for prevalence, was based on publicly available statistics from national population registers. Information on marketing authorisations, indications and reimbursement status of ADHD drugs was obtained from the national agencies for medicines control and institutions of national health insurance (22–31).

Data on dispensed ADHD drugs from 1 January 2007 to 31 December 2007 were retrieved from nationwide prescription databases. In each country, the database holds data on all prescribed drugs dispensed to patients in ambulatory care, containing patients' identity number, gender and age, and the ATC code of the dispensed medicinal product (20). All prescription databases contain data on products both with and without marketing authorisation. Reimbursed and non-reimbursed prescription drug purchases are registered in all databases except the Finnish, in which only reimbursed drug purchases are registered. In this study, we used data on dispensed drugs to the outpatient population, hence those who were dispensed drugs only within a hospital or a nursing facility did not appear in the analyses. The completeness of the Nordic prescription databases is high (20), containing over 95% of all pharmacy records in outpatient care.

Analysis

Prevalence of ADHD drug use was defined as the number of individuals who were dispensed at least one prescription during the year 2007 per 1000 inhabitants in the population. The denominator for prevalence was composed by the number of inhabitants in each country at the end of 2007, according to population statistics, with the relevant stratifications. An individual who was dispensed an ADHD drug (N06BA) once or multiple times in 2007 appeared only once in the nominator for prevalence of use. An individual using more than one type of chemical substances appeared once for each substance, but still counted as only one individual for prevalence of 'any type of ADHD drug'. Prevalence was stratified by chemical

substance, patients' country of residence, gender and age group. Patient age was grouped into six categories (years 0–6, 7–10, 11–15, 16–20, 21–26 and 27+). To describe use among children, we used the age category 7–15 years to coincide with the age range at which ADHD is most prevalent.

To show the variation of use between countries, we used the Mantel–Haenszel method to estimate age-adjusted prevalence ratios (Prev.Ratio, country ratios) of use for each country and the corresponding 95% confidence intervals (95% CI) (28), with prevalence of ADHD drug use in Sweden as a reference category. In the same manner, to show the variation of use between men and women, we estimated age-adjusted gender ratios (Prev.Ratio, gender ratios) of ADHD drug use both overall and for each country, with prevalence among women as a reference category. When adjusting for age in these analyses, we divided age into four categories (0–6, 7–15, 16–20 and 21+).

Ethics

The study was approved by the Icelandic Bioethics Committee (VSNb2007120009/03-7) and reported to the Icelandic Data Protection Authority (S3681). In Finland, Denmark, Norway and Sweden, ethical approvals were not needed for this study.

Results

Availability and reimbursement

Available ADHD drugs and their reimbursement status varied somewhat between the Nordic countries (Table 1). Methylphenidate was the only substance that had marketing authorisation and was reimbursable in all five countries. It was the most prevalent chemical substance used in all countries, dispensed to 57 273 individuals (83.3% of all ADHD drug users) during the year 2007. Atomoxetine was the second most used substance, dispensed to 8280 individuals (12.0% of all ADHD drug users). At the time of the study, atomoxetine was not reimbursable in Finland and did thus not appear in the results for the Finnish population. Different from other chemical substances used within the Nordic countries, modafinil was not indicated for ADHD in any country at the time of the study, but rather for narcolepsy among adults. However, in Denmark, the use of modafinil for ADHD could be reimbursed if treatment with methylphenidate was unsuccessful. All other chemical substances with valid marketing authorisation were indicated for ADHD in children and adults.

Table 1. Availability of attention-deficit/hyperactivity disorder drugs (ATC-group N06BA) by chemical substance in each Nordic country in 2007

Substance*	Denmark	Finland	Iceland	Norway	Sweden
Amfetamine					
Marketing authorisation	No	No	Yes	No	No
Reimbursable	Yes	Yes	Yes	Yes	Yes
Dexamfetamine					
Marketing authorisation	No	No	No	No	No
Reimbursable	Yes	Yes	No	No	Yes
Methylphenidate					
Marketing authorisation	Yes	Yes	Yes	Yes	Yes
Reimbursable	Yes	Yes	Yes	Yes	Yes
Modafinil†					
Marketing authorisation	Yes	No	Yes	Yes	Yes
Reimbursable	Yes	Yes	Yes	No	Yes
Atomoxetine					
Marketing authorisation	Yes	Yes	Yes	Yes	Yes
Reimbursable	Yes	No	Yes	No	Yes

*Other chemical substances within *centrally acting sympathomimetics* (ATC-group N06BA) not marketed in the Nordic countries.
†In general only indicated and reimbursable for narcolepsy in adults.

Prevalence by country

In total, the study population included 24 919 145 individuals living in the Nordic countries at the end of the year 2007. Among them, 68 776 individuals (2.76 per 1000 inhabitants) were dispensed an ADHD drug at least once during the study period (Table 2). Prevalence varied considerably between the Nordic countries and was highest in Iceland (12.46 per 1000) and lowest in Finland (1.23 per 1000).

When adjusted for age, Icelanders were nearly five times more likely than Swedes to have used ADHD drugs in 2007, while Finns were half as likely as Swedes (Table 3). Among children aged 7–15 years, the relative difference of prevalence of ADHD drug use, compared to Sweden, was most pronounced for Iceland (Prev.Ratio = 4.91, 95% CI: 4.68–5.15).

Prevalence by gender and age group

Prevalence of ADHD drug use by age and gender differed somewhat between the countries (Fig. 1a,b). For men, the prevalence of use peaked at age 11–15 years in Iceland (72.04 per 1000), Norway (33.97 per 1000) and Sweden (17.93 per 1000), but at age 7–10 years in Finland (11.30 per 1000). Among women, prevalence was likewise highest at age 11–15 years in both Iceland (26.29 per 1000) and Sweden (4.63 per 1000), at age 7–10 years in Finland (1.90 per 1000) and among 16 to 20 -year-old women in Norway (10.92 per 1000).

Table 2. One-year prevalence* of attention-deficit/hyperactivity disorder (ADHD) drug use by chemical substance in five Nordic countries in 2007

Prevalence of use by country						
Age in years	Denmark	Finland	Iceland	Norway	Sweden	Nordic Countries
Any ADHD drug						
All ages	2.41	1.23	12.46	4.73	2.52	2.76
7–15	9.30	6.43	47.03	18.10	9.58	11.17
Methylphenidate						
All ages	2.06	1.17	10.60	4.10	1.89	2.30
7–15	8.96	6.41	42.78	16.36	8.55	10.31
Atomoxetine						
All ages	0.21	†	1.61	0.68	0.37	0.33
7–15	1.03	†	6.26	2.66	1.78	1.49
Modafinil						
All ages	0.28	0.05	0.60	0.06	0.30	0.20
7–15	0.03	0.01	–	–	0.02	0.01
Dexamfetamine						
All ages	–	0.03	–	0.15	0.05	0.05
7–15	–	0.02	–	0.25	0.04	0.07
Amfetamine						
All ages	–	–	0.36	0.04	0.11	0.05
7–15	–	–	–	0.03	0.12	0.05
Total study population						
All ages	5 447 084	5 300 328	307 672	4 681 134	9 182 927	24 919 145
7–15	623 276	557 626	40 085	561 102	949 266	2 731 413

–, No use.
*Prevalence is expressed as number of individuals per 1000 in the population dispensed one or more prescriptions.
†Atomoxetine does not appear in the Finnish prescription database because the database only holds information on reimbursable drugs, and this chemical substance is not reimbursed in Finland.

Table 3. Prevalence ratios* of attention-deficit/hyperactivity disorder drug use between the Nordic countries in 2007†

Age in years	Prev.Ratio	95% CI
Denmark		
All ages	0.90	(0.88; 0.92)
7–15	0.88	(0.85;0.91)
Finland		
All ages	0.54	(0.53; 0.55)
7–15	0.83	(0.80; 0.86)
Iceland		
All ages	4.53	(4.38; 4.69)
7–15	4.91	(4.68; 5.15)
Norway		
All ages	1.79	(1.75; 1.82)
7–15	1.89	(1.84; 1.95)
Sweden		
All ages	1.00	Ref.
7–15	1.00	Ref.
Nordic countries		
All ages	1.08	(1.07; 1.10)
7–15	1.17	(1.14; 1.20)

*Stratum specific (age 7–15 years) and pooled prevalence ratios (Prev.Ratio) shown with corresponding 95% confidence intervals (CI).
†Use in Sweden as reference (Prev.Ratio = 1.00).

Overall, Nordic men were roughly two times more likely than Nordic women to have used ADHD drugs in 2007 (Table 4). Among children aged 7–15 years, boys were over four times more likely than girls to have been dispensed an ADHD drug. For adults (age 21+), this gender ratio was diminished (Prev.Ratio = 1.24, CI: 1.21–1.27). The gender ratio of use was most pronounced among those living in Finland (Table 4).

Discussion

Main results

There was a significant difference in the accessibility of ADHD drugs and the extent of drug utilisation between the Nordic countries in 2007. The prevalence of use in the total population varied from a low 1.23 per 1000 inhabitants in Finland to a high 12.46 per 1000 in Iceland. Children aged 7–15 years were almost five times more likely in Iceland than in Sweden to have been dispensed an ADHD drug, while Finnish children were 17% less likely than Swedish children. Methylphenidate was the most commonly used ADHD drug in all countries, accounting for over 80% of ADHD drug users.

Age and gender distribution

Our results on age and gender distribution of ADHD drug use in the Nordic Countries coincide rather well with the epidemiologic patterns of ADHD. We found that drug treatment for was most common for boys aged 11–15 years. ADHD has the highest prevalence among 9 to 14 -year-old children, and it is three to four times more common among boys than girls (32, 33). Recent

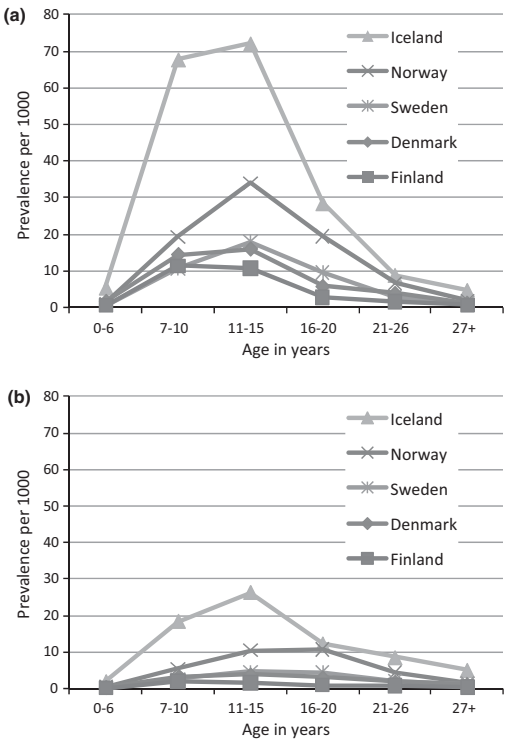

Fig. 1. (a) Prevalence* of attention-deficit/hyperactivity disorder (ADHD) drug use among men in 2007 by age group and country of residence. (b) Prevalence* of ADHD drug use among women in 2007 by age group and country of residence. *Prevalence is expressed as number of individuals per 1000 in the population with one or more prescriptions.

Table 4. Prevalence ratios* of attention-deficit/hyperactivity disorder drug use between men and women in the Nordic countries in 2007†

Country	Age in years	Prev.Ratio	95% CI
Denmark	All ages	**2.20**	(2.12; 2.28)
	7–15	4.29	(4.01; 4.58)
Finland	All ages	**3.59**	(3.38; 3.81)
	7–15	6.36	(5.77; 7.00)
Iceland	All ages	**1.88**	(1.76; 2.01)
	7–15	3.04	(3.04; 3.40)
Norway	All ages	**2.15**	(2.09; 2.21)
	7–15	3.34	(3.18; 3.50)
Sweden	All ages	**1.97**	(1.92; 2.02)
	7–15	3.95	(3.75; 4.16)
Nordic Countries	All ages	**2.18**	(2.14; 2.21)
	7–15	4.28	(3.70; 4.96)

*Stratum specific (age 7–15 years) and pooled prevalence ratios (Prev.Ratio) shown with corresponding 95% confidence intervals (CI).
†Use among women as reference (Prev.Ratio = 1.00).

research shows substantial diagnostic continuity into young adulthood as well as increases in first time diagnoses of ADHD among adults (12, 14, 34). Follow-up studies of children with the disorder have found that 15% still have the full diagnosis at 25 years and that a further 50% are in partial remission as young adults (35). Among adults, women are as likely as men to be diagnosed with ADHD (2, 36), which is in accordance with our results showing a diminished gender ratio after adolescence.

Prevalence of ADHD and use of drugs

The overall prevalence of ADHD drug use in the Nordic area (2.76 per 1000) is considerably lower than the reported use in the United States between 2000 and 2005, which was 29–45 per 1000 among children, depending on populations, and 8 per 1000 among adults (1, 5, 7, 37). Iceland is the only Nordic country where use of ADHD drugs approximates the United States rates. Generally, drug treatment rates for ADHD in the Nordic countries seem to be more in line with, or slightly higher than, previously published rates for children in European countries; 12 per 1000 among children (0–19 years) in the Netherlands in 2002, 7.1 per 1000 children (0–19 years) in Germany in 2000, 2.9 per 1000 children (0–19 years) in the United Kingdom in 2001 and 1.8 per 1000 among children (6–18 years) in France in 2005 (37–39). Previous research indicates increasing use of ADHD drugs in the Nordic area over the past decade as in many other European countries (3, 4, 38–42).

In our study, relative to use in Sweden, use of ADHD drugs was nearly fivefold in Iceland and double in Norway. In Denmark, use was as prevalent as in Sweden, but in Finland only half of that. Prevalence of ADHD has been shown to be relatively stable across the world, estimated 4–6% among children and 2–4% among adults, with research suggesting that variability of this prevalence be explained by methodological characteristics of studies, rather than geographical location (10–13). Thus, the variation in drug use we found is most probably a reflection of clinical trends and health care policies rather than a reflection of epidemiologic patterns of ADHD. This significant difference in prevalence of drug utilisation between neighbouring countries, with relatively homogeneous populations, similar culture and national health care systems, invokes questions.

Possible explanations for varying use in the Nordic countries

Several factors such as accessibility of drugs, available treatment alternatives, clinical practice

and national guidelines, may influence the patterns of prescribing and use of ADHD drugs in the Nordic countries.

In each Nordic country, drugs are approved for use through separate national application procedures and different reimbursement regulations are applied. Although the countries all have comprehensive drug coverage, reimbursement rates vary by country, by drug and by patient characteristics. For this reason, accessibility of ADHD drugs was not the same between the Nordic countries at the time of the study. Methylphenidate was the only substance validly marketed and reimbursable in all five countries in 2007. Based on the number of marketing authorisations and reimbursability for substances, accessibility seems to have been the most in Iceland but the least in Finland in 2007.

The validity of ADHD diagnosis has been a source of debate in many countries, giving rise to worries of possible over-diagnoses and treatment. Like for many other psychiatric illnesses, the diagnosis is based on non-biological measures. The condition may be diagnosed as ADHD either with the criteria of the International Classification of Diseases, 10th Edition (ICD-10) for hyperkinetic disorders (F90.0-F98.8) or with the tools of the Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition (DSM-IV). The diagnostic criteria of the latter system are viewed to be being less stringent (10, 43). We cannot conclude whether these different diagnostic criteria are contributing factors to the national variation found in ADHD drug use, because we do not know to which extent the prescribing physicians relied upon either system. But in addition to diagnostic criteria, drug prescribing is a likely function of professional training and traditions of physicians and other mental health care providers. Previous studies that have demonstrated large regional differences of stimulant use for ADHD, for example within Iceland, Norway and Finland (3, 4, 40), support this view.

All five Nordic countries have clinical guidelines, and to some extent reimbursement regulations, that restrict initiation of treatment with ADHD drugs to specialists in psychiatry, neurology, or to physicians with special knowledge in psychic and physical development of children and adolescents (27, 29, 31, 44, 45). Access to such medical specialists may vary by country and thereby influence prescription rates. Different from customary practice in the Nordic countries, patients in Iceland generally do not need to be referred to a specialist by primary care practitioners.

Additionally, the availability of non-pharmacological interventions for ADHD in each country, such as behavioural treatment and specialised learning support within schools, may influence prescribing rate. We were, however, unable to assess this because the study data only included use of drugs, not other treatment alternatives.

Study strengths and limitations

The major strength of this study is the completeness of the data it rests on. The Nordic prescription databases hold information on drug purchases of the entire national outpatient population in all five countries, demonstrating a clear and representative picture of the patterns and variations of ADHD drug use. Owing to regulations and other incentives motivating Nordic pharmacies to collect and send data of pharmacy records electronically to the national prescription databases, the accuracy and completeness of the databases is high (20). By measuring drug use with pharmacy records from national databases, we minimise the risk of recall bias, often associated with survey data, and selection bias associated with use of localised community data (46).

The study does have limitations. First, its data only covered drug use in outpatient care, not within hospitals or nursing homes. However, as the vast majority of individuals with ADHD is treated in outpatient care, the results should estimate well use of ADHD drugs in each country. Secondly, different from the other Nordic countries, the Finnish database lacked information on non-reimbursed drugs. For that reason, use of atomoxetine in Finland did not appear in the results, thereby underestimating the overall ADHD drug use. But wholesale statistics from Finland indicate this to be a minor limitation because consumption of atomoxetine in 2007 was only 0.02 defined daily doses per 1000 inhabitants per day (47). Thirdly, we did not have access to the underlying indications for drug use nor to the specialty of the prescribing physicians. Thus, the appropriateness of ADHD drug prescribed in the Nordic remains largely unanswered. The study was restricted to use of *centrally acting sympathomimetics* (ATC-group N06BA), and hence drugs outside this group did not appear in the results although they might possibly have been used in the treatment of ADHD. Neither did the results contain any information on co-medication of the treated individuals. Although all studied chemical substances, apart from modafinil, had ADHD as a specified indication in 2007, they might have been used to treat other conditions as well. Modafinil was indicated to treat narcolepsy in adults, according to marketing authorisations, but recent research suggests

that the drug might also be effective in improving symptoms of ADHD among children and adolescents (48, 49). Finally, the data covered only 1 year of dispensed drugs, hence the results show no time trends of ADHD drug use.

In conclusion, although widely researched as a drug group, the long-term risks and benefits of ADHD drug use are still unclear (16). The drugs remain controversial in spite of the evidence of their efficacy in relieving the core symptoms of ADHD, i.e. attention deficit, hyperactivity and impulsivity. Unresolved safety issues and unintended side effects, such as cardiovascular risk and sudden death (50, 51), have illuminated this controversy as have concerns about overuse and misuse of the drugs. In this study, we are unable to conclude on any possible over- or undertreatment for ADHD in the Nordic countries but as elsewhere, it is important that continued attention is paid to factors affecting the drug prescribing rates. Future studies should address whether the variance in national drug use is accompanied by differences in outcomes both in the short- and long term, e.g. the quality of life and functional ability of individuals with ADHD.

This is the first population-based study to examine the use of ADHD drugs within all of the Nordic countries. With near-complete coverage of almost 25 million individuals, the results show considerable national variation in prevalence of use, but quite similar patterns with respect to age, gender and drug selection. We recommend that the Nordic countries put joint effort into assessing the quality of treatment and support mechanisms for ADHD, in order to enhance rational drug use and overall treatment success.

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Declaration of interest

The study funders had no role in the study design; in the collection, analysis, and interpretation of data; in the writing of the manuscript; or in the decision to submit the article for publication. Independence of researchers from funders is declared. PHT is a recipient of consultant fees from Novartis, Janssen-Cilag and Eli-Lilly, and he serves on the advisory board of Eli-Lilly in Denmark. Other authors (HZ, KF, MH, AS and JM) have no competing interests to declare.

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Stimulant Drug Treatment for ADHD and Academic Progress in Children

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ABSTRACT

BACKGROUND

Evidence is sparse regarding long-term effects of stimulant treatment on academic progress among children with attention-deficit/hyperactivity disorder (ADHD). We evaluated the extent to which academic progress among 9-to 12-year old Icelandic children is related to initiation of stimulant treatment.

METHODS

We linked data from the Icelandic Medicines Registry and the Database of National Scholastic Examinations. We included 11,872 children born 1994-1996 who took standardized tests in 4th and 7th grade, classifying them with respect to psychotropic drug prescription fills and test results in mathematics and language arts. We estimated the probability of academic decline (drop of ≥5.0 percentile points) according to drug exposure and timing of treatment start between examinations.

RESULTS

In contrast with non-medicated children in the general population, children starting stimulant treatment between their 4th and 7th grade tests were more likely to decline in test performance. The crude probability of academic decline was 72.9% in mathematics and 42.9% in language arts for children with a treatment start 25-36 months after the 4th grade test. Compared with those starting treatment earlier (≤12 months after tests), the multivariable adjusted risk ratio [RR] for decline was 1.7 (95% confidence interval [CI] 1.2 to 2.4) in mathematics and 1.1 (95%CI 0.7 to 1.8) in language arts. The adjusted risk ratio of mathematics decline with later treatment was higher among girls (RR, 2.7; 95%CI 1.2 to 6.0), than boys (RR, 1.4; 95%CI 0.9 to 2.0).

CONCLUSION

Later start of stimulant drug treatment for ADHD is associated with academic decline in mathematics.

INTRODUCTION

Attention-deficit/hyperactivity disorder (ADHD) is a neurodevelopmental disorder affecting 5-10% of school-aged children in the US and Europe.[1, 2] Drug treatment for ADHD with stimulants (and atomoxetine) is now widely used as a therapeutic option in the US and increasingly in Europe.[1, 3-10] Nevertheless, the increasing use of ADHD drugs is debated, chiefly because of concerns of over-use, addiction and uncertainty of the long-term outcomes of treatment.

Stimulant treatment has consistently been shown effective in improving inattention, hyperactivity and impulsivity, the core symptoms of ADHD among school-aged children,[11, 12] but evidence supporting gains in academic performance is equivocal.[13-15] Controlled trials have reported acutely improved cognitive performance following short durations of treatment,[16-20] but studies on longer-term academic effects in naturalistic settings are scarce. Existing studies, with follow-ups from 6-13 years, have indicated improved performance in mathematics,[21, 22] but inconsistent results for reading improvement.[21, 23] Gender-specific effects have not been reported and several methodological limitations, including reliance on self-reports of medication use, have hindered interpretation.

In Iceland the use of stimulants to treat children with ADHD is more common than in most European countries, and is reportedly similar to use in the US.[1, 24] With almost 100% complete national registration of prescription drug utilization and mandatory standardized scholastic tests for all children at age 9 and 12, Iceland offers a unique setting to study academic performance among children medicated for ADHD. In this study we examined the effect of later versus earlier drug treatment for ADHD on academic progress.

METHODS

STUDY SETTING AND POPULATION

Our source population was all 13,617 children born in 1994, 1995 and 1996 and registered in the Icelandic school system. We obtained data from January 1, 2003 through December 31, 2008 on psychotropic drug prescription fills and standardized test results in mathematics and language arts for this national cohort. Using the personal identification number unique to every citizen, we linked records from the National Population Registry to the Icelandic Medicines Registry and the Database of National Scholastic Examinations. The final study population comprised all children who took a standardized test in both 4th (age 9) and 7th grade (age 12), (n=11,872). Of these, 11,619 took both mathematics examinations and 11,542 took both examinations in language arts.

ADHD DRUG EXPOSURE

The Icelandic Medicines Registry contains information for each person dispensed prescription drugs as an outpatient since January 1, 2003. Completeness ranges from 93.7 to 99.9% of all dispensed outpatient prescriptions for the years 2003 to 2008. For each dispensed prescription in the study, we received information on drug name, number of defined daily doses (DDDs), ATC code, date and pharmacy of the filled prescription.

ADHD drugs were defined according to the World Health Organization Anatomic Therapeutic Chemical (ATC) classification as drugs within the category of *centrally acting sympathomimetics* (N06BA).[25] Chemical substances included were amphetamine (N06BA01), methylphenidate (N06BA04) and atomoxetine (N06BA09). Other chemical substances within the ATC category N06BA were not available in Iceland or not prescribed to children at the time during the study period. All drugs included had ADHD as their main indication, according to clinical guidelines and drug package inserts.[26, 27] The Icelandic Medicines Registry does not hold information on the indication for drug treatment. In Iceland, however, an ADHD diagnosis must be verified by a pediatric, psychiatric or neurological specialist for reimbursement. Thus, it is reasonable to assume that essentially all medicated children fulfilled the DSM-IV criteria[28] for ADHD before treatment.

We defined the start of therapy to be the first prescription following a period of at least 11 months during which no prescriptions for an ADHD drug were filled. After this period, we considered the start date of treatment for each child to be the date of the first dispensing of a prescription for an ADHD drug (stimulant or atomoxetine). To reduce confounding by indication, we restricted the main analyses to children who started treatment between test dates in 4th and 7th grade. We categorized medicated children according to the timing of their treatment initiation after their 4th grade test: within 12 months, 13-24 months or 25-36 months after the 4th grade test. The last category we designated as later treatment. We considered treatment to have been discontinued early if children filled less than 90 DDDs of an ADHD drug. We classified children as treated on their test day in 7th grade if the number of DDDs on the last prescription overlapped with the test day.

We assumed that children were being treated concurrently with other psychotropic drugs if a prescription was filled for another psychotropic drug within the 90-day period following the dispensing of an ADHD drug. Other psychotropic drugs were defined as all drugs pertaining to ATC drug category *Nervous system (*N) including antidepressants (N06A), antipsychotics (N05A), anxiolytics, hypnotics and sedatives (N05B, N05C) and other psychotropic drugs (N01, N02, N03, N04, N06C, N06D, N07).

ACADEMIC OUTCOMES

The standardized tests in mathematics and language arts are nationally coordinated assessments within the Icelandic school system, mandatory for all children in 4th grade (9-year olds) and 7th grade (12-year olds). These tests are ideal for within-individual comparisons, as they measure age-adjusted performance. We obtained the test scores, test dates, school and school region for each child who took tests during 2003-2008. Some test scores were missing owing to disability, illness on the test day, migration to or from Iceland between tests, or unspecified absence.

Tests are scored on a scale of 0.0-10.0. We converted these to a percentile scale (0-100) that was ranked within each test year. Our assessment of academic performance was based on these percentile rankings. Change in performance was found by subtracting the 4th grade percentile rank from the 7th grade rank for each individual. We defined an academic decline to be a drop of 5.0 or more percentile points.

DATA ANALYSIS

We described medicated and non-medicated populations by demographic characteristics and by ADHD drug treatment, e.g. type of drugs used, early discontinuation, concurrent psychotropic drug treatment and treatment on test day, according to time of treatment start. We estimated risks, as well as risk ratios and differences, for a drop in performance in the mathematics and language arts test. First we estimated crude measures and then we controlled for performance level on the 4th grade test (categorized into terciles), sex, birth month (categorized as Jan-May, Jun-Aug, Sep-Dec), birth place (urban, rural, outside Iceland), school region (urban, rural), change of schools, concurrent psychotropic drug treatment, treatment on test day and early discontinuation of ADHD drug treatment (<90 DDDs). For stratified analyses, we standardized results to the distribution of the total medicated test-participating population 2003-2008.[29] In these analyses, we excluded children who scored in the lowest 5th percentile on the 4th grade test, as they were unable to decline in rank by at least 5.0 percentile points. We also conducted a modified Poisson regression analysis to adjust for all confounders simultaneously.[30] Finally, we ran a sensitivity analysis to assess the influence of selection bias that would result if untested children had a different association between later treatment start and academic decline than did the children tested. [31] We assumed a hypothetical range of risk combinations and risk ratios in the group of children not taking either or both exams. For those with early treatment we assumed values of 25%, 33%, 50% and 75% for the risk of academic decline. For each of these assumed values, we then applied a range of 0-100% risk of decline for children with later treatment, as they could

have had either a greater or lesser academic decline than test-participating children. These assumptions produced a range of risk ratios from 0.0 to 4.0 among non-test-participants with later treatment, which we then took into account to get an overall estimate that included projected results from these missing children.

We used PASW Statistics (version 18) and Excel spreadsheets to run analyses. This study was approved by the National Bioethics Committee (VSNb2008040016/03-7) and the Data Protection Authority (2008040343) in Iceland.

RESULTS

Of the 13,617 children registered in the Icelandic school system, 1029 children (8%) were treated with ADHD drugs at any time during the study period. Test participation, i.e. children taking tests in both 4th and 7th grade in either mathematics or language arts, was lower for the total medicated population (72%) than the non-medicated general population (88%) (Figure 1). Of 317 children who began treatment between 4th and 7th grade test, 236 took both tests; resulting in 65%, 85% and 75% participation respectively for children starting medication ≤12 months, 13-24 months and 25-36 months after the date of 4th grade tests. Demographic and baseline characteristics among test-participants varied only slightly by timing of treatment start (Table 1). Overall, boys were more likely to be medicated than girls, as were children born in the last third of the calendar year compared with those born earlier. Medicated children scored considerably lower on their 4th grade tests (taken before their start of treatment) than the non-medicated population.

Nearly all medicated test-participating children were treated with methylphenidate (96%); 9% were simultaneously treated with the non-stimulant atomoxetine, and 34% concurrently with another psychotropic drug (Table 2). Of the medicated population, 14% discontinued treatment within 3 months

of initiation, i.e. filled less than 90 DDDs of an ADHD drug. Children who started treatment within 12 months after 4th grade tests received on average over double the supply (DDD) of ADHD drugs before tests in 7th grade, compared with those who started later (Table 2).

CHANGE IN ACADEMIC PERFORMANCE

Among children in the non-medicated general population, performance on average did not change much between tests in 4th and 7th grade; the crude mean percentile score change was 0.4 (95%CI, 0.0 to 0.8) in mathematics and 0.0 (95%CI, -0.3 to 0.4) in language arts. In contrast, mean performance level among medicated children declined. The decline was concentrated among those with later treatment initiation and was much more striking for mathematics than for language arts, with a mean decline of 9.4 percentile points in mathematics for those with delayed treatment initiation (Table 3). In mathematics, the risk of a decline of 5 percentile points or more was high among all medicated students, but especially high (crude risk ratio 1.8, 95%CI 1.3 to 2.5) for children who started treatment 25-36 months after their 4th grade test. The absolute increase in risk of a decline in mathematics for the later starters on medication was 32% (95%CI, 14% to 48%). For language arts, in contrast, the crude risk ratio of academic decline with later treatment was 1.1 (95%CI, 0.7 to 1.7), and the absolute increase in risk for academic decline among later starters was only 4% (95%CI, -14% to 22%).

Table 4A shows the results for mathematics stratified singly by children's performance level on their 4th grade test, sex and concurrent psychotropic drug treatment. In each stratified display, there is some variation in the estimates across strata, but in each case the standardized estimates were similar to the crude estimates, indicating little confounding by each of the stratification variables. Later treatment had a larger effect for children who scored in the lowest third (RR, 2.1) and mid third (RR, 1.9) on their 4th grade test than for those who scored in the highest third (RR, 1.1). The absolute risk of academic

decline in mathematics was higher for girls than boys (86.7% versus 66.7%), as was the risk ratio, 3.6 for girls versus 1.4 for boys. Furthermore, the effect of later treatment start was slightly stronger for children not receiving any concurrent psychotropic drug treatment than for those treated concurrently with other psychotropic drugs. Finally, the estimated effect was increased for children still being treated with ADHD drugs on their test day in 7th grade (RR, 1.9) compared with those no longer being treated on test day (RR, 1.5).

Table 4B shows the association between later start of ADHD drug treatment and decline in language arts performance stratified by children's performance on their 4th grade test, sex and concurrent psychotropic drug treatment. The adjusted effect estimates did not differ much from the crude estimates and indicated weak associations. The estimated effect of later treatment on decline in language arts was slightly elevated for boys (RR, 1.5), but showed an inverse association for girls (RR, 0.6). There was an effect among those still being treated on test day in 7th grade (RR, 1.6), but not among those no longer being treated (RR, 0.8).

The adjusted estimates of the effect of later drug treatment on academic performance remained the same, or changed only minimally, when we stratified the data by other covariates (birth year, -month, -place, school region and change of school; data not shown), indicating only negligible confounding by these variables. Similarly, the risk ratios reported in Tables 3-4 remained nearly the same when controlling simultaneously for all covariates in a Poisson regression analysis: RR=1.7 (95% CI 1.2 to 2.4) in mathematics and RR=1.1 (95% CI 0.7 to 1.8) in language arts. Finally, compared with the non-medicated general population, we found that the adjusted risk of academic decline was 1.6 times greater (95%CI, 1.4 to 1.8) in mathematics and 1.3 times greater (95%CI, 1.1 to 1.6) in language arts for children who started treatment anytime between tests in 4th and 7th grade.

SENSITIVITY ANALYSIS

Figure 3 displays the estimated risk ratio from the main analysis adjusted for hypothetical selection bias (y-axis) given the assumed risk ratios among non-test-participants (x-axis). The depicted lines, one for each assumed reference risk, represent adjusted risk ratios for a range of associations between later treatment and academic decline among non-test-participants children. These adjusted risk ratios varied from 1.0 to 2.2 in mathematics and 0.6 to 1.7 in language arts. The sensitivity analysis indicates that the basic findings would look roughly the same, potentially somewhat weaker, over a broad range of assumptions about the risks and associations among children who did not take both tests.

DISCUSSION

The results of this population-based, nationwide study indicate earlier, sustained treatment with ADHD drugs (stimulants or atomoxetine) between 9- and 12-years of age is associated with a lower risk of a decline in academic performance, particularly in mathematics. Our data indicate that the apparent advantage of earlier treatment differs for boys and girls. Girls show a definite benefit only in mathematics, whereas boys show marginal benefits in both mathematics and language arts.

The study has several important limitations. First, we have no information of the underlying ADHD diagnosis, subtype, severity of the condition or potential co-morbid learning- or psychiatric disorders. In Iceland the studied drugs are not reimbursable unless a diagnosis for ADHD has been made by a specialist. To limit confounding by indication, we restricted the primary comparison to children who started treatment for ADHD sometime between their tests in 4th and 7th grade, so that all in the analysis had indications for ADHD treatment at some point. Confounding by indication may still arise from differences that relate to the age at initiating treatment. Children with severe symptoms and more

persistent academic problems might be expected to begin medicating earlier than those with less severe symptoms. Our results, however, indicate that those who started drug treatment soonest after the 4th grade test declined the least academically in mathematics. We attempted to capture co-existing psychiatric disorders by accounting for concurrent psychotropic drug treatment and found that the observed effect of late treatment on academic performance was stronger among those medicated exclusively with stimulants, i.e. not concurrently with other psychotropic drugs.

Second, the study lacks information on concurrent behavioral therapy or educational school services received by children in the study population. Availability of such services in Iceland is low, however, and in light of evidence indicating that combined therapy provides only modest advantages over drug treatment alone,[12, 32] this limitation may not be of major concern. Third, it is possible that children initiating treatment early also have family- or social support that aids their academic performance. Because our findings are based on self-matched comparisons that contrast 7th grade test results with 4th grade test results, any aspect of the family setting would not confound the results unless it changed during the time between the two tests. Such time-related changes are possible. For example, parents could become increasingly aware of the child's problem after the 4th grade test results and take additional measures to improve academic performance.

Finally, our study population is limited to exam takers in both 4th and 7th grade, and test-participation was, as expected, lower among the medicated population than in the non-medicated population. Test-participation also varied between early and late treatment initiators between the 4th and 7th grade tests. We assessed this potential source of bias with a sensitivity analysis. Assuming a null-association among the non-test-participants, we found that the adjusted main effect estimates did not vary greatly from

those reported among test-participants. We caution that our main findings, however, may not apply to children too impaired by ADHD or its co-morbidities to participate in regular school activities.

Consistent with the previously established association between ADHD and poor academic outcomes,[22, 33-35] we found that children medicated for ADHD fare worse academically compared with their non-medicated peers and that their performance generally declines with time, particularly in mathematics, when initiation of drug treatment is delayed. Our data indicate that children in the lower two terciles of test performance before treatment may avoid further declines in mathematics performance if treatment is started earlier; few children in the top tercile initiated stimulant treatment between exams and their performance decline seems independent of when treatment started.

Previous studies lend support to some of our findings. Interestingly, Molina et al. found that mathematics scores were the only functional outcome positively associated with past-year parent-reported medication use during follow-up of participants of the Multimodal Treatment Study of Children with ADHD (MTA), at years 3, 6 and 8 after enrollment, suggesting a beneficial effect of continued medication treatment that may be unique to mathematic achievement.[22] Studies indicate that language disorders and mathematical disability have separate cognitive profiles [36] Possibly, stimulant drug treatment has more positive effects on the cognitive function underlying mathematical ability than on that underlying language ability. Scheffler et al. recently found that parent-reported drug treatment was associated with higher mathematic achievement test scores within a US sample of 594 elementary school children with ADHD, but higher reading scores were dependent upon longer treatment durations.[21] Barbaresi et al. demonstrated that stimulant treatment of children with ADHD was associated with improved reading achievement, decreased school absenteeism and decreased grade retention within a population-based sample of 349 ADHD diagnosed children.[23]

The gender differences in our data could reflect random variability from small numbers, but they might also be consequent to real differences in the academic benefit of stimulant treatment. Girls diagnosed with ADHD present predominantly with symptoms of inattention and have lower levels of hyperactivity than boys with ADHD, [37, 38] which may play a role in how early the disorder is detected and when treatment starts. Previous studies, however, have not found sex nor ADHD sub-type as modifiers of stimulant treatment outcomes. [20, 39, 40]

In sum, the results of this nationwide follow-up study indicate that early, rather than later, initiation of sustained drug treatment is associated with a reduced risk of declining academic performance among boys and girls with ADHD, especially in mathematics.

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Figures and Tables

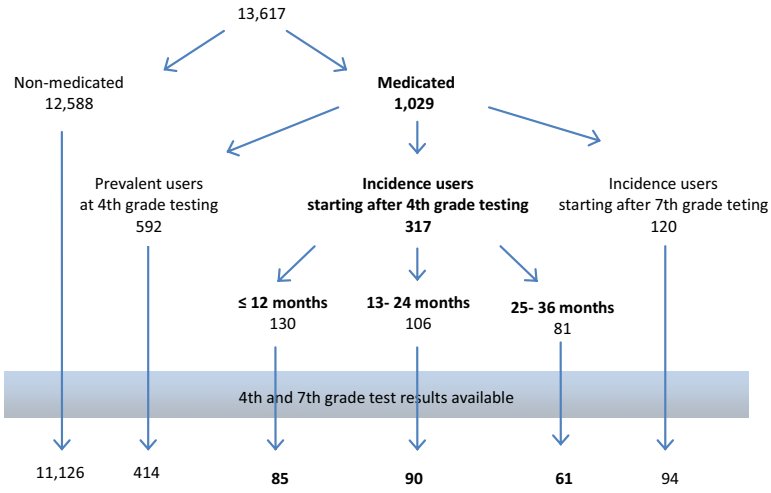

Figure 1. Origin of study population.

Prevalent users are children already being treated before the 4th grade tests. Incidence users are children who began treatment after the 4th grade tests.

Table 1. Characteristics of study population by exposure to ADHD drug treatment.

	Non-medicated population	Medicated population		
		Time since 4th grade test until ADHD drug treatment		
		≤12months	**13-24 months**	**25- 36 months**
Total	N= 11,126 (100%)	N= 85 (100%)	N= 90 (100%)	N= 61 (100%)
Sex				
male	5458 (49%)	59 (69%)	65 (72%)	41 (67%)
female	5668 (51%)	26 (31%)	25 (28%)	20 (33%)
Birth year				
1994	3751(34%)	36 (42%)	34 (38%)	17 (28%)
1995	3636 (33%)	17 (20%)	28 (31%)	22 (36%)
1996	3739 (34%)	32 (38%)	28 (31%)	22 (36%)
Birth month				
Jan-Apr	3682 (33%)	23 (27%)	26 (29%)	18 (30%)
May-Aug	3895(35%)	24 (28%)	27 (30%)	19 (31%)
Sep-Dec	3459 (32%)	38 (45%)	37 (41%)	24 (39%)
Birth place				
urban	6906 (62%)	56 (66%)	64 (71%)	38 (62%)
rural	3522 (32%)	24 (28%)	22 (24%)	19 (31%)
outside Iceland	698 (6%)	5 (6%)	4 (4%)	4 (7%)
School region 4th grade				
urban	6627 (60%)	52 (61%)	64 (71%)	42 (69%)
rural	4499 (40%)	33 (39%)	26 (29%)	19 (31%)
Mathematic test 4th grade percentile rank				
66.7th- 100th	3803 (34%)	10 (12%)	13 (15%)	8 (14%)
33.4th- 66.6th	3699 (34%)	21 (25%)	21 (24%)	14 (24%)
0.1- 33.3rd	3512 (32%)	52 (63%)	55 (62%)	36 (62%)
Language art test 4th grade percentile rank				
66.7th- 100th	3815 (35%)	5 (6%)	8 (9%)	5 (8%)
33.4th- 66.6th	3706 (34%)	23 (27%)	17 (19%)	20 (33%)
0- 33.3rd	3459 (31%)	57 (67%)	63 (72%)	35 (58%)

*Total number of children registered in the Icelandic school system was 13,617 out of which 11,872 (87.2%) took standardized tests in 4th and 7th grade; 746 (72.5%) out of 1,029 in medicated population and 11,126 (88.4%) out of 12,588 in non-medicated population.

Jan, January. Apr, April. Jun, June. Aug, August. Sep, September. Dec, December.

Table 2. Characteristics of ADHD drug treatment among medicated children.

	Time since 4th grade test until ADHD drug treatment		
	≤ 12 months	13-24 months	25-36 months
Children treated with			
any N06BA drug (N06BA)	**N= 85 (100%)**	**N= 90 (100%)**	**N= 61 (100%)**
methylphenidate (N06BA04)	84 (99%)	87 (97%)	55 (90%)
atomoxetine (N06BA09)	10 (12%)	11 (12%)	11 (18%)
both (N06BA04 and N06BA09)	9 (11%)	8 (9%)	5 (8%)
Mean age in years (min-max) at treatment start			
any N06BA drug	9.8 (9.0 to 10.7)	10.7 (10.0 to 11.6)	11.7 (11.0 to 12.7)
Mean number (min-max) of DDDs*			
any N06BA drug between 4th and 7th grade test	427 (10 to 1,972)	325 (10 to 1,188)	175 (6 to 594)
any N06BA drug over total study period	662 (10 to 4,302)	547 (10 to 2,250)	361 (20 to 1,278)
Discontinued treatment early (*< 90 DDDs any N06BA drug)*			
no	67 (79%)	77 (86%)	53 (87%)
yes	18 (21%)	13 (14%)	8 (13%)
Treated on test day 7th grade with any N06BA drug			
yes	34 (40%)	35 (39%)	41 (67%)
no	51 (60%)	55 (61%)	20 (33%)
Treated concurrently† with			
any psychotropic drug (N)	33 (39%)	22 (24%)	25 (41%)
antidepressants (N06A)	25 (29%)	20 (22%)	17 (28%)
amitryptilyn (N06AA09)	12 (14%)	8 (9%)	5 (8%)
antipsychotic (N05A)	12 (14%)	7 (8%)	12 (20%)
anxiolytic or hypnotic & sedative (N05B or N05C)	0 (0%)	1 (1%)	2 (3%)
other psychotropic drugs than above	4 (5%)	5 (6%)	3 (4%)

* One DDD equals to 30 mg of methylphenidate, 80 mg of atomoxetine or 15 mg of amphetamine.

† Concurrent treatment defined as a filled prescription for another psychotropic drug within three months after a prescription fill for an N06BA drug.

DDDs, Defined Daily Doses. Min, minimum. Max, maximum.

Table 3. Crude risks, risk differences and risk ratios of academic decline (5 percentile points or more) according to timing of ADHD drug treatment initiation.

	ADHD drug treatment started number of months after 4th grade test		
Mathematics	**≤ 12 months**	**13-24 months**	**25-36 months**
Mean percentile score change (95%CI)	-0.3 (-4.8 to 4.3)	-5.7 (-10.5 to 1.0)	-9.4 (-14.4 to -1.4)
Declined in performance ≥ 5.0 percentile	28	36	35
Total	68	76	48
Crude risk	41%	47%	73%
Risk difference (95%CI)	0.0 (ref.)	6% (10% to 22%)	32% (14% to 48%)
Risk ratio (95%CI)	1.0 (ref.)	1.2 (0.80 to 1.7)	1.8 (1.3 to 2.5)
Language Arts			
Mean percentile score change (95%CI)	0.7 (-3.4 to 4.8)	-1.7 (-5.4 to 2.0)	-3.4 (-9.2 to 2.5)
Declined in performance ≥ 5.0 percentile	25	31	21
Total	65	72	49
Crude risk	39%	43%	43%
Risk difference (95%CI)	0.0 (ref.)	5% (-12% to 21%)	4.4 (-14% to 22%)
Risk ratio (95%CI)	1.0 (ref.)	1.1 (0.75 to 1.7)	1.1 (0.71 to 1.7)

CI, confidence interval

Table 4 (Part A). The risks and standardized* effect estimates of decline in mathematics according to timing of ADHD drug treatment initiation, stratified by performance level on 4th grade test, sex, concurrent psychotropic drug treatment.

		Time since 4th grade test until ADHD drug treatment		
Performance on 4th grade test		**≤ 12 months**	**13-24 months**	**25-36 months**
	Scored in lowest third			
	Declined in performance ≥ 5.0 percentile	11	14	16
	Total	38	42	26
	Risk	29%	33%	62%
	Scored in mid third			
	Declined in performance ≥ 5.0 percentile	9	12	12
	Total	20	21	14
	Risk	45%	57%	86%
	Scored in highest third			
	Declined in performance ≥ 5.0 percentile	8	10	7
	Total	10	13	8
	Risk	80%	77%	88%
	Standardized risk	42%	47%	73%
	Standardized risk difference (95%CI)	0% (ref.)	5% (-10% to 21%)	31% (14% to 47%)
	Standardized risk ratio (95%CI)	1.0 (ref.)	1.1 (0.79 to 1.6)	1.7 (1.3 to 2.4)
Sex				
	Boys			
	Declined in performance ≥ 5.0 percentile	23	26	22
	Total	47	55	33
	Risk	49%	47%	67%
	Girls			
	Declined in performance ≥ 5.0 percentile	5	10	13
	Total	21	21	15
	Risk	24%	48%	87%
	Standardized risk	42%	47%	72%
	Standardized risk difference (95%CI)	0% (ref.)	6% (-11% to 22%)	31% (13% to 48%)
	Standardized risk ratio (95%CI)	1.0 (ref.)	1.1 (0.79-1.6)	1.7 (1.3 to 2.4)
Concurrent psychotropic drug treatment				
	No			
	Declined in performance ≥ 5.0 percentile	14	26	18
	Total	42	57	27
	Risk	33%	46%	67%
	Yes			
	Declined in performance ≥ 5.0 percentile	14	10	17
	Total	26	19	21
	Risk	54%	53%	81%
	Standardized risk	43%	49%	73%
	Standardized risk difference (95%CI)	0% (ref.)	6% (-12% to 24%)	30% (13% to 48%)
	Standardized risk ratio (95%CI)	1.0 (ref.)	1.1 (0.77-1.7)	1.7 (1.2 to 2.4)

*Standardized to the distribution of the total medicated test-participating population 2003-2008. CI, confidence interval.

Table 4 (Part B). The risks and standardized* effect estimates of decline in language arts according to timing of ADHD drug treatment initiation, stratified by performance level on 4th grade test, sex, concurrent psychotropic drug treatment.

		Time since 4th grade test until ADHD drug treatment		
Performance on 4th grade test		**≤ 12 months**	**13-24 months**	**25-36 months**
	Scored in lowest third			
	Declined in performance ≥ 5.0 percentile	11	16	7
	Total	38	47	24
	Risk	29%	34%	29%
	Scored in mid third			
	Declined in performance ≥ 5.0 percentile	11	10	10
	Total	22	17	20
	Risk	50%	59%	50%
	Scored in highest third			
	Declined in performance ≥ 5.0 percentile	3	5	4
	Total	5	8	5
	Risk	60%	63%	80%
	Standardized risk	38%	44%	41%
	Standardized risk difference (95%CI)	0% (ref.)	6% (-11% to 22%)	3% (-16% to 21%)
	Standardized risk ratio (95%CI)	1.0 (ref.)	1.2 (0.77 to 1.7)	1.1 (0.67 to 1.7)
Sex				
	Boys			
	Declined in performance ≥ 5.0 percentile	14	24	16
	Total	42	51	31
	Risk	33%	47%	52%
	Girls			
	Declined in performance ≥ 5.0 percentile	11	7	5
	Total	23	21	18
	Risk	48%	33%	28%
	Standardized risk	38%	43%	45%
	Standardized risk difference (95%CI)	0% (ref.)	6% (-11% to 22%)	7% (-11% to 26%)
	Standardized risk ratio (95%CI)	1.0 (ref.)	1.2 (0.76 to 1.7)	1.2 (0.76 to 1.9)
Concurrent psychotropic drug treatment				
	No			
	Declined in performance ≥ 5.0 percentile	13	23	8
	Total	38	53	28
	Risk	34%	43%	29%
	Yes			
	Declined in performance ≥ 5.0 percentile	12	8	13
	Total	27	19	21
	Risk	44%	42%	62%
	Standardized risk	39%	43%	44%
	Standardized risk difference (95%CI)	0% (ref.)	4% (-14% to 21%)	5% (-13% to 23%)
	Standardized risk ratio (95%CI)	1.0 (ref.)	1.1 (0.71- 1.7)	1.1 (0.73- 1.8)

*Standardized to the distribution of the total medicated test-participating population 2003- 2008.
CI, confidence interval.

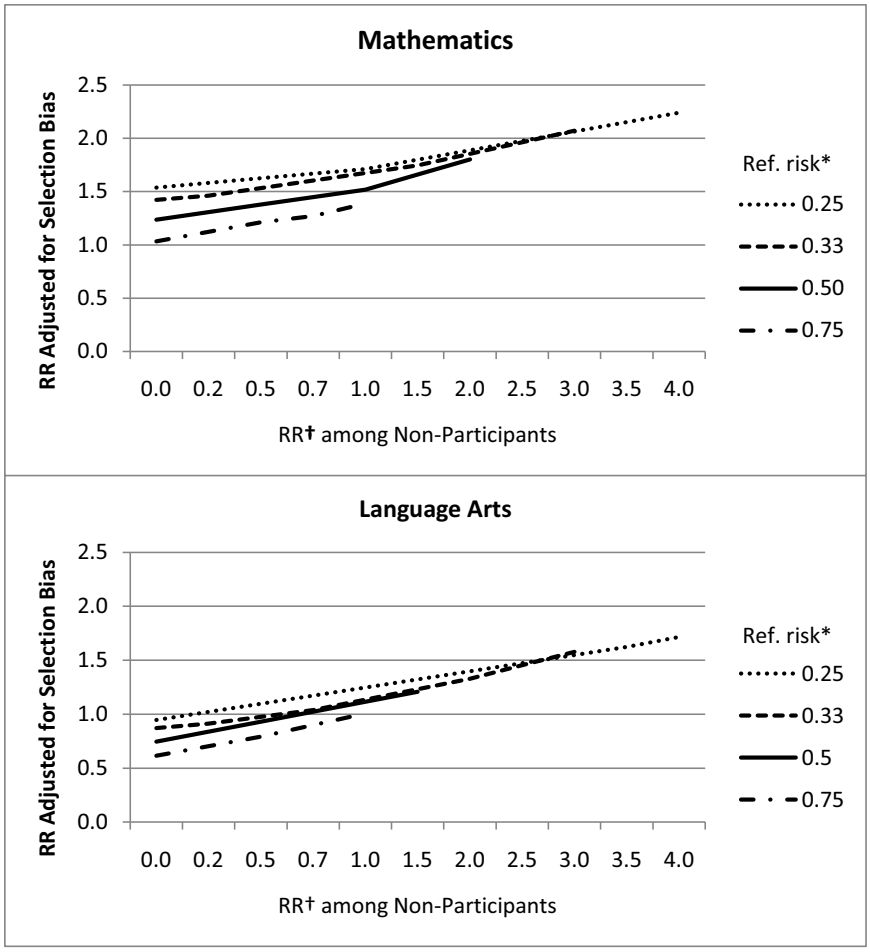

Figure 3. Analysis correcting for possible selection bias, assuming a range of risks of academic decline for non-test-participants. Mathematics decline in upper panel; language arts decline in lower panel.

*Ref. risk, refers to the risk of academic decline in non-test-participants who started treatment early (≤ 12 months after 4th grade tests).

†RR, refers to the risk ratio of academic decline in children who started treatment later (25-36 months after 4th grade tests) versus those who started early (≤ 12 months after 4th grade tests).

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Appendix

a. Anatomical Therapeutic Chemical Drug Classification System

N NERVOUS SYSTEM

N01 ANESTHETICS

N02 ANALGESICS

N03 ANTIEPILEPTICS

N04 ANTI-PARKINSON DRUGS

N05 PSYCHOLEPTICS

N05A ANTIPSYCHOTICS

N05B ANXIOLYTICS

N05C HYPNOTICS AND SEDATIVES

N06 PSYCHOANALEPTICS

N06A ANTIDEPRESSANTS

N06AA Non-selective monoamine reuptake inhibitors

N06AB Selective serotonin reuptake inhibitors

N06AF Monoamine oxidase inhibitors, non-selective

N06AG Monoamine oxidase A inhibitors

N06AX Other antidepressants

N06B PSYCHOSTIMULANTS, AGENTS USED FOR ADHD AND NOOTROPICS

N06BA Centrally acting sympathomimetics

		DDD	unit
N06BA01	amfetamine	15	mg
N06BA02	dexamfetamine	15	mg
N06BA03	metamfetamine	15	mg
N06BA04	methylphenidate	30	mg
N06BA05	pemoline	40	mg
N06BA06	fencamfamin	-	

N06BA07	modafinil	0.3	g
N06BA08	fenozolone	-	
N06BA09	atomoxetine	80[a]	mg
N06BA10	fenetylline	-	
N06BA11	dexmethylphenidate		
N06BA12	lisdexamfetamine	30	mg

N06BC Xanthine derivatives

N06BX Other psychostimulants and nootropics

N06C PSYCHOLEPTICS AND PSYCHOANALEPTICS IN COMBINATION

N06D ANTI-DEMENTIA DRUGS

N07 OTHER NERVOUS SYSTEM DRUGS

a. Since atomoxetine is approved for use both in children, adolescents and in adults, the DDD is based on the treatment of a 70 kg person. The majority of the users will, however, probably be under 18 years of age.

b. Study Approvals

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Anna Birna Almarsdóttir, prófessor
Hofsvallagata 53
107 Reykjavík

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Reykjavík 19. desember 2007

Tilvísun: VSNb2007120009/03-7 Námsverkefni - nemarannsóknir almennar/BH/--

Varðar: 07-152-afg Geðlyfjanotkun meðal barna á Íslandi 2003 til 2007.

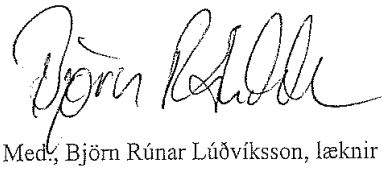
Á fundi sínum 18.12.2007 fjallaði Vísindasiðanefnd um umsókn þína dags. 07.12.2007, vegna ofangreindrar rannsóknaráætlunar. Meðrannsakendur þínir eru Matthías Halldórsson, aðstoðarlandlæknir, Gísli Baldursson, barna- og unglingageðlæknir, Unnur Valdimarsdóttir, dósent og forstöðumaður MLV, Helga Zoega, doktorsnemi og Anna Lára Steingrímsdóttir, meistaranemi.

Markmið rannsóknarinnar er að greina algengi og þróun geðlyfjaflokka meðal barna á Íslandi frá árinu 2003 til 2007. Notkunarmynstur verður greint eftir kyni, aldri og búsetu sjúklings, meðferðarlengd og sérgrein læknis sem ávísar lyfinu. Jafnframt er ætlunin að bera geðlyfjanotkun íslenskra barna saman við notkun meðal barna á Norðurlöndunum. Um er að ræða lýsandi áhorfsrannsókn sem byggir á gögnum úr lyfjagagnagrunni Landlæknisembættisins, tölfræðigrunni Tryggingastofnunar ríkisins (TR) og gögnum úr lyfjagagnagrunnum á Norðurlöndum. Rannsóknin mun ná til barna (0-18 ára) sem leystu út geðlyf á Íslandi (og í nágrannalöndunum) á tímabilinu 2003 til 2007.

Engin heildstæð úttekt hefur áður verið gerð á umfangi og þróun geðlyfjanotkunar meðal barna á Íslandi. Má að einhverju leyti rekja það til skorts á gögnum en nýr lyfjagagnagrunnur Landlæknisembættisins og tölfræðigrunnur Tryggingastofnunar ríkisins hafa opnað tækifæri til faraldsfræðilegrar rannsóknar sem þessarar. Rannsóknin mun enn fremur verða fyrsta samanburðarrannsóknin á geðlyfjanotkun barna á Norðurlöndunum. Hvert og eitt Norðurlandanna hýsir nú gagnagrunn sem nær yfir notkun lyfseðilskyldra lyfja á landsvísu utan sjúkrastofnana. Um er að ræða úrvinnslu gagna úr gagnabanka Landlæknisembættisins og tölfræðigrunni TR um lyfjanotkun. Upplýsingar um þátttakendur umfram dulkóðuð gögn sem þegar liggja hjá Landlæknisembættinu verða ekki notuð til rannsóknarinnar.

Eftir að hafa farið vandlega yfir rannsóknaráætlun þína og innsend gögn sér Vísindasiðanefnd ekki ástæðu til að gera athugasemd við framkvæmd rannsóknarinnar. Endanlegt leyfi nefndarinnar er hér með veitt.Vísindasiðanefnd bendir rannsakendum vinsamlegast á að birta VSN tilvísunarnúmer rannsóknarinnar þar sem vitnað er í leyfi nefndarinnar í birtum greinum um rannsóknina. Jafnframt fer Vísindasiðanefnd fram á að fá send afrit af, eða tilvísun í, birtar greinar um rannsóknina. Rannsakendur eru minntir á að tilkynna rannsóknarlok til nefndarinnar.

Með kveðju,
f.h. Vísindasiðanefndar,



Dr. Med., Björn Rúnar Lúðvíksson, læknir
Formaður Vísindasiðanefndar

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Háskóli Íslands, Læknagarður
Unnur Anna Valdimarsdóttir, dósent
v/Suðurgötu
107 Reykjavík
Ísland

Reykjavík 10. júní 2008
Tilv.: VSNb2008040016/03-7

Efni: Varðar: 08-089-S1-V1 Hefur örvandi geðlyfjameðferð jákvæð áhrif á námsárangur barna með ADHD?

Vísindasiðanefnd þakkar svarbréf þitt, dags. 03.06.2008 vegna áðursendra athugasemda við ofangreinda rannsóknaráætlun sbr. bréf nefndarinnar dags. 05.05. 2008. Í bréfinu koma fram svör og skýringar til samræmis við athugasemdir Vísindasiðanefndar og því fylgdi leyfi frá Persónuvernd dags. 26.05.2008.

Fjallað var um svarbréf þitt og innsend gögn á fundi Vísindasiðanefndar 10.06.2008 og voru þau talin fullnægjandi. Viðbót nr. 1 um að lengja rannsóknartímabilið um tvö ár þannig að það verði 2003 til 2009 í stað 2005 til 2009 eins og fram kom í upphaflegri umsókn er samþykkt. Meðfylgjandi var samþykki Persónuverndar fyrir vinnslu persónuupplýsinga frá árunum 2005 til 2009. Óskað er eftir því að skrifstofu VSN berist afrit af leyfi Persónuverndar fyrir notkun gagna frá 2003 og 2004 þegar það berst rannsakendum.

Rannsóknaráætlunin er endanlega samþykkt af Vísindasiðanefnd.

Vísindasiðanefnd bendir rannsakendum vinsamlegast á að birta VSN tilvísunarnúmer rannsóknarinnar þar sem vitnað er í leyfi nefndarinnar í birtum greinum um rannsóknina. Jafnframt fer Vísindasiðanefnd fram á að fá send afrit af, eða tilvísun í, birtar greinar um rannsóknina. Rannsakendur eru minntir á að tilkynna rannsóknarlok til nefndarinnar.

Með kveðju,
f.h. Vísindasiðanefndar

dr. med., Björn Rúnar Lúðvíksson, læknir, formaður

Miðstöð Háskóla Íslands
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Reykjavík, 26. maí 2008
Tilvísun: 2008040343 ÞÞJ/--

Heimild til vinnslu persónuupplýsinga, skv. 3. mgr. 9. gr. l. nr. 77/2000, og 1., 3. og 5. tölul. 1. mgr. 7. gr. reglna nr. 698/2004 um tilkynningarskylda og leyfisskylda vinnslu persónuupplýsinga, sbr. 33. gr. laga nr. 77/2000 um persónuvernd og meðferð persónuupplýsinga

I.
Umsókn

Persónuvernd hefur borist umsókn frá Unni A. Valdimarsdóttur, f.h. Miðstöðvar Háskóla Íslands í Lýðheilsuvísindum, og Matthíasi Halldórssyni aðstoðarlandlækni, dags. 25. apríl sl., um heimild til vinnslu persónuupplýsinga í tengslum við rannsókn sem ber heitið „Hefur örvandi geðlyfjanotkun jákvæð áhrif á námsárangur barna með ADHD?". Samkvæmt umsókninni er rannsóknin hluti af doktorsnámi Helgu Zoëga í lýðheilsuvísindum og lyfjafaraldsfræði við Háskóla Íslands.

Í umsókninni kemur fram að tilgangur verkefnisins sé að kanna hvort örvandi geðlyfjameðferð hafi jákvæð áhrif á námsárangur barna ADHD. Í öðrum gögnum kemur fram að tilgangur rannsóknar sé að greina notkunarmynstur og faraldsfræði geðlyfja meðal barna á Íslandi árin 2003 til 2008. Einnig er gert ráð fyrir að bera það notkunarmynstur saman við notkun lyfjanna meðal barna á Norðurlöndunum.

Samkvæmt umsókninni byggist val þátttakenda á því að þeir hafi þreytt 4. bekkjar samræmt próf árið 2004 eða 2005, 7. bekkjar samræmt próf þremur árum síðar 2007 eða 2008, og fengið útleyst lyf við ADHD á því tímabili. Þá segir að gögnin ná því yfir lyfjanotkun við ADHD og námsárangur tveggja árganga (f. 1996, 1997) íslenskra skólabarna.

Í umsókninni segir að upplýsingar um lyfjanotkun og námsárangur barna verði aflað úr lyfjagagnagrunni Landlæknisembættisins og úr gagnabanka Námsmatsstofnunar um námsárangur í samræmdum prófum. Ennfremur segir að upplýsingar um einstaklinga umfram dulkóðuð gögn sem þegar liggja hjá Landlæknisembætti og Námsmatsstofnun verði ekki notaðar til rannsóknarinnar.

Í gögnum málsins kemur fram að persónuauðkenni verði dulkóðuð á sama hátt í báðum grunnum, þ.e. lyfjagagnagrunni og gagnabanka Námsmatsstofnunar, og upplýsingarnar síðan keyrðar saman. Einnig segir að lykill að dulkóðun kennitalna verði að tenginu lokinni varðveittur hjá Landlæknisembættinu. skv. öryggishandbók embættisins. Að lokum kemur fram að tengilykli verði eytt eigi síðar en 30. júní 2012.

II.

Lögmæti og leyfisskyld vinnsla persónuupplýsinga

Af framangreindu er ljóst að til að framkvæma rannsóknina þarf að fá aðgang að viðkvæmum persónuupplýsingum hjá tveimur aðilum og samkeyra þær upplýsingar. Nánar til tekið er um að ræða upplýsingar um lyfjameðferð einstaklinga sem greindir hafa verið með ADHD og niðurstöður þeirra í samræmdum prófum.

Vinnsla persónuupplýsinga, þ.á m. samkeyrsla þeirra, er heimil ef uppfyllt er eitthvert skilyrða 8. gr. laga nr. 77/2000. Kemur hér til greina 5. tölul. 1. mgr. þar sem mælt er fyrir um að vinnsla persónuupplýsinga sé heimil sé hún nauðsynleg vegna verks sem unnið er í þágu almannahagsmuna. Ef um er að ræða viðkvæmar persónuupplýsingar í skilningi laga nr. 77/2000 þarf ennfremur eitthvert skilyrða 9. gr. laganna að vera uppfyllt. Umræddar upplýsingar Landlæknisembættisins og gagnabanka Námsmatsstofnunar teljast viðkvæmar persónuupplýsingar í skilningi c-liðar 8. tölul. 2. gr. laga nr. 77/2000. Þarf því að uppfylla bæði skilyrði 8. og 9. gr. laganna.

Það ákvæði sem helst kemur til greina í 1. mgr. 9. gr. er ákvæði 9. tölul. sem kveður á um að vinnsla viðkvæmra persónuupplýsinga sé heimil sé hún nauðsynleg vegna tölfræði- eða vísindarannsókna, enda sé persónuvernd tryggð með tilteknum ráðstöfunum eftir því sem við á. Í framkvæmd hefur ákvæði þetta hins vegar ekki verið talið fullnægjandi heimild eitt og sér, heldur stendur það öðrum heimildum, þ.e upplýstu samþykki (1. tölul.) og lagaheimild (2. tölul.) til fyllingar. Það er því ljóst að heimild til aðgangsveitingar og notkunar rannsakanda á upplýsingunum á sér ekki stoð í neinu ákvæða 1. mgr. 9. gr. laga nr. 77/2000. Persónuvernd getur hins vegar heimilað vinnslu viðkvæmra persónuupplýsinga sem ekki á sér stoð í 1. mgr. 9. gr. telji hún brýna hagsmuni mæla með því, sbr. 3. mgr. 9. gr., og getur bundið slíka heimild þeim skilyrðum sem hún telur nauðsynleg hverju sinni.

Um tilteknar vinnsluaðgerðir með viðkvæmar persónuupplýsingar fer samkvæmt 7. gr. reglna Persónuverndar nr. 698/2004 um tilkynningarskylda og leyfisskylda vinnslu persónuupplýsinga, sbr. 33. gr. laga nr. nr. 77/2000. Þar er mælt fyrir um að samkeyrsla skrár, sem hefur að geyma viðkvæmar persónuupplýsingar, við aðra skrá, hvort sem sú hefur að geyma almennar eða viðkvæmar persónuupplýsingar, sé háð leyfi Persónuverndar. Ber að líta til 3. tölul. 7. gr. reglnanna er segir að við vinnslu upplýsinga um refsiverðan verknað manns og sakaferil, upplýsingar um lyfja-, áfengis- og vímuefnanotkun, kynlíf og kynhegðan, sé háð leyfi Persónuverndar nema vinnslan sé nauðsynlegur og eðlilegur þáttur í starfsemi viðkomandi aðila eða byggist á upplýstu samþykki hins skráða. Einnig er vinnsla upplýsinga um félagsleg vandamál manna eða önnur einkalífsatriði háð leyfi Persónuverndar, sbr. 5. tölul. 7. gr. reglnanna.

Af framangreindu leiðir að bæði aðgangur að umræddum skrám og samkeyrsla þeirra er háð leyfi Persónuverndar. Persónuvernd hefur nú ákveðið, m.a. í ljósi þess tilgangs sem að baki umræddri vinnslu býr, og að virtum ákvæðum 29., 33. og 34. gr. í formálsorðum persónuverndartilskipunarinnar nr. 95/46/EB, að veita umbeðna heimild til vinnslu persónuupplýsinga í þágu rannsóknarinnar: „Hefur örvandi geðlyfjanotkun jákvæð áhrif á

námsárangur barna með ADHD?“.

III.

Leyfisskilmálar sem varða Námsmatsstofnun

Leyfi þetta gildir til 1. júlí 2012 og er bundið eftirfarandi skilyrðum varðandi ábyrgðaraðila þeirra gagna sem afhent verða rannsakendum:

1. Landlæknir og Namsmatsstofnun eru ábyrgðaraðilar þeirra upplýsinga sem þar eru skráðar í skilningi 4. tölul. 2. gr. laga nr. 77/2000. Samkvæmt því bera þessir aðilar ábyrgð á allri meðferð upplýsinganna, þ.á m. miðlun þeirra. Fer forsvarsmaður hvers aðila með allt fyrirsvar gagnvart Persónuvernd hvað þetta varðar, þ.á m. álitaefni, er upp kunna að rísa, um það hvort meðferð upplýsinganna hafi verið í samræmi við lög, reglur og ákvæði þessa leyfis.

2. Hver ábyrgðaraðili skal tryggja að engum öðrum en rannsakanda eða þeim sem starfar á hans ábyrgð verði veittur aðgangur að upplýsingunum. Í því augnamiði skal lagt fyrir Unni A. Valdimarsdóttur og Matthías Halldórsson að undirrita trúnaðaryfirlýsingar þess efnis.

3. Hver ábyrgðaraðili skal skrá og varðveita yfirlit um þær upplýsingar sem veittur er aðgangur að í því skyni að geta fullnægt skyldum sínum samkvæmt 18. gr. laga nr. 77/2000 um upplýsingarétt hins skráða. Í yfirlitinu skal koma fram heiti rannsóknar og nafn ábyrgðaraðila hennar skv. kafla IV.

4. Ef upplýsingar eru afhentar út úr húsnæði ábyrgðaraðila ber að gera það með öruggum hætti með hliðsjón af eðli gagnanna. Óheimilt er að senda upplýsingarnar með faxi eða ódulkóðuðum tölvupósti. Ef aðgangur að upplýsingunum er veittur í húsnæði ábyrgðaraðila, þ.e. án þess að farið verði með gögnin út úr húsakynnum hans, ber að veita rannsakanda fræðslu um gildandi verklags- og öryggisreglur.

5. Ábyrgðaraðilum ber að veita Persónuvernd, starfsmönnum og tilstjónarmönnum hennar allar umbeðnar upplýsingar um vinnslu persónuupplýsinganna sé eftir því leitað í þágu eftirlits.

6. Eðli málsins samkvæmt tekur ábyrgð hvers og eins aðila og skilmálar III. kafla eingöngu til miðlunar á upplýsingum til rannsakanda, en ekki til eftirfarandi vinnslu rannsakanda á upplýsingunum í þágu vísindarannsóknar sinnar.

IV. Leyfisskilmálar er varða rannsakanda

Leyfi þetta gildir til **1. júlí 2012** og er bundið eftirfarandi skilyrðum:

1. Ábyrgðaraðili að vinnslu persónuupplýsinga

Unnur A. Valdimarsdóttir og Matthías Halldórsson (sem hér eftir kallast leyfishafar), teljast vera ábyrgðaraðilar vinnslunnar í skilningi 4. tölul. 2. gr. laga nr. 77/2000. Fara leyfishafar með allt fyrirsvar gagnvart Persónuvernd um alla þætti er varða þetta leyfi, þ. á m. álitaefni, er upp kunna að rísa, um það hvort vinnsla persónuupplýsinga hafi verið í samræmi við lög, reglur og ákvæði þessa leyfis.

2. *Lögbundnir leyfisskilmála*

a. Þegar leyfishafar fer þess á leit við Landlækni og Námsmatsstofnun, að fá aðgang að viðkomandi skrám, ber þeim að framvísa leyfi þessu.
b. Leyfi þetta er veitt í ljósi þess að ábyrgðarmenn umræddra skráa hafa lýst því yfir að þeir séu því samþykkir fyrir sitt leyti að leyfishafar fái aðgang að þeim.

3. Lögmæt vinnsla persónuupplýsinga og þagnarskylda

a. Leyfishafar bera ábyrgð á því að vinnsla persónuupplýsinga vegna rannsóknarinnar fullnægi ávallt kröfum 1. mgr. 7. gr. laga nr. 77/2000.
b. Þagnarskylda hvílir á leyfishöfum og öðrum þeim sem koma að verkefninu um þær upplýsingar sem unnið er með. Þagnarskylda helst að rannsókn lokinni.
c. Leyfi þetta heimilar einvörðungu að safnað verði þeim upplýsingum sem gildi hafa fyrir rannsókn leyfishafa og samrýmast markmiðum hennar.

4. Auðkenning rannsóknargagna

a. Rannsóknargögn skulu auðkennd með dulkóðunarnúmerum. Þó er heimilt að notast við kennitölur þegar fram fer samkeyrsla lyfjameðferðarupplýsinga og gagnabanka Námsmatsstofnunar. Að samkeyrslu lokinni skal afmá kennitölur af gögnum og setja númer í þeirra stað.
b. Heimilt er að varðveita lykil sem gerir kleift að tengja saman númer og kennitölur. Skal hann geymdur á öruggum stað og varðveittur aðskilinn frá öðrum rannsóknargögnum. Skal honum eytt eigi síðar en 1. júlí 2012.

5. Öryggi við vinnslu persónuupplýsinga

Leyfishafa ber að gera viðeigandi tæknilegar og skipulagslegar öryggisráðstafanir til að vernda persónuupplýsingar gegn óleyfilegum aðgangi í samræmi við 11. og 12. gr. laga nr. 77/2000. Þar er meðal annars áskilið:

a. að beita skuli ráðstöfunum sem tryggja nægilegt öryggi miðað við áhættu af vinnslunni og eðli þeirra gagna sem verja á, með hliðsjón af nýjustu tækni og kostnaði við framkvæmd þeirra; og
b. að tryggja skuli að áhættumat og öryggisráðstafanir við vinnslu persónuupplýsinga séu í samræmi við lög, reglur og fyrirmæli Persónuverndar um hvernig tryggja skal öryggi upplýsinga, þ.m.t. þá staðla sem hún ákveður að skuli fylgt.

Leyfishafi ber ábyrgð á því að hver sá er starfar í umboði hans og hefur aðgang að persónuupplýsingum vinni aðeins með þær í samræmi við skýr fyrirmæli sem hann gefur og að því marki að falli innan skilyrða leyfis þessa, nema lög mæli fyrir á annan veg, sbr. 3. mgr. 13. gr. laga nr. 77/2000.

6. Almennir skilmálar

a. Ávallt skal tryggt að rannsóknargögn séu varðveitt á tryggum stað og aðeins þar sem lögum samkvæmt er heimilt að varðveita þau.
b. Leyfishafi ber ábyrgð á að farið sé með öll persónuauðkennd gögn í samræmi við lög, reglur og ákvæði þessa leyfis.
c. Leyfishafi skal ábyrgjast að engir aðrir en hann fái í hendur persónugreinanleg gögn sem sérstaklega verður aflað í þágu þessarar rannsóknar.
d. Óski leyfishafi þess að hætta rannsókn ber honum að leggja þetta leyfi inn til Persónuverndar á skriflegan og sannanlegan hátt. Skal þá tilgreina hvort þeim persónuupplýsingum, sem unnar voru á grundvelli þessa leyfis, hafi verið eytt. Að öðrum kosti úrskurðar Persónuvernd um hvort persónuupplýsingunum skuli eytt eða þær varðveittar með ákveðnum skilyrðum.
e. Leyfishafa ber að veita Persónuvernd, starfsmönnum og tilsjónarmönnum hennar allar umbeðnar upplýsingar um vinnslu persónuupplýsinga sé eftir því leitað í þágu eftirlits. Brot á ákvæði þessu getur varðað afturköllun á leyfinu.

f. Persónuvernd getur látið gera úttekt á því hvort leyfishafi fullnægi skilyrðum laga nr. 77/2000 og reglna sem settar eru samkvæmt þeim eða einstökum fyrirmælum. Getur Persónuvernd ákveðið að hann skuli greiða þann kostnað sem af því hlýst. Persónuvernd getur einnig ákveðið að leyfishafi greiði kostnað við úttekt á starfsemi, við undirbúning útgáfu vinnsluleyfis og annarrar afgreiðslu. Persónuvernd skal þá gæta þess að sá sérfræðingur, sem framkvæmir umrædda úttekt, undirriti yfirlýsingu um að hann lofi að gæta þagmælsku um það sem hann fær vitneskju um í starfsemi sinni og leynt ber að fara eftir lögum eða eðli máls. Brot á slíkri þagnarskyldu varðar refsingu samkvæmt 136. gr. almennra hegningarlaga. Þagnarskyldan helst þótt látið sé af starfi.

g. Leyfi þetta er háð því skilyrði að einungis verði safnað þeim upplýsingum sem *nauðsynlegar* eru vegna rannsóknarinnar.

Virðingarfyllst

Sigrún Jóhannesdóttir

Miðstöð Háskóla Íslands í Lýðheilsuvísindum
Unnur A. Valdimarsdóttir, dósent
v/ Hringbraut
101 REYKJAVÍK

Persónuvernd

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Reykjavík, 7. október 2008
Tilvísun: 2008040343 ÞÞJ/--

Persónuvernd hefur borist erindi frá yður þar sem óskað er eftir að breytingar verði gerðar á leyfi til vinnslu persónuupplýsinga sem gefið var út vegna rannsóknarinnar „Hefur örvandi geðlyfjanotkun jákvæð áhrif á námsárangur barna með ADHD?“ þann 26. maí árið 2008. Í erindi yðar segir eftirfarandi m.a.

„Undirrituð sækja hér með um heimild Persónuverndar til vinnslu persónuupplýsinga frá árunum 2003, 2004 og 2009 úr lyfjagagnagrunni landlæknis og gagnagrunni Námsmatsstofnunar um námsárangur barna í samræmdum grunnskólaprófum.“

Einnig segir í bréfinu:

„Óskin er sett fram með tilliti til nýrra lyfjalaga, sem samþykkt voru á Alþingi 30. maí 2008 og öðlast gildi 1. október nk. Ákvæði þeirra kveða á um að lengingu varðveislutíma gagna í lyfjagagnagrunni úr þremur árum í þrjátíu. Við það myndi rannsóknartímabil doktorsverkefnis Helgu Zoega lengjast um tæp þrjú, yrði frá 1. janúar 2003 til 31. desember 2009.

Að öllu öðru leyti mun vinnsla persónuupplýsinga vegna umræddrar rannsóknar verða í samræmi við þegar veitta leyfisskilmála Persónuverndar.“

Það tilkynnist yður hér með að Persónuvernd gerir ekki athugasemdir við þá breytingu á framkvæmd rannsóknar sem felst í að rannsóknartímabil rannsóknarinnar „Hefur örvandi geðlyfjanotkun jákvæð áhrif á námsárangur barna með ADHD?” lengist um tæp þrjú ár að því tilskyldu að við framkvæmd rannsóknar verði í einu og öllu farið að skilmálum leyfisins sem gefið var út vegna rannsóknarinnar þann 26. maí 2008.

Virðingarfyllst

Þórunn J. Finnbogadóttir