A Nationwide Study of ADHD Drug Use among Adults in Iceland 2003-2012

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Thesis for the degree of Master of Public Health Sciences
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HÁSKÓLI ÍSLANDS

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Lyfjameðferð fullorðinni með ADHD á Íslandi 2003-2012

Algengi, nýgengi og meðferðarlengd

Drífa Pálín Geirs

Ritgerð til meistaragráðu í lýðheilsuvísindum

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Abstract

In this study we leveraged on complete nationwide prescription data for the total adult population in Iceland (N=227,000), to examine how attention-deficit/hyperactivity disorder (ADHD) drugs have been used over the past decade. In particular we aimed to describe the prevalence, incidence and duration of use of stimulants and atomoxetine, among adults (≥19 years) in Iceland, with regard to sex, age, type of drug and specialty of the prescribing physician.

Our results indicate that the 1-year period prevalence of ADHD drug use rose, from 2.9 to 12.2 per 1,000 adults between 2003 and 2012, with the most pronounced increases among young adults (19-24 years). The annual incidence increased 3-fold, similarly among men and women. Extended release methylphenidate formulations were the most commonly used ADHD drugs. Specialists in psychiatry initiated treatment in 79% of new adult ADHD drug users. The proportion of users still receiving treatment after one year varied from 43.0% (19-24 years), 57.2% (25-49 years) to 47.5% (50+ years). After 3 years, the corresponding proportions still on treatment were 12.4%, 24.5% and 24.3%, and after 5 years 7.9%, 15.9% and 16.8%.

These results of increasing ADHD drug use and short treatment durations call for further investigation of the quality of treatment regimens for adults with ADHD and better follow-up of patients treated with ADHD drugs.

Keywords: attention deficit/ hyperactivity disorder; ADHD; pharmacoepidemiology; drug utilization; treatment duration; central nervous system stimulants; adults

Ágrip

Rannsóknir sýna að 50% einstaklinga sem greindir eru með einkenni athyglisbrests með ofvirkni (Attention Deficit Hyperactivity Disorder; ADHD) í æsku hafa enn einkenni á fullorðinsárum. Rannsóknir sem gerðar hafa verið á umfangi og þróun notkunar ADHD lyfja á Íslandi hafa fyrst og fremst snúið að börnum. Engin heildstæð úttekt hefur verið gerð á ADHD lyfjanotkun hjá fullorðnum einstaklingum á Íslandi.

Markmið þessarar rannsóknar var að lýsa algengi og nýgengi ADHD lyfjanotkunar sem og meðferðarlengd meðal fullorðinna á Íslandi á árunum 2003-2012. Mynstur notkunar var greint með tilliti til kyns, aldurs, tegund lyfja og sérgrein læknis sem ávísaði lyfinu. Rannsóknin er lýsandi lyfjanotkunarrannsókn sem byggir á gögnum úr Lyfjagagnagrunni Embætti landlæknis. Þýði rannsóknarinnar voru einstaklingar búsettir á Íslandi eldri en 18 ára á rannsóknartímabilinu.

Árlegt algengi ADHD lyfjanotkunar hækkaði úr 2,9 á hverja 1000 fullorðna árið 2003 í 12,2 á hverja 1000 árið 2012. Aukningin var mest áberandi hjá aldurshópnum 19-24 ára. Þreföld aukning var á nýjum notendum yfir rannsóknartímabilið. Langvirkandi metýlfenidat reyndist vera algengasta ADHD lyfið. Upphaf ADHD lyfjameðferðar hófst í 79% tilfella hjá sérfræðingum á sviði geðlækninga. Hlutfall þeirra notenda sem enn voru í meðferð eftir 1 ár var frá 43.0% (19-24 ára), 57.2% (25-49 ára) og 47.5% (50 ára og eldri). Eftir þrjú ár, voru 12.4%, 24.5% og 24.3% einstaklinga í sömu aldurshópum enn í meðferð og 7.9%, 15.9% og 16.8% eftir 5 ár.

Niðurstöður okkar sýna töluverða aukningu á notkun ADHD lyfja hjá fullorðnum á Íslandi síðastliðinn áratug en jafnframt að meirihluti einstaklinga hættir notkun á innan við ári frá upphafi meðferðar. Bendir þetta til að nauðsynlegt sé að skoða nánar gæði meðferðarúrræða fyrir fullorðna einstaklinga með ADHD sem og eftirfylgni í lyfjameðferð á Íslandi.

Lykilorð: athyglisbrestur með ofvirkni; ADHD; lyfjafaraldsfræði; lyfjanotkun; meðferðarlengd; örvandi lyf; fullorðnir

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To my beautiful, clever, funny and cheeky little girl, mommy is doing this all for you. Thank you for being my inspiration, thank you for showing me how wonderful the world is and thank you for making me want to be a better person. “*Veistu hvað ég elska þig mikið? – Já, svona og svona!”*

Table of contents

List of figures

List of tables

List of abbreviations

ADHD	Attention-Deficit/Hyperactivity Disorder
ATC	Anatomical Therapeutic Chemical
DDD	Defined Daily Dose
DSM-IV	Diagnostic and Statistical Manual of Mental Disorders, fourth edition
DSM-5	Diagnostic and Statistical Manual of Mental Disorders, fifth edition
EU	European Union
ICD-10	International Classification of Disease
INCB	International Narcotics Control Board
LSH	Landspítali University Hospital (Landspítali Háskólasjúkrahús)
NICE	National Institute for Health and Clinical Excellence
UK	United Kingdom
US	United States
WHO	World Health Organization

Introduction

1 Attention-Deficit/Hyperactivity Disorder

Attention-Deficit/Hyperactivity Disorder (ADHD) is among the most commonly diagnosed psychiatric disorders throughout most of Europe and the United States (US) (Kooij et al., 2010). It was long thought that ADHD was limited to children and adolescents and had no persistent impact in adult life. However, more recent studies have shown that ADHD symptoms are still present in about 50% of individuals who have been identified in childhood (Biederman et al., 2010; Kooij et al., 2010; Mannuzza et al., 1993; Mannuzza et al., 1991; Wilens et al., 2011). Studies on the extent of ADHD indicate that the prevalence among children and adolescents is between 3-9% of the general population and up to 5% in adults (Kessler et al., 2006; Polanczyk et al., 2007).

1.1 Adult ADHD

ADHD is a common heterogeneous behavioral disorder characterized by the primary symptoms of hyperactivity, impulsivity and inattention (National Institute for Health and Clinical Excellence, 2008). As the varying nature of the disorder can lead to different manifestation of symptoms among patient the symptomology has been categories into three subtypes, predominantly inattentive type, predominantly hyperactive-impulsive type and combined type (American Psychiatric Association., 2000; Kooij et al., 2010; National Institute for Health and Clinical Excellence, 2008). According to the fourth edition of Diagnostic and Statistical Manual of Mental Disorders (DSM-IV) (American Psychiatric Association., 2000) the current diagnosis criteria includes a list of 18 symptom items, with nine for hyperactivity-impulsivity and nine for inattention. The definition of the condition is more restricted in the International Classification of Disease (ICD-10) (World Health Organisation, 1993), and is referred to as hyperkinetic disorder.

Although all of the symptoms can persevere from childhood into adulthood, inattention tends to be more visible amongst adults whereas hyperactivity can diminish throughout the course of the condition (Asherson et al., 2012; Faraone et al., 2000; McCarthy et al., 2013). Adults with ADHD also show symptoms of inability to sustain attention, disorganization, forgetfulness and poor time management skills. Furthermore, some adults continue to have problems with symptoms of hyperactivity and impulsivity; and mood instability such as irritability, volatility and swift mood changes (Skirrow et al., 2009). Though mood instability is not considered a core symptom of ADHD, it is increasingly being recognized as a related symptom, especially amongst adults with untreated ADHD (McCarthy et al., 2013; Skirrow et al., 2009). These differences in symptomology from childhood to adulthood are not currently addressed, in either of the diagnostic criteria. The issues pertaining the differences in symptomology will be discussed further in section 1.1.1.

Co-morbidity is very common among both adults and children with ADHD. It has been estimated that almost two-thirds of children have one or more co-morbid conditions and three-fourths of adults have at

least one other disorder (Kooij et al., 2010). Co-morbid condition can include oppositional defiant and conduct disorder, anxiety and mood disorders, tics or Tourette syndrome, learning disorders, pervasive developmental disorders, personality and substance use disorders (Biederman et al., 1993; Kooij et al., 2010; Murphy & Barkley, 1996; Murphy et al., 2002; Reinhardt & Reinhardt, 2013).

During childhood, boys are about three to five times more likely to be diagnosed with ADHD than girls (Kooij et al., 2010). However, research suggests that in adulthood the sexes are equally affected by ADHD, resulting in more women than men diagnosed for the first time as adults (Biederman et al., 2002; Fayyad et al., 2007; Kooij et al., 2010; Nutt et al., 2007; Simon et al., 2009).

As seen in figure 1, developed by Asherson et al. (2012), the psychosocial burden of adult ADHD is quite vast and can affect most aspects of day to day life. As well as the increased risk of other psychopathological conditions, ADHD in adults can have adverse effects on relationships and increased rates of both accidents and criminal behavior (Asherson et al., 2012; Chang et al., 2014; Lichtenstein et al., 2012; Moya et al., 2014; Reinhardt & Reinhardt, 2013).

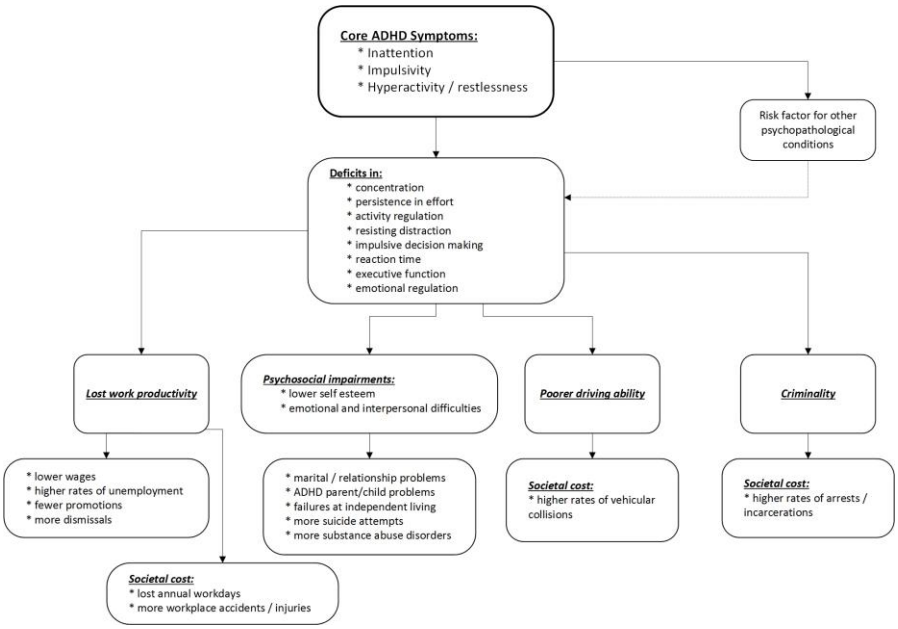

Figure 1: Psychosocial burden of adult ADHD

Reprinted from "Under diagnosis of adult ADHD: cultural influences and societal burden," by Asherson, et al., 2012, *Journal of attention disorders*, 16(5 Suppl), p. 275.

1.1.1 Diagnosis

The most commonly used criteria used for diagnosis are either based the ICD-10 (see appendix A) - then as hyperkinetic disorder or with the DSM-IV (see appendix A). As there is no single definitive test for ADHD, whether psychological or biological, the diagnosis should follow a multi-agency and multi-professional approach. Due to the heterogeneous nature of the disorder, establishing the diagnosis in adults relies on a thorough examination performed by a specialist. The examination needs to assess any psychopathology – both past and present, impairments caused by the symptoms, the age of onset

and course of the symptoms, how the disorder presents itself in different circumstances and if the disorder is the only possible explanation for the symptoms (Asherson et al., 2012; National Institute for Health and Clinical Excellence, 2009).

The ADHD diagnosis criteria have been at the center of constant controversies over the years. The main criticisms can be summarized into three categories technical, sociological and validity-based (National Institute for Health and Clinical Excellence, 2009). The focus of the technical critiques is on the practicableness of the diagnosis criteria. Specifically in regards to the wording and specificity of the criteria, lack of criteria and guidance for adult diagnosis and accurate differentiation from coexisting conditions (National Institute for Health and Clinical Excellence, 2009). The sociological critiques focus on the fact that the diagnosis criteria does not provide adequate adjustments and considerations for sex, class or ethnicity, the effects of social pressure, stereotyping and the inflated media reports (National Institute for Health and Clinical Excellence, 2009). Finally, the validity critiques question the very existence of the disorder and emphasize the institutional and social conditions upon which they claim the diagnosis is contingent (National Institute for Health and Clinical Excellence, 2009).

The issue of adult diagnosis criteria in DSM-IV was addressed in 2013, when the American Psychiatric Association released the fifth edition of the Diagnostic and Statistical Manual of Mental Disorders (DSM-5). The changes in the criteria included an increase in the permitted age of onset; the addition of age-adjusted descriptions of ADHD symptoms that are suitable for use in adults; the inclusion of behaviors that reflect deficits of executive functions and emotional instability; an adjustment of symptom threshold; to allow co-morbidity with pervasive developmental disorders (see table 1) (American Psychiatric Association., 2013; UK Adult ADHD Network, 2013).

Table 1: Changes in the DSM-5

- Examples added to accommodate a lifespan relevance of each symptom and to improve clarity
- Cross-situational strengthened to “several” symptoms in each setting
- The onset criterion changed from “symptoms that caused impairment were present before age 7 years” to “several inattentive or hyperactive-impulsive symptoms were present prior to age 12”;
- The three subtypes have been replaced with presentation specifiers that map directly to the prior subtypes
- Autism is now included in the criterion as a co-morbid disorder
- The symptom threshold for adults changed to reflect their substantial evidence of clinically significant ADHD impairment, with the cutoff for ADHD of five symptoms, instead of six required for younger persons, both for inattention and for hyperactivity and impulsivity**.**

Note: adapted from *Highlights of Changes from DSM-IV-TR to DSM-5,* p.2, by American Psychiatric Association, 2013, Arlington,VA: American Psychiatric Publishing.

As international guidelines have not been revised since DSM-5’s publication, the recommended criteria to be used for all ages is the previous symptom criteria, though with adjusted age-appropriate changes in behavior (National Institute for Health and Clinical Excellence, 2009). In 2005, Asherson comprised an age-appropriate criterion that is currently being used in the diagnosis for adults (see table 2).

Table 2: Age-adjusted ADHD symptoms for use with adults

Inattention
• *Often fails to give close attention to detail.* Has difficulty remembering where they put things. At work, this may lead to costly errors. Tasks that require detail and are considered tedious (eg, income tax returns) become very stressful. This may include overly 'perfectionist'-like and rigid behavior, and needing too much time for tasks involving details in order to prevent forgetting any of them
• *Often has difficulty sustaining attention.* Inability to complete routine tasks (e.g., tidying a room or mowing the lawn) without forgetting the objective and starting something else. Inability to sustain sufficient attention to read a book that is not of special interest, although there is no reading disorder. Inability to keep accounts, write letters, or pay bills. Attention often can be sustained during exciting, new, or interesting activities (e.g., using internet, chatting, and computer games). This does not exclude the criterion when boring activities are not completed
• *Often does not seem to listen when spoken to.* Receive complaints that they do not listen or that it is difficult to gain their attention. Even where they appear to have heard, they forget what was said and do not follow through. These complaints reflect a sense that they are 'not always in the room,' 'not all there,' or 'not tuned in'
• *Fails to follow through on instructions and complete tasks.* Adults with ADHD may observe difficulty in following other people's instructions (eg, inability to read or follow instructions in a manual for appliances). Failure to keep commitments undertaken (eg, work around the house)
• *Difficulty organizing tasks or activities.* Recurrent errors (eg, lateness, missed appointments, missing critical deadlines). Sometimes a deficit in this area is seen in the amount of delegation to others such as secretary at work or spouse at home
• *Avoids or dislikes sustained mental effort.* Puts off tasks such as responding to letters, completing tax returns, organizing old papers, paying bills, establishing a will. These adults often complain of procrastination
• *Often loses things needed for tasks* (eg, misplacing purse, wallet, keys, assignments from work, where car is parked, tools, and even children!)
• *Easily distracted by extraneous stimuli.* Subjectively experience distractibility and describe ways in which they try to overcome this. This may include listening to white noise, multi-tasking, requiring absolute quiet, or creating an emergency to achieve adequate states of arousal to complete tasks. Often has many projects going simultaneously and has trouble with completion of tasks
• *Forgetful in daily activities.* May complain of memory problems. For example, a patient may head out to the supermarket with a list of things, but end up coming home having failed to complete their tasks or having purchased something other than what they intended to buy
Hyperactivity
• *Fidgets with hands or feet.* This item may be observed, but it is also useful to ask patient about this. Fidgeting may include picking their fingers, shaking knees, tapping hands or feet, and changing position. Fidgeting is most likely to be observed while the patient is waiting in the waiting area of the clinic
• *Leaves seat in situations in which remaining seated is usual.* Adults may be restless. For example, patients become frustrated with dinners out in restaurants or are unable to sit during conversations, meetings, and conferences. This may also manifest as a strong internal feeling of restlessness when waiting
• *Wanders or runs excessively or feels frequent subjective feelings of restlessness.* Adults may describe their subjective sense of always needing to be 'on the go,' or feeling more comfortable with stimulating activities than with more sedentary types of recreation. They may pace during the interview
• *Difficulty engaging in leisure activities quietly.* Adults may describe an unwillingness to/dislike of staying home or engaging in quiet activities. They may complain that they are workaholics, in which case detailed examples should be given
• *Often 'on the go' or act as if 'driven by a motor.'* Significant others may have a sense of the exhausting and frenetic pace of these adults. Adults with ADHD will often appear to expect the same frenetic pace from others. Holidays may be described as draining since there is no opportunity for rest
• *Talks excessively.* Excessive talking makes dialogue difficult. This may interfere with a spouse's sense of 'being heard' or achieving intimacy. This chatter may be experienced as nagging and may interfere with normal social interactions. Clowning around, repartee, or other means of dominating conversations may mask an inability to engage in give-and-take conversation
Impulsivity
• *Answers before questions have been completed.* This will usually be observed during the interview. This may also be experienced by probands as a subjective sense of other people talking too slowly and finding it difficult to wait for them to finish. Tendency to say what comes to mind without considering timing or appropriateness
• *Difficulty waiting in turn.* Adults find it difficult to wait for others to finish tasks at their own pace, such as children. They may feel irritated waiting in line or in a restaurant and may be aware of their own intense efforts to force themselves to wait. Some adults compensate for this by carrying something to do at all times
• *Interrupts or intrudes on others.* This is most often experienced by adults as social ineptness at social gatherings or even with close friends. An example might be inability to watch others struggle with a task (such as trying to open a door with a key) without jumping in to try the task for themselves
Note: reprinted from *Handbook for Attention Deficit Hyperactivity Disorder in Adults* p.11-12, by UK Adult ADHD Network, 2013, London: Springer Healthcare Limited.

1.1.2 Treatment options

According to both the clinical guidelines issued by the National Institute for Health and Clinical Excellence (NICE) (National Institute for Health and Clinical Excellence, 2008) and the consensus statement by the European Network Adult ADHD (Kooij et al., 2010), a multimodal approach should be taken in the treatment of children and adults with ADHD. The multimodal approach includes psycho-education, pharmacotherapy, coaching, cognitive behavior therapy and family therapy. As adults face increased responsibilities and demands of life, a greater emphasis is on the need for different range of psychological treatments for adults (Kooij et al., 2010). Treatment options should always be guided by the severity of symptoms and the association of co-morbid disorders (Kooij et al., 2010). The guidelines recognize the importance ADHD management services dedicated to adults. They recommend that these adult dedicated services should include monitor drug treatment, provide psychological support, provide child-adult transitional services and provide first-time diagnosis (National Institute for Health and Clinical Excellence, 2009).

As previously stated the heterogeneous nature of the disorder paired with considerable co-morbidity can lead to idiosyncratic response to treatment. Though there are those who do not benefit from any of the recommended treatment option, studies assessing the long-term outcome versus non-treatment has shown a clear benefit of available treatment options. A recent systematic review (Shaw et al., 2012) found that treated individuals with ADHD had a more positive long-term outcomes compared to untreated individuals. Positive benefits were observed in academic, driving, self-esteem, social function, obesity and drug use/addictive behavior outcomes (Dias et al., 2013; Shaw et al., 2012). Studies have also shown that adults with untreated ADHD have higher rates of academic failure, lower socio economic status, increased risk of addiction, criminality and accidents, have fewer social relationships and have an increased risk of the development of co-morbid psychiatric symptoms such as anxiety and depression (Chang et al., 2014; Faraone et al., 2000; Kessler et al., 2006; Kooij et al., 2010; Mannuzza et al., 2008; McCarthy et al., 2009; Moya et al., 2014).

1.1.2.1 Pharmacological treatment

In Europe, stimulants such as methylphenidate or dexamphetamine are considered the first-line treatment option for both children and adults. This recommendation is based on the vast data available on the safety and efficacy of stimulants (Banaschewski et al., 2006; National Institute for Health and Clinical Excellence, 2009). The non-stimulant, atomoxetine, is considered second-line drug in cases of treatment failure, intolerance or contra-indication to stimulants and is recommended if there is a previous history of substance abuse (Kooij et al., 2010; National Institute for Health and Clinical Excellence, 2008). Less common, is the use of such drugs as clonidine, bupropion, modafinil, antidepressants and atypical antipsychotics, in ADHD treatment (see table 3). Though these less common drugs are not nearly as effective as stimulants in treating ADHD symptoms, they can be valuable as a part of multi pharmacological treatment or in dealing with co-morbid symptoms (Kooij et al., 2010; National Institute for Health and Clinical Excellence, 2008). For the purpose of this study, we will use the term ADHD drugs for the combination of stimulants and non-stimulants used in the treatment of ADHD.

In spite of these guideline recommendations, in 2013, the licensed approval to use stimulant and non-stimulant pharmacotherapy for adults with ADHD was very limited both within the European Union (EU) and outside (European Medicines Agency, 2009; Huss et al., 2014). Currently, in 2014, only three countries within the EU have approved medications for treatment of newly diagnosed adult ADHD patients, i.e., methylphenidate in Germany (Medice, 2011; Ramos-Quiroga et al., 2013) and atomoxetine in the UK and Denmark (Institut for Rationel Farmakoterapi, 2013; McKee, 2013 Jun 3; Medicines and Healthcare Products Regulatory Agency, 2013) – causing a mixed message and conflicting directives to the public.

The short-term efficacy and safety of pharmacological treatments has been well established among children (Kooij et al., 2010; National Institute for Health and Clinical Excellence, 2008), but documentation for adults is still somewhat scarce. However, findings from a recent systematic review (Fredriksen et al., 2013) suggests that the pharmacologic treatment of ADHD in adults leads to higher educational levels and occupational status, better self-esteem, fewer accidents, and less delinquency.

Table 3: Drugs used in the pharmacological treatment of ADHD

	Main indication for use	**Age authorized for use in the EU**
Methylphenidate	ADHD	Only licensed in the use for children and adolescents. Exception: Germany authorized for all ages since 2011
Dexamfetamine [a] / Amphetamine [b]	ADHD / Narcolepsy	Licensed in the use for children from the age of 3
Atomoxetine	ADHD	Only licensed in the use for children and adolescents. Exceptions: UK and Denmark, all ages since 2013.
Clonidine [c]	Hypertension, Migraine and menopausal flushing	Only licensed for adult use.
Bupropion [d]	Smoking cessation aid	Only licensed for adult use.
Modafinil [e]	Narcolepsy and other sleep disorders	Only licensed for adult use.
Antidepressants	Depression, anxiety, compulsive disorder, eating disorders, Tourette's syndrome, chronic pain, post-traumatic stress disorder etc.	Licensed from the age of 6, though depended on the indication.
Atypical antipsychotics	Psychoses, bipolar disorder, psychotic depression, obsessive-compulsive disorder, Tourette's syndrome and autistic spectrum disorders etc.	Licensed from the age of 5, though depended on the indication and pre-existing conditions.

Note: table comprised by author.

Adapted from *Attention deficit hyperactivity disorder: Diagnosis and management of ADHD in children, young people and adults* (p. 235-291), by National Institute for Health and Clinical Excellence, 2009, London: British Psychological Society.

a. Not available in Iceland
b. See table 4
c. Off-licensed use for tics, Tourette's syndrome and ADHD for all ages
d. Not licensed in the use for ADHD treatment
e. Off-licensed use for ADHD for all ages

1.1.2.2 Psychological treatment

Research suggests that psychological treatment, especially cognitive behavioral therapy, can prove valuable in the treatment of ADHD in adults (UK Adult ADHD Network, 2013). The combination of cognitive behavioral therapy with medication has been found more beneficial in treating ADHD symptoms than medication alone (Emilsson et al., 2011; Hirvikoski et al., 2011; Rostain & Ramsay, 2006; Safren et al., 2005; Safren et al., 2010; Solanto et al., 2010).

Guidelines state that cognitive behavioral therapy should be considered if drug therapy is ineffective; if a person decides against drug treatment or if symptoms are remitting and functional impairments are mild or moderate (National Institute for Health and Clinical Excellence, 2008).

1.1.3 Diagnosis and treatment options in Iceland

The first national guidelines (Baldursson et al., 2012) for the diagnosis and treatment of ADHD in Iceland were issued by the Directorate of Health in 2007. These guidelines were then renewed in 2012 after the International Narcotics Control Board (INCB) issued a warning to the Icelandic government expressing concern over the amounts of sold stimulants in Iceland (International Narcotics Control Board, 2011). Currently, Iceland follows the same diagnostic criteria and procedures as recommended in international guidelines (Baldursson et al., 2012; Emilsson et al., 2009). Figure 2 illustrates the current diagnosis procedure used in Landspítali University Hospital (Landspítali Háskólasjúkrahús; LSH) for adult ADHD.

Though LSH has been involved in diagnosing ADHD in adults since 2004, there have not been any dedicated services available for adults within the health care system (Emilsson et al., 2009). The number of specialists taking on diagnosis and treatment management is, and has been, very limited. This has led to a strenuous waiting period, during both the diagnosis phase as well as the treatment phase (Emilsson, 2013). Both international and national guidelines have recommended the implementation of ADHD service focusing on adults (Baldursson et al., 2012; National Institute for Health and Clinical Excellence, 2009). Based on those recommendations, the LSH implemented a specialized service for adult ADHD diagnosis in early 2013. The service is based on referrals from healthcare providers that will subsequently provide treatment support after a valid diagnosis has been made (Emilsson, 2013).

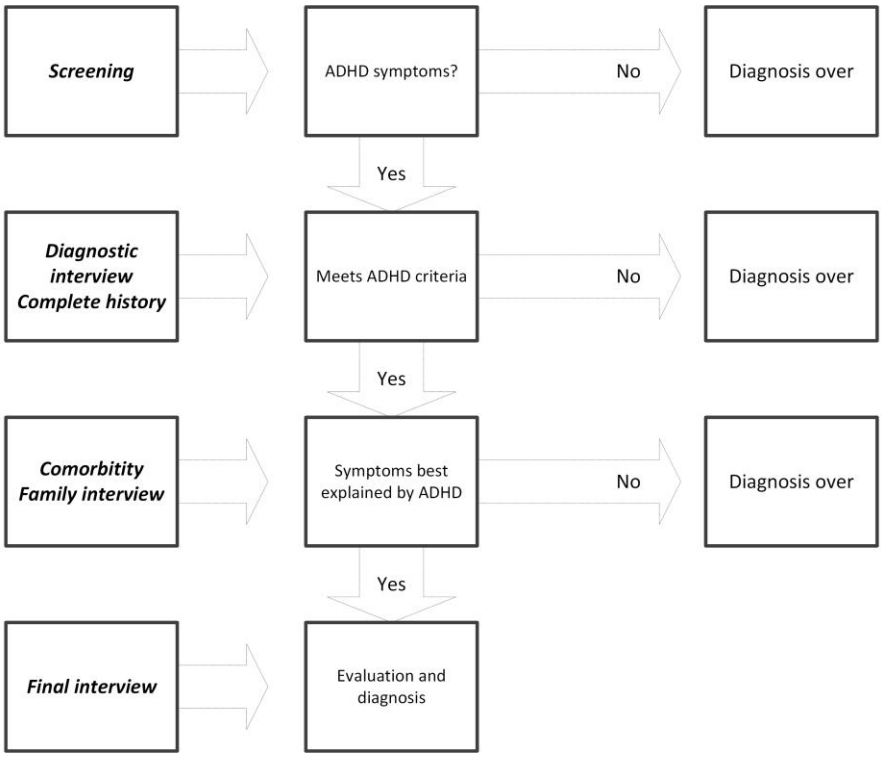

Figure 2: The Icelandic diagnosis procedure

Reprinted from "Greiningar sálfræðinga á fullorðnum með ofvirkni (ADHD)," by Emilsson et al., 2009, *Geðvernd,* 38(1), p. 23.

There are several discrepancies regarding suggested treatment options for adults in the national guidelines. Firstly, there is the issue regarding the drug treatment, the guidelines' state that the first choice of drugs should be methylphenidate, followed by atomoxetine (Baldursson et al., 2012). According to the Icelandic Medicine Agency, none of the ADHD drugs has any indication for adult use (Icelandic Medicine Agency, 2010-2013). Secondly, there is the issue of availability of suggested non-pharmacological treatments, the guidelines clearly state the need for psychological treatment for ADHD, either as part of a multimodal treatment plan or as an option for those who are not suited for pharmacological treatment (Baldursson et al., 2012). According to the Icelandic Health Insurance, the only ADHD treatment option subjected to reimbursements are drug treatments, though only if certain conditions are met. To be eligible for ADHD drug reimbursement, individuals need to have a valid ADHD diagnosis performed by a specialist (Baldursson et al., 2012; Emilsson, 2013; Emilsson et al., 2009; The Icelandic Health Insurance, 2013). Further restrictions to the prescription of ADHD drugs can be seen in table 4.

2 Centrally acting sympathomimetics

In recent years, the use of stimulant drugs has increased in most of the Western world (Scheffler et al., 2007) and studies have shown that there is a considerable increase in stimulant prescriptions for ADHD (Asheim et al., 2007; Donker et al., 2005; Lillemoen et al., 2012; Schmidt-Troschke et al., 2004; van den Ban et al., 2010; Zetterqvist et al., 2013; Zoëga et al., 2011; Zoega H. et al., 2007). Studies on the scope and trends of stimulants use in the treatment of ADHD have mostly originate from the US (Zuvekas et al., 2006). European research has also shown a significant increase in the therapeutic use of stimulants. In Sweden an average yearly increase of 34% was noted between 2006 and 2009, in ADHD drug prescriptions (Zetterqvist et al., 2013). Methylphenidate sales increased by 6% in England during a 12-month period from June 2008 until June 2009 (National Institute for Health and Clinical Excellence, 2008). Icelandic Health Insurance noted an 8% increase in the number of individuals who dispensed at least one methylphenidate prescription between 2010-2011, with a previous increase of 12% in both 2009 and 2010 (The Icelandic Health Insurance, 2011). The noted increase was greater amongst adults than children. Zoëga et al. (2011) found that the drug use for ADHD is most widespread in Iceland, compared with the other Nordic countries. With rates similar to what has been reported within the US, the INCB raised its concerns and issued a warning to the Icelandic government (International Narcotics Control Board, 2011).

Stimulants were first used for medical purposes in 1937 (Bradley, 1937; Patrick et al., 2009). Well over 300 studies have been conducted on the efficacy of stimulants in children compared with 40 studies in adults (Action, 2002; Patrick et al., 2009; Wilens et al., 2011). The most widely prescribed psychotropic medications used primarily in the treatment of ADHD for children, and increasingly adults, are: methylphenidate (MPH), dextroamphetamine (DEX), mixed-salts amphetamine (AMP), and pemoline (PEM) (Action, 2002).

The growing popularity of the non-stimulant atomoxetine, that first was first licensed in the US in 2003 and in 2005 in Iceland (Baldursson et al., 2012; Icelandic Medicine Agency, 2013), can be attributed to the fact that it is less likely to be misused and is not subjected to the same stringent prescription conditions as stimulants (National Institute for Health and Clinical Excellence, 2009).

2.1 The Anatomical Therapeutic Chemical drug classification system

Drugs in this study are classified according to Anatomical Therapeutic Chemical/Defined Daily Dose (ATC/DDD) classification system developed by the World Health Organization (WHO) in 1976 (WHO Collaborating Centre for Drug Statistics Methodology, 2013). According to the WHO (2013), the ATC/DDD purpose “is to serve as a tool for drug utilization research in order to improve quality of drug use”. The availability of such a system simplifies the process of statistical comparison and presentation of drug consumption, both nationally and internationally. Drugs are divided into five tiers according to the active substances. The first level in the classification is comprised of fourteen anatomical groups followed by the therapeutic subgroup. The third and fourth levels are chemical/pharmacological/therapeutic subgroups and the fifth level is the chemical substance (WHO

Collaborating Centre for Drug Statistics Methodology, 2013). The classification of the drugs used in this study demonstrate the structure of the code as seen in table 4.

Table 4: Structure of ATC code

N Anatomical group	Nervous system
N06 Therapeutic group	Psychoanaleptics
N06B Pharmacological group	Psychostimulants, agents used for ADHD and nootropics
N06BA Chemical group	Centrally acting sympathomimetics
N06BA01	Amphetamine
N06BA04	Methylphenidate
N06BA09	Atomoxetine

Throughout this text, we will be using the term ADHD drugs when referring to the drugs in the ATC groups N06BA01/04/09. ATC-groups and DDD-definitions are shown for each drug in table 5.

Table 5: ADHD drugs with marketing authorization in Iceland 2003-2012

Name	DDD (mg)	Adult indication (SmPC / Guidelines)[c]	Prescription restrictions	Year of marketing authorization [g]
Amphetamine	15	No / Yes	Controlled substance [d] max dosage 30 days	1991-2011[h]
Methylphenidate	30[a]	No / Yes		
instant release			Controlled substance max dosage 30 days	1965
extended release			Controlled substance max dosage 100 days [e]	2002
Atomoxetine	80[b]	Yes / Yes	Prescriptions by specialists only[f]	2005[i]

a. Same DDD for both immediate-release and long-acting methylphenidate products (World Health Organization, 2013).
b. 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 (World Health Organization, 2013).
c. According to drug package insertion and national clinical guidelines.
d. Categorized as controlled substance by the INCB and prescriptions should be monitored (Directorate of Health Iceland, 2013; International Narcotics Control Board, 2011).
e. Prior to 2006 the max dosage was 30 days.
f. Reimbursement only available for prescriptions issued by specialists.
g. Reference (Icelandic Medicine Agency, 2013)
h. Original marketing authority in 1991 deregistered in 2011. Current marketing authority under exemption and not registered.
i. Atomoxetine available in Iceland unlicensed from 2003.

3 Pharmacoepidemiology

Strom and Kimmel (2006) define pharmacoepidemiology as *the study of the use of and the effects of drugs in large numbers of people*. As the name suggests, the field is a combination of pharmacology and epidemiology (Strom & Kimmel, 2006). This relatively new field serves as a bridge between clinical pharmacology and epidemiology and applies the methods of epidemiology to the content area of clinical pharmacology (Strom & Kimmel, 2006).

Even though methods pharmacoepidemiology can be useful in both pre and post drug-marketing research, its major application is in the latter - predominantly in post-marketing drug surveillance. The limiting nature of pre drug-marketing research makes it impossible to detect adverse drug effects that are uncommon, delayed, unique to high risk populations or due to misuse of drugs by either prescribers or patients (Strom & Kimmel, 2006). By performing nonexperimental epidemiological studies after marketing, researchers are able to follow up on actual drug usage over extended periods in large populations. Pharmacoepidemiology can therefor contribute valuable information about drug safety and effectiveness that is not available from premarketing studies (Strom & Kimmel, 2006).

Pharmacoepidemiology studies can be either analytical or descriptive. Analytical studies examine the associations of drug exposure and outcomes, mostly on the individual level. Descriptive studies often involve examination of drug utilization on a population level. This study is an example of a descriptive drug utilization study (Strom & Kimmel, 2006).

3.1 Prescription registers

In the past decades, there has been a substantial increase in the development and subsequently the use of automated healthcare databases (Strom & Kimmel, 2006). The available information in healthcare databases can derive for example from administrative data – data gathered on patients' healthcare use – or from medical records. According to Schneeweiss and Avorn (2005), there are substantial differences in healthcare databases throughout the world. These differences are most notable in their population representativeness; the extent, quality, completeness and detail of available information; and the availability to link their data with other sources (Schneeweiss & Avorn, 2005). Prescription registries are an example of databases that gather information from an administrative perspective and usually contain data on the prescribed or dispensed drug, such as on drug name, strength, dose, quantity and date of dispensing, and basic characteristics of the users.

In the last half a century, the Nordic countries have established a tradition of using healthcare registries in epidemiology research. The availability of data gathered population-based health registries such as in-patient registers, outpatient registers of health care centers, cancer registers, birth registers, cause-of-death registers and registers with socioeconomic and demographic characteristics has given researchers a unique opportunity to further the scientific knowledge in the field of health (Furu et al., 2010; Rosen, 2002). The Nordic registries distinctiveness stems from the use of a personal identification number issued to every person at birth or upon immigration. This identification number is included in all population-based registries within each of Nordic countries' making linkage between registries possible (Furu et al., 2010).

The Nordic prescription registries started gathering data on pharmacy dispensed drugs by outpatients in Finland and Denmark in 1994 followed by Iceland in 2003, Norway in 2004 and Sweden in 2005 (Furu et al., 2010; Zoega et al., 2009). The registries contain sociodemographic information on both patients and prescribers (age, sex, personal identifier, residence, the physician specialty and place of practice), product information on prescribed drug (e.g., the Nordic article number, a number of packages, Anatomical Therapeutic Chemical classification code, an amount in defined daily doses, prescription category, reimbursement code, prescribing date, dispensing date and price) and pharmacy information (Furu et al., 2010).

The high completeness and coverage of the Nordic prescription registers can be attributed to legislation, as pharmacies are required by law to send electronic data to national registries. Though the registries contain a vast amount of different variables pertaining prescription drugs, no information is available on the indication of use (Furu et al., 2010; Zoëga, 2011).

3.2 Drug utilization studies

As the focus of pharmacoepidemiology can be on the drug, the prescriber or the patient, drug utilization studies are an integral part pharmacoepidemiology as it describes the extent, nature and determinants of drug exposure. The WHO's (2003) definition of drug utilization is "the marketing, distribution, prescription, and use of drugs in a society, with special emphasis on the resulting medical, social and economic consequences." The nature of drug utilization studies is not purely descriptive as they can just as well be analytical. The emphasis of descriptive drug utilization studies is to describe the utilization patterns and to identify problem areas in need for further research. Analytical studies have the ultimate goal of assessing whether drug therapy is rational or not, by linking drug utilization data to figures on mortality, the outcome of treatment and quality of care. Descriptive drug utilization studies often serves as a precursor of analytical studies as they seek to answer questions such as "what-who-where-when" which can lead to the "why-how" aspect of analytical studies (Rothman, 2012; Strom & Kimmel, 2006; WHO International Working Group for Drug Statistics Methodology. et al., 2003). For example, this study seeks to estimate the duration of ADHD drug use among the adult population of Iceland and the results of that estimation could lead to an analytical research hypothesis.

3.2.1 Biases in registry based drug utilization studies

Just as other pharmacoepidemiological methods, registry based utilization studies are not impervious to systematic errors. Firstly, even though most prescription registries contain complete and accurate data on drug prescriptions, no information is available on the actual drug use. This can lead to misclassification of drug exposure (see figure 3). Secondly, the likelihood of confounding by indication is quite high when measuring drug exposure with prescription data, as it does not contain any information for the actual indication for the prescription. This holds especially true when the drug exposure in question holds several different indications of use (Cox et al., 2009; Strom & Kimmel, 2006). The possibility of systematic errors based on selection is greatly reduced when subjects are selected through registries as it eliminates referral, self-selection and case prevalence bias (Strom & Kimmel, 2006).

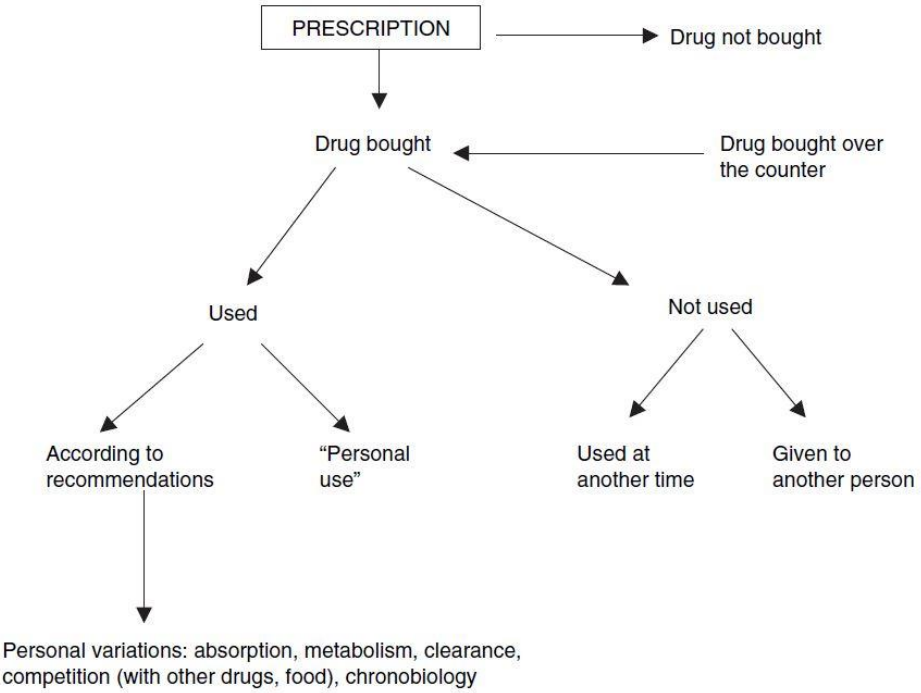

Figure 3: Factors influencing drug exposure

Reprinted from *Textbook of pharmacoepidemiology* (p. 266), by B. L. Strom and S. E. Kimmel, 2006, Chichester: John Wiley & Sons.

Confounding by indication for a prescription is perhaps the most important confounding factor in pharmacoepidemiology since, there has to be a reason for a prescription and because the reason is often associated with the outcome of interest. Confounding by indication is subjected to change as it is directly related to the outcome studied and prescribing practices that can vary between countries and over time (Strom & Kimmel, 2006). As the prescription data used in this study do not include any information on the reasons or underlying indication behind the prescription, we can only speculate on the indication for use. However, the strict regulation regarding the reimbursements for ADHD drugs in Iceland and the rarity of other possible uses for said drugs, could reduce the effect of confounding by indication in this study. As seen in table 3, the first and second-line drugs recommended by international guidelines, have very few, if any other indications for use then ADHD, which also reduce the effects of confounding by indication.

3.3 The Icelandic Medicines Registry

As previously stated, Iceland started collecting data on pharmacy-dispensed drugs as early as 2003; however, the establishment of regulated national prescription registries did not materialize until 2005. In 2003, the Icelandic parliament passed an amendment to the Medicinal Products Act, no. 93/1994 in order to facilitate the establishment of two individual databases. The establishment of a medicinal product database and a statistical database was to ensure that the Directorate of Health, the Icelandic Medicine Agency, the Chief Epidemiologist and the Icelandic Health Insurance were able to fulfill their legally mandated role of monitoring controlled substances as well as general prescription practices. A

temporary provision ensured a two-year transitional period until the laws came to full pass (Bergsdóttir, 2013; Directorate of Health Iceland, 2013; Landlæknisembættið, 2008).

Though similar in nature, the two databases have a very distinctive purpose. Firstly, the purpose of the statistical database, operated by the Icelandic Health Insurance, is to monitor the cost and national consumption of medicinal products. Neither patients nor physicians can be identified through the data in the statistical database. Secondly, the purpose of the medicinal product database (later the Icelandic Medicine Registry), operated by The Directorate of Health, is to monitor both prescription practices and controlled substance as well as ensure the safety of patients, quality in health services and in scientific research (Landlæknisembættið, 2008; Lyfjadeild Sjúkratrygginga Íslands, 2013). To ensure that the registry would serve its purpose of facilitating quality scientific research, a second amendment to the Medicinal Products Act was made in 2008, extending the data storage time from three years to thirty years (Landlæknisembættið, 2008).

One of the main strengths of the Icelandic Medicine Registry is the high completeness of the registry data. As pharmacies are required by law to supply the Icelandic Health Insurance with all information indicated on prescription forms on the dispensing of medicinal products with personal information encrypted, the registry is able to retain near all dispensed prescription data in Iceland (Medicinal Product Act, no.93/1994).

4 Aims

With this background, our overall aim is to provide a comprehensive description of ADHD drug use among the total adult population in Iceland. The lack of studies, both in Iceland and internationally, focusing solely on adults indicates that further research is needed. For the purpose of this study we defined ADHD drugs as all drugs pertaining to the ATC groups N06BA01 (amphetamine), N06BA04 (methylphenidate) and N06BA09 (atomoxetine). Our main aim is to describe the utilization patterns of ADHD drugs for adults in Iceland from 2003 to 2012, specifically:

1. To determine the prevalence of ADHD drug use among adults in Iceland, and potential changes thereof, during the study period, stratified by type of drug (methylphenidate – instant and extended release -, amphetamine and atomoxetine), users' age and sex.
2. To estimate any possible changes in the number of new users of ADHD drugs (incidence of use) over the study period, stratified by users' sex and age.
3. To establish which specialties of the prescribing physician are most likely to initiate ADHD drug treatment for adults in Iceland.
4. To estimate the duration of ADHD drug use among adults in Iceland, in regards to users' age and sex.

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A Nationwide Study of Attention-Deficit/Hyperactivity Disorder Drug Use among Adults in Iceland 2003–2012

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Abstract: In this study, we leveraged on complete nationwide prescription data for the total adult population in Iceland (N – 227,000) to examine how attention-deficit/hyperactivity disorder (ADHD) drugs have been used over the past decade. In particular, we aimed to describe the prevalence, incidence and duration of use of stimulants and atomoxetine, among adults (≥19 years) in Iceland, with regard to sex, age, type of drug and specialty of the prescribing physician. Our results indicate that the 1-year period prevalence of ADHD drug use rose, from 2.9 to 12.2 per 1000 adults between 2003 and 2012, with the most pronounced increases among young adults (19–24 years). The annual incidence increased 3 times, similarly among men and women. Extended-release methylphenidate formulations were the most commonly used ADHD drugs. Specialists in psychiatry initiated treatment in 79% of new adult ADHD drug users. The proportion of users still receiving treatment after 1 year varied from 43.0% (19–24 years), 57.2% (25–49 years) to 47.5% (50+ years). After 3 years, the corresponding proportions still on treatment were 12.4%, 24.5% and 24.3%, and after 5 years 7.9%, 15.9% and 16.8%. These results of increasing ADHD drug use and short treatment durations call for further investigation of the quality of treatment regimens for adults with ADHD and better follow-up of patients treated with ADHD drugs.

Primarily used in treatment of children with attention-deficit/hyperactivity disorder (ADHD), stimulants are in growing use among adults in many Western countries [1 13]. According to both clinical guidelines issued by the National Institute for Health and Clinical Excellence [14] and the consensus statement by the European Network Adult ADHD [15], pharmacotherapy should be the first-line treatment for adults with ADHD. Stimulants such as methylphenidate should be the first-choice treatment option and the non-stimulants atomoxetine as second choice. Yet, in 2013, the approval of stimulant and non-stimulant pharmacotherapy for adults with ADHD was very limited both within the EU and outside [16,17]. Currently, in 2014, only three countries within the EU have approved medications for treatment of newly diagnosed adult ADHD patients, that is methylphenidate in Germany [18,19] and atomoxetine in the UK and Denmark [20 22], causing a mixed message and conflicting directives to the public. The controversy of how to treat ADHD in adults is rooted in a debate of the validity of underlying diagnoses [3,15,23 28], as well as in concerns of potential misuse of the drugs [29].

Previous research shows that overall use of stimulants and atomoxetine in Iceland is up to five times the use in other Nordic countries [4], at a similar rate as has been reported within the United States [30]. Recently, the International Narcotics Control Board (INCB) issued a warning to the Icelandic government expressing concern over the amounts of sold stimulants in Iceland [29].

Very little is known about the patterns of drug utilization for ADHD among adults. A few studies have combined descriptions of paediatric and adult treatment [3,4,9,12,13,31], but none of these focus specifically on treatment patterns in the adult population.

Aims of the study.

In this study, we leveraged on complete nationwide prescription data to examine how stimulants and atomoxetine have been used among adults in Iceland over the past decade. In particular, we aimed to explore the prevalence, incidence and duration of use with regard to sex, age of the patient and specialty of the prescribing physician.

Materials and Methods

This descriptive drug utilization study was based on the nationwide Medicines Registry in Iceland [32,33]. We obtained prescription data for the total adult population (≥19 years) living in Iceland during the study period of 1 January 2003 to 31 December 2012. On average, 227,000 adults resided in Iceland during this time [34].

The Medicines Registry contains data on all prescription drugs dispensed to the outpatient population in Iceland since 2003. It holds individual-level information, both of patients and of prescribing physicians stored under encrypted personal identification numbers. The recorded information used in this study includes demographic data on the patient (encrypted personal identification number, sex and age on the last day of each year); prescriber's specialty; dates of prescribing and dispensing; and data on the dispensed drug substance (brand

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name, formulation, package and volume). The Medicines Registry does not hold information on the underlying indication for the prescribed drugs. Table S1 shows the current indications for the studied ADHD drugs according to package inserts and national clinical guidelines in Iceland [35,36].

Study drugs. Drugs were classified according to the World Health Organization Anatomical Therapeutic Chemical/Defined Daily Dose (ATC/DDD) classification [37]. We focused on the subgroup *centrally acting sympathomimetics* (N06BA). Substances within this group available in Iceland during the study period were the following: *amphetamine* (N06BA01), *methylphenidate* (N06BA04) and *atomoxetine* (N06BA09). Throughout this text, we used the term ADHD drugs when referring to these drugs. *Modafinil* (N06BA07), which comprised 5.6% of all filled N06BA prescriptions, was excluded from the study, as its primary indication was for narcolepsy and cataplexy and should only have been considered as a last treatment option for ADHD [38].

Data analysis.

Prevalence and incidence. We defined the 1-year period prevalence proportion of ADHD drug use as the number of individuals per 1000 in the population who filled at least one prescription for an ADHD drug in the given year.

We further defined the point prevalence of ADHD drug use as the number of individuals per 1000 in the population, who on any given day either filled an ADHD drug prescription or had previously filled a prescription with enough doses to cover that day. A filled ADHD drug prescription generally lasts for 3 months in Iceland (table S1); therefore, the duration of each prescription was estimated as 108 days, corresponding to 90 days plus 20% to allow for any irregularity in prescription refills and stockpiling. This assumption of duration was validated using the method proposed by Pottegård and Hallas [39] that is based on the waiting time distribution [40]. This validation showed that 90 days was in good agreement with the refill pattern seen in the data material (data not shown). The point prevalence was estimated for every day of the study period.

We defined the annual incidence of ADHD drug use as the number of individuals per 1000 in the population who filled their *first* prescription for an ADHD drug in the relevant calendar year. The start of treatment was defined as the first prescription after a period of at least 12 months during which no prescriptions for an ADHD drug were filled.

The annual incidence, period and point prevalence of ADHD drug use was calculated stratified by individuals' sex and age group (19–24, 25–49 and 50+ years). As age was calculated at the end of each calendar year, those aged 18 years could not be included in the analysis. In all calculations of prevalence and incidence, the total number of adults within each relevant sex and age group living in Iceland on 1 January the following year, according to Statistics Iceland [34], was used as the denominator.

Prescribing physicians – treatment initiation. We examined initiation of ADHD drug treatment using annual prescription incidence according to the medical specialty of prescribers. The specialty of prescribing physicians was categorized into the following three categories: psychiatry and neurology (including child and adolescent psychiatry), primary care practice and other (or no) specialty.

Treatment duration. We used the Kaplan–Meyer curve to estimate the duration of ADHD drug use among adults in Iceland, specified by age group (using the age at time of initiation, that is only including users initiating treatment after having turned 19). For each user, the duration of treatment was calculated from the day the first prescription was

Table 1.

New users of ADHD drugs among adults (19 years and older) in Iceland 2004–2012.

	Incidence[1] (n) 2004	Incidence (n) 2005	Incidence (n) 2006	Incidence (n) 2007	Incidence (n) 2008	Incidence (n) 2009	Incidence (n) 2010	Incidence (n) 2011	Incidence (n) 2012
Overall	1.3 (281)	1.8 (380)	2.1 (479)	2.0 (470)	2.2 (520)	2.8 (645)	3.1 (713)	3.3 (777)	4.6 (1085)
Sex									
Male	1.5 (154)	2.0 (214)	2.4 (276)	2.0 (241)	2.4 (285)	2.9 (341)	3.0 (348)	3.5 (407)	4.9 (576)
Female	1.2 (127)	1.5 (166)	1.8 (203)	2.0 (229)	2.0 (235)	2.6 (304)	3.1 (365)	3.1 (370)	4.3 (509)
Age group									
19-24	2.0 (52)	4.0 (101)	3.9 (102)	4.3 (117)	4.9 (138)	5.5 (155)	6.5 (185)	7.6 (219)	8.9 (261)
25-49	1.7 (182)	2.0 (214)	2.6 (287)	2.6 (293)	2.6 (305)	3.5 (394)	4.0 (440)	4.3 (468)	6.2 (676)
50+	0.6 (47)	0.8 (65)	1.0 (90)	0.7 (60)	0.9 (77)	1.0 (96)	0.9 (88)	0.9 (90)	1.5 (148)
Total population, N	208,044	210,696	216,192	223,472	230,629	232,289	233,254	234,900	237,418

ADHD, Attention-deficit/hyperactivity disorder.
[1]Incidence defined as the number of individuals per 1000 in the population who filled their first prescription for an ADHD drug in the relevant calendar year.

filled and until treatment was terminated. Users who initiated treatment in 2003 were disregarded. We defined treatment as a sequence of prescriptions with no more than 180 days between two consecutive prescriptions. By choosing a long interval between prescriptions, we avoided a false termination of use among those who had long pauses between prescriptions.

All calculations were performed with STATA Release 12.0 (StataCorp, College Station, TX, USA). The study was approved by the Icelandic Bioethics Committee (VSNb2013010018/03.07) and the Icelandic Data Protection Authority (2013010062TS/–).

Results

We identified 5292 adults (≥19 years) who used ADHD drugs during the study period (2003 2012), filling a total of 91,766 prescriptions. Methylphenidate was the most commonly filled prescription (42,772 prescriptions for extended-release formulations and 33,389 prescriptions for instant-release formulations), followed by amphetamine (10,221 prescriptions) and atomoxetine (5384 prescriptions).

The 1-year period prevalence for ADHD drug use in Iceland increased over the study period, from 2.9 per 1000 in 2003 to 12.2 per 1000 in 2012. As seen in Fig. 1, this steady rise was driven by increasing use of extended-release methylphenidate formulations, and to some extent atomoxetine, while use of amphetamine and instant-release methylphenidate formulations decreased during the study period. The point prevalence (fig. 2) shows that the increase in use between 2003 and 2012 was most pronounced among young adults (19 24 years), from 1.7 to 17.8 per 1000 young females and 2.7 to 24.0 per 1000 young males. The 1-year period prevalence revealed a similar time trend and differences in use of ADHD drugs between sex and age groups, as depicted in the point prevalence (data not shown).

The annual incidence of ADHD drug use among adults in Iceland increased 3 times (table 1), similarly among men and women. As for the prevalence estimates, we noted the highest increase among young adults (19 24 years) (from 2.0 to 8.9 per 1000) and lowest among adults 50 years and older (from 0.6 to 1.5 per 1000). Specialists in psychiatry initiated ADHD

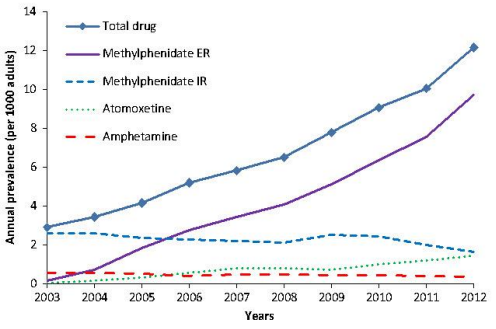

Fig. 1. Prevalence* of ADHD drug use among adults (19 years and older) in Iceland 2003–2012. *Prevalence (prev.) proportions are expressed as number of adults per 1000 adults in the population filling at least one prescription in the relevant year. ADHD, Attention-deficit/hyperactivity disorder.

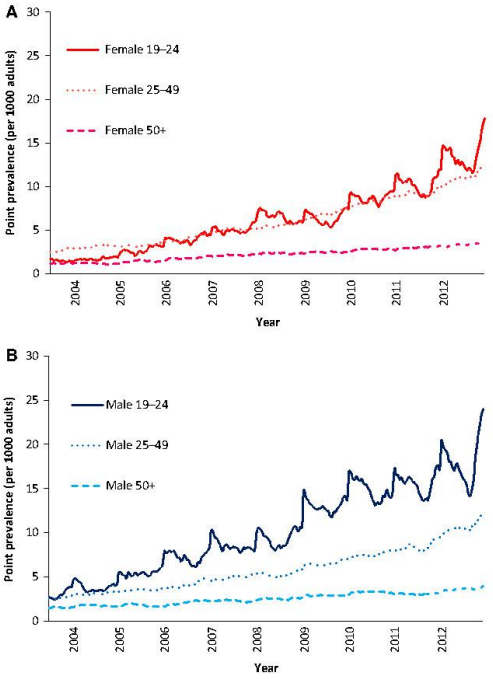

Fig. 2. (A) Point prevalence* of ADHD drug use among females (19 years and older) in Iceland 2003–2012. (b) Point prevalence* of ADHD drug use among males (19 years and older) in Iceland 2003–2012. *Point prevalence defined as the number of individuals per 1000 in the population who on any given day either filled an ADHD drug prescription or had previously filled a prescription with enough doses to cover the given day. ADHD, Attention-deficit/hyperactivity disorder.

drug treatment in 79% of new adult users, while primary care practitioners initiated treatment in 10% of the first-time adult cases. Prescribers with another specialty, or no specialty, issued the first ADHD prescription to 8% and 3%, respectively, of all adult users.

A total of 4069 individual users were eligible to assess treatment duration. The proportion of ADHD drug users still receiving treatment after 1 year varied from 43.0% (19 24 years; males 39.9%, females 47.2%), 57.2% (25 49 years; males 56.4%, females 57.9%) to 47.5% (50– years; 46.2% males, 48.2% females; fig. 3). The corresponding proportions still on treatment after 3 years were 12.4%, 24.5% and 24.3%, respectively, in each age group, and after 5 years 7.9% (males 6.8%, females 9.6%), 15.9% (males 14.3%, females 17.3%) and 16.8% (16.6% males, 17.1% females).

Discussion

Main results.

With near-complete coverage of the total adult population in Iceland, we found roughly a 4 times increase in use of ADHD

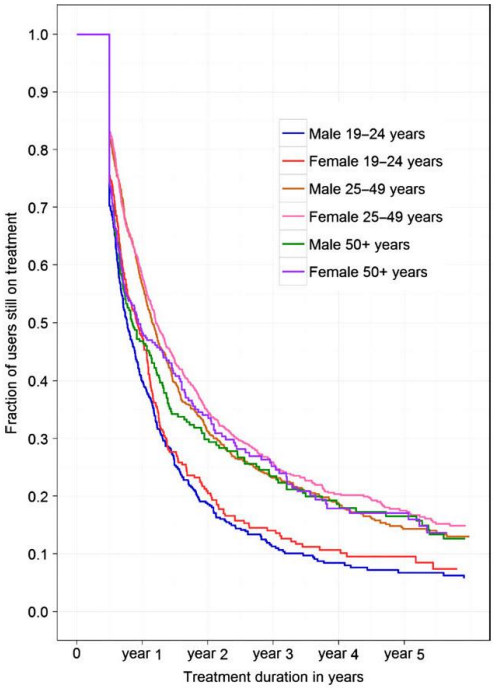

Fig. 3. Kaplan–Meier curve of duration* of ADHD drug treatment according to age group and sex. *Treatment was considered terminated when 180 days had passed without an ADHD prescription fill. ADHD, Attention-deficit/hyperactivity disorder.

drugs in Iceland between 2003 and 2012. This rise was driven by increasing use of extended-release methylphenidate and to some extent atomoxetine, while use of amphetamine and instant-release methylphenidate decreased. While the levels of ADHD drug use varied somewhat between men and women, differences according to drug type and calendar time were similar between the sexes. Treatment, as well as discontinuation, was most pronounced among young adults (19 24 years). Only 12.4% of young adults were still receiving treatment 3 years after starting, compared with 24.5% of users aged 25 49 years.

Strengths and limitations.

This is among the first studies to describe ADHD drug use among an entire national adult population. The high completeness and accuracy of the study data over 10 years [32] allows us to interpret our results with confidence. Given the conflicting messages of treatment options for adult ADHD and ongoing concern of potential misuse of stimulants, the reported results should be of major public health interest.

This study is not without limitations. Firstly, the Icelandic Medicines Registry does not contain information on underlying diagnosis or severity of condition treated. Therefore, we can only speculate whether those receiving ADHD drug prescriptions did indeed have a diagnosis for ADHD. Secondly, we did not conduct any analysis on drug dosages and were thus unable to assess treatment intensity or conclude whether the prescribed amounts were according to clinical guidelines for adults. Lastly, we had no way of knowing whether the individuals actually consumed the prescribed ADHD drug in question. However, patterns of repeated prescription fills to the same individual increase the likelihood that he or she actually consumed the drug.

Prevalence and incidence.

Epidemiological studies have estimated that the prevalence for ADHD in adults is in the range of 2 5% [15,26,41,42]. Whereas ADHD is more commonly diagnosed among boys than among girls during childhood [15], research suggests that in adulthood the sexes are equally affected by ADHD, resulting in more women than men diagnosed for the first time as adults [15,26,41,42]. Our findings show a higher proportion of women than men aged 25 49 years using ADHD drugs, but the gender ratio is reversed in the younger (19 24 years) and older (50− years) age groups, with more men than women receiving treatment.

Not all individuals diagnosed with ADHD need, or will benefit from, drug treatment. Thus, it is not surprising that the prevalence of ADHD drug use observed in our data (e.g. 1.2% in 2012) does not exceed the reported disease prevalence of 2 5% among adult populations [15,26,41,42]. However, the estimated utilization in Iceland is indeed higher than what has been reported for adults in Sweden in 2009, 3.6 per 1000 (22 45 years) [9]; Denmark in 2011, 7 11 per 1000 (18 24 years), 4 5 per 1000 (25 49 years) [12]; and the UK in 2008, 1.1 per 1000 (18 24 years), <1 per 1000 (25 45 years) [31]. This variance of treatment rates across countries warrants further investigation and is unlikely to be explained by a varying distribution of the underlying condition between these populations. Factors such as access to treatment options for ADHD, reimbursement regulations and prescribing habits of physicians in each country are likely to play a role in differing drug utilization. During the time of this study, drugs were the only reimbursed treatment option for adults with ADHD in Iceland [44]. We underscore, although, that the study data did not allow for a direct assessment of treatment quality or appropriateness of drug prescribing.

Our results are consistent with previous reports showing increasing adult use of ADHD drugs in Europe over the past decade [4,9,12,31]. The steady increase we observed over the 10-year period is reflected in an increased clinical and public awareness of ADHD in adults, as well as increased availability of drugs to treat ADHD (i.e. extended-release methylphenidate and non-stimulant atomoxetine). We found slightly higher increases in use among women than in men between 2003 and 2012. This pattern corresponds with results found in the UK [31] and Sweden [9], demonstrating higher increases in ADHD drug use among women than among men. Similar to reports from Denmark [12], Sweden [9] and the UK [31], we

also found that, throughout the study period, new users were mainly young adults (19 24 years) and increases in utilization were most pronounced in this age group.

In recent years, ADHD has become recognized as a lifelong impairing condition, estimated to affect two-thirds of diagnosed children into adulthood [14,15,26 28,44]. According to both European [14,15,26] and Icelandic [35] clinical guidelines, adult ADHD diagnosis is based on careful and systematic assessment of a life-time history of symptoms and impairments. Central to this process is the assessment of childhood onset, current symptoms of ADHD and the presence of symptoms and impairment in at least two domains (school, work, home and interpersonal contacts). Icelandic guidelines recommend psychological treatment and education as a first-line treatment for adults and that drug treatment should only be considered if previous options fail. Paradoxically, no non-pharmacological treatment options are subjected to government reimbursements for adults in Iceland and therefore severely limiting access to such interventions.

The national guidelines were reissued in 2012 to address the concerns from the INCB [29] regarding overall volume of stimulants sold in Iceland and potential misuse. The changes were in line with the European guidelines [14,35], although in case of any concerns of potential drug misuse, atomoxetine is suggested as a first-line drug. Atomoxetine is currently the only ADHD drug with an adult indication in Iceland, causing further confusion in regard to the treatment options available to adults.

Discontinuation.

Corroborating previous reports, our data show that discontinuation of ADHD drug treatment is most common among young adults [9,12,45 47], while discontinuation patterns among individuals who start treatment in adulthood have been documented to a lesser extent. We found that 1 year after treatment initiation, 43% of the youngest adult users (19 24 years) but 57% of those aged 25 49 years were still receiving drug treatment for ADHD. Three years after drug treatment initiation, less than an eighth (12%) of the youngest adults and a fourth of those older were still in treatment. These proportions show that discontinuation of ADHD treatment within the first 3 years of initiation is high among adults in Iceland compared with what has been reported for adults in Denmark and Sweden. Based on nationwide data from Denmark, Pottegård *et al.* [12] demonstrated that within 3 years of ADHD drug treatment, 24%, 34% and 43% of users, respectively, aged 18 24 years, 25 49 years and 50− years had quit treatment. Similarly, Zetterqvist *et al.* [9] found, using nationwide prescription data from Sweden, that 34% of users aged 15 21 years were still in treatment after the first 3 years of initiation.

This substantial difference in treatment duration between neighbouring countries warrants further investigation. As ADHD symptoms have been shown to persist throughout the life course [14,15,26,41,42], the high number of adults in Iceland who discontinue treatment within a few years of starting may suggest lack of treatment monitoring and follow-up of adults with ADHD within the Icelandic health care system. But such monitoring should be a priority in a country where the estimates of ADHD drug utilization are among the highest in the world.

In sum, based on complete nationwide data, we found high and growing use of ADHD drugs among adults in Iceland, as well as relatively short treatment durations. These results call for further investigation of the quality of treatment regimens for adults with ADHD and follow-up of patients being treated with ADHD drugs.

Acknowledgements

We thank the Directorate of Health in Iceland for their collaboration in extracting data from the national Medicines Registry for this study.

Declaration of Interest

Drifa Palin Geirs, Helga Zoëga and Matthias Halldorsson have no conflict of interest to declare in general or in relation to this study. Anton Pottegård has participated in research projects funded by Astellas, with grants paid to the institution where he was employed. Anton Pottegård declares no conflicts of interest in relation to this study.

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Supporting Information

Additional Supporting Information may be found in the online version of this article:

Table S1. ADHD drugs with marketing authorization in Iceland 2003 2012.

Appendix A – Diagnosis criteria

Table #: Appendix A - DSM-IV diagnostic criteria for ADHD

A. Either 1 or 2

1. Six (or more) of the following symptoms of inattention have persisted for at least 6 months to a degree that is maladaptive and inconsistent with developmental level:

Inattention

a) Often fails to give close attention to details or makes careless mistakes in schoolwork, work, or other activities
b) Often has difficulty sustaining attention in tasks or play activities
c) Often does not seem to listen when spoken to directly
d) Often does not follow through on instructions and fails to finish schoolwork, chores, or duties in the workplace (not due to oppositional behavior or failure to understand instructions)
e) Often has difficulty organizing tasks and activities
f) Often avoids, dislikes, or is reluctant to engage in tasks that require sustained mental effort (such as schoolwork or homework)
g) Often loses things necessary for tasks or activities (e.g., toys, school assignments, pencils, books, or tools)
h) Is often easily distracted by extraneous stimuli
i) Is often forgetful in daily activities

2. Six (or more) of the following symptoms of hyperactivity-impulsivity have persisted for at least 6 months to a degree that is maladaptive and inconsistent with developmental level:

Hyperactivity

a) Often fidgets with hands or feet or squirms in seat
b) Often leaves seat in classroom or in other situations in which remaining seated is expected
c) Often runs about or climbs excessively in situations in which it is inappropriate (in adolescents or adults, may be limited to subjective feelings of restlessness)
d) Often has difficulty playing or engaging in leisure activities quietly
e) Is often on the go or often acts as if driven by a motor
f) Often talks excessively

Impulsivity

g) Often blurts out answers before questions have been completed
h) Often has difficulty awaiting turn
i) Often interrupts or intrudes on others (e.g., butts into conversations or games)

B. Some hyperactive-impulsive or inattentive symptoms that caused impairment were present before age 7 years

C. Some impairment from the symptoms is present in two or more settings (e.g., at school [or work] and at home)

D. There must be clear evidence of interference with developmentally appropriate social, academic or occupational functioning.

E. The symptoms do not occur exclusively during the course of a pervasive developmental disorder, schizophrenia, or other psychotic disorder and are not better accounted for by another mental disorder (e.g., mood disorder, anxiety disorder, dissociative disorder, or a personality disorder)

Based on these criteria, 3 types of ADHD are identified:

- ADHD, Combined Type: if both criteria A1 and A2 are met for the previous 6 months
- ADHD, Predominantly Inattentive Type: if criterion A1 is met but criterion A2 is not met for the previous 6 months
- ADHD, Predominantly Hyperactive-Impulsive Type: if criterion A2 is met but criterion A1 is not met for the previous 6 months

Broader subtypes of ADHD:
In partial remission: this subtype applies to individuals (especially adolescents and adults) who currently have symptoms that no longer meet full criteria.

ADHD not otherwise specified: this subtype includes disorders with prominent inattention or hyperactivity-impulsivity that do not meet criteria for ADHD. Examples include:

- individuals who meet criteria for ADHD but whose age of onset is 7 years or older,
- individuals with clinically significant impairment who present with inattention and whose symptom pattern does not meet the full diagnostic criteria for ADHD, but have a behavioral pattern marked by sluggishness, daydreaming, and hypoactivity.

Note: From *Diagnostic criteria from DSM-IV-TR* by American Psychiatric Association, 2000, Washington D.C.: American Psychiatric Association

Table #: Appendix A - ICD-10 criteria and recommendations for use in clinical practice

Demonstrable abnormality of attention, activity and impulsivity at home, for the age and developmental level of the child, as evidenced by (1), (2), and (3):

1. Patient demonstrates at least three of the following attention problems:
   A. short duration of spontaneous activities
   B. often leaving play activities unfinished
   C. over-frequent changes between activities
   D. undue lack of persistence at tasks set by adults
   E. unduly high distractibility during study (homework or reading assignment)
2. Patient also demonstrates at least three of the following activity problems:
   A. very often runs about or climbs excessively in situations where it is inappropriate
   B. seems unable to remain still
   C. markedly excessive fidgeting and wriggling during spontaneous activities
   D. markedly excessive activity in situations expecting relative stillness (e.g., mealtimes, travel, visiting, church)
   E. often leaves seat in classroom or other situations when remaining seated is expected; often has difficulty playing quietly
3. Patient also demonstrates at least one of the following impulsivity problems:
   A. often has difficulty awaiting turns in games or group situations;
   B. often interrupts or intrudes on others (e.g., interrupts others' conversations or games);
   C. often blurts out answers to questions before questions have been completed

Demonstrable abnormality of attention and activity at school or nursery (if applicable), for the age and developmental level of the child, as evidenced by both (1) and (2):

1. Patient demonstrates at least two of the following attention problems:
   A. undue lack of persistence at tasks
   B. unduly high distractibility (i.e., often orienting toward extrinsic stimuli)
   C. over frequent changes between activities when choice is allowed
   D. excessively short duration of play activities
2. Patient also demonstrates at least three of the following activity problems:
   A. continuous (or almost continuous) and excessive motor restlessness (e.g., running, jumping in situations allowing free activity)
   B. markedly excessive fidgeting and wriggling in structured situations
   C. excessive levels of off-task activity during tasks
   D. unduly often out of seat when required to be sitting
   E. often has difficulty playing quietly

Directly observed abnormality of attention or activity. This must be excessive for the child's age and developmental level. The evidence may be any of the following:

1. direct observation of the criteria above (i.e., not solely the report of parent or teacher);
2. observation of abnormal levels of motor activity, or off-task behavior, or lack of persistence in activities in a setting outside home or school (e.g., in a clinic or laboratory)
3. significant impairment of performance on psychometric tests of attention

Does not meet criteria for pervasive developmental disorder, mania, depressive, or anxiety disorder.

Onset before the age of 7 years.

Duration of at least 6 months.

IQ above 50.

Note:

Table content from *The ICD-10 Classification of Mental and Behavioural Disorders* by World Health Organization, 1993, Geneva: World Health Organization. Available from: http://www.who.int/classifications/icd/en/GRNBOOK.pdf?ua=1

Table layout from *Handbook for Attention Deficit Hyperactivity Disorder in Adults* p.8, by UK Adult ADHD Network, 2013, London: Springer Healthcare Limited.

Appendix B – Study Approvals

VÍSINDASIÐANEFND

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Helga Zoéga
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Reykjavík 29. janúar 2013
Tilv.: VSNb2013010018/03.07

Efni: 13-012-afg. Notkun örvandi lyfja við ADHD (ofvirkni með athyglisbrest) meðal fullorðinna á Íslandi 2003-2012.

Á fundi sínum 29.01.2012 fjallaði Vísindasiðanefnd um umsókn þína, vegna ofangreindrar rannsóknaráætlunar. Meðrannsakendur þínir eru: Matthías Halldórsson, Þórólfur Þórlindsson, Grétar Sigurbergsson og Drífa Pálín Geirsdóttir.

Eftir að hafa farið vandlega yfir umsókn þína og innsend gögn gerir Vísindasiðanefnd ekki athugasemdir við framkvæmd rannsóknarinnar, en áréttar meginreglu nefndarinnar um að rannsóknargögnum verði eytt innan fimm ára frá rannsóknarlokum. Rannsóknaráætlunin er endanlega samþykkt með framangreindri áréttingu.

Óskað er eftir að leyfi Persónuverndar verði sent skrifstofu Vísindasiðanefndar þegar það berst rannsakendum.

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.

Áréttað er að allar fyrirhugaðar breytingar á þegar samþykktri rannsóknaráætlun þurfa að koma inn til nefndarinnar til umfjöllunar. Jafnframt ber ábyrgðarmanni að láta stofnanir, sem veitt hafa leyfi vegna framkvæmdar rannsóknarinnar eða öflunar gagna vita af fyrirhugðum breytingum.

Með kveðju,
f.h. Vísindasiðanefndar,
Gísli Ragnarsson
Gísli Ragnarsson, varaformaður

Helga Zoéga
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Reykjavík, 7. mars 2013
Tilvísun: 2013010062TS/--

Heimild

skv. 9. mgr. 27. gr. lyfjalaga nr. 93/1994,
3. mgr. 15. gr. laga nr. 74/1997 um réttindi sjúklinga

I.
Umsókn

Persónuvernd hefur borist umsókn Helgu Zoega, lektor við Háskóla Íslands, Drífu Pálín Geirsdóttur, meistaranema í lýðheilsuvísindum, Matthíasi Halldórssyni, lækni á geðsviði Landspítalans, Þórólfi Þórlindssyni, prófessor á Félagsvísindasviði Háskóla Íslands, og Grétari Sigurbergssyni, geðlækni á læknamiðstöðinni Uppsölum, dags. 31. janúar 2013, vegna rannsóknar sem ber yfirskriftina „Notkun örvandi lyfja við ADHD (ofvirkni með athyglisbrest) meðal fullorðna á Íslandi 2003-2012“, um heimild til aðgangs að lyfjagagnagrunni Landlæknisembættisins vegna framangreindrar rannsóknar.

Í umsókninni er tilgangi vinnslunnar lýst á eftirfarandi hátt:

> „Í ljósi umræðu og vísbendinga um fjölþjóðlega aukningu á notkun örvandi lyfja meðal fullorðinna er rannsókn þessi gerð. Höfuðmarkmið rannsóknarinnar er að skoða þróun notkunnar á örvandi lyfjum við ADHD meðal fullorðinna á Íslandi frá árinu 2002 til 2012. Þessi þróun verður greind eftir bæði algengi (allir notendur) og nýgengi (nýir notendur). Mynstur notkunar verður greint eftir kyni, aldri og búsetu sjúklings (landsfjórðungum), verkunartíma lyfs og sérgrein læknis sem ávísaði lyfinu. Lýsandi áhorfsrannsókn (descriptive observational study) sem byggir á gögnum úr Lyfjagagnagrunni Embættis Landlæknis. Um er að ræða úrvinnslu fyrirliggjandi gagna um lyfjanotkun. Rannsóknin

mun ná til fullorðinna einstaklinga sem leyst hafa út lyf samkvæmt ATC (Anatomical-Therapeutical-Chemical) flokkun N06BA (Adrenvirk lyf með verkun á miðtaugakerfið) á Íslandi á tímabilinu 2002 til og með 2012. Rannsóknin mun einskorðast við eftirfarandi þrjá flokka: amfetamín (N06BA01), metýlfenídat (N06BA04) og atomxetinum (N06BA09). Algengi notkunar örvandi lyfja er skilgreint sem fjöldi einstaklinga á hverja 1000 íbúa sem innleysti eina eða fleiri lyfjaávísun á örvandi lyf ár hvert. Nýgengi notkunar á örvandi lyfjum er skilgreint sem fjöldi nýrra einstalinga á hverja 1000 íbúa sem byrja að leysa út eina eða fleiri lyfjaávísun á örvandi lyf ár hvert.

Þær rannsóknir sem gerðar hafa verið á umfangi og þróun notkunar örvandi lyfjum við ADHD á Íslandi hafa að mestu náð til barna. Úttektir sem gerðar hafa verið á notkun örvandi lyfja við ADHD hjá fullorðnum benda til þess að þörf sé á rannsókn af þessu tagi sem skoðar nánar mynstur lyfjanotkunar eftir tíma, lyfjaflokkum, kyni og aldri sjúklinga sem og séfræðigrein þess sem ávísar lyfjunum. Lyfjagagnagrunnur Embættis landlæknis um lyfjanotkun hafa opnað tækifæri til rannsóknar sem þessarar. Markmið er að rannsóknin gagnist sem grunnur að frekari rannsóknum. Samanburður við notkun örvandi lyfja við ADHD hjá fullorðnum einstaklingum annarra þjóða er þarft rannsóknarefni og undirmarkmið rannsóknarinnar. Enn frekmur er mikilvægt að kostnaður geðlyfjameðferðar fullorðinna verði í framtíðinni borinn saman við ábatann sem af henni hlýst."

Samkvæmt umsókninni verður úrtakið valið með eftirfarandi hætti:

„Um er ða ræða úrvinnslu gagna úr Lyfjagagnagrunni Embættis landlæknis. Rannsóknin mun ná til allra fullorðinna einstaklinga (18 ára og eldri) sem leyst hafa út lyf með ATC flokkun N06BA N06BA (Adrenvirk lyf með verkun á miðtaugakerfið) á Íslandi á tímabilinu 2002 til og með 2012. Upplýsingar um þessa einstaklinga umfram dulkóðuð gögn sem þegar liggja hjá Embætti Landlæknis verða ekki notuð til rannsóknarinnar. Til útreikninga á algengi og nýgengi lyfjanotkunar verða notaðar opinberar tölur um mannfjölda á Íslandi 1. janúar ár hvert samkvæmt Hagstofu Íslands. Ekki verður haft samband við þátttakendur rannsóknarinnar."

Samkvæmt umsókninni er fyrirhugað að afla upplýsinga úr Lyfjagagnagrunni landlæknis. Eftirfarandi upplýsingum verður safnað í þágu rannsóknarinnar:

„Upplýsingar um lyfjanotkunr einstaklinga (18 ára og eldri) verður aflað úr Lyfjagagnagrunni Embættis landlæknis. Gögn um þátttakendur verða ekki sótt til þeirra sjálfra, né haft samband við þá meðan á rannsókn stendur. Öll gögn úr Lyfjagagnagrunni verða dulkóðuð þegar rannsakendur fá gögn í hendur en hver einstaklingur mun hafa sérstakt rannsóknarnúmer til auðkenningar. Á engu stigi máls munu rannsakendur hafa undir höndum upplýsingar um nöfn, kennitölur eða nákvæma búsetu einstaklinga."

Varðandi skráningu persónuauðkenna og varðveislu rannsóknargagna í tengslum við rannsóknina segir eftirfarandi:

„Öll gögn úr Lyfjagagnagrunni verða dulkóðuð þegar rannsakendur fá gögn í hendur en hver einstaklingur verður merktur sérstöku rannsóknarnúmeri til auðkenningar. Á engu stigi máls munu rannsakendur hafa undir höndum upplýsinagr um nöfn, kennitölur eða nákvæma búsetu einstaklinga."

Af framangreindu er ljóst að í rannsóknninni felst öflun upplýsinga um einstaklinga úr Lyfjagagnagrunni landlæknis. Samkvæmt 9. mgr. 27. gr. lyfjalaga nr. 93/1994, 3. mgr. 15. gr. laga nr. 74/1997 um réttindi sjúklinga, þarf leyfi Persónuverndar til aðgangs að Lyfjagagnagrunni landlæknis í þágu vísindarannsókna. Getur stofnunin bundið slíkt leyfi þeim skilyrðum sem hún telur nauðsynleg hverju sinni.

II.
Leyfisskilmálar og leyfisskilmálar

Persónuvernd hefur nú ákveðið, m.a. að virtum ákvæðum 29., 33. og 34. gr. í formálsorðum persónuverndartilskipunarinnar nr. 95/46/EB, 9. tölul. 1. mgr. 9. gr. laga nr. 77/2000 um persónuvernd og meðferð persónuupplýsinga, að veita Helgu Zoega, Drífu Pálín Geirsdóttur, Matthíasi Halldórssyni, Þórólfi Þórlindssyni og Grétari Sigurbergssyni, umbeðið leyfi til vinnslu persónuupplýsinga vegna rannsóknarinnar „Notkun örvandi lyfja við ADHD (ofvirkni með athyglisbrest) meðal fullorðna á Íslandi 2003-2012".

Með leyfinu er heimiluð vinnsla upplýsingar úr lyfjagagnagrunni Landlæknisembættisins, eins og nánar greinir hér á eftir. Leyfið gildir til **5. mars 2015** og er bundið eftirfarandi skilyrðum:

1. Ábyrgðaraðilar að vinnslu persónuupplýsinga
Helga Zoega, Drífa Pálín Geirsdóttir, Matthías Halldórsson, Þórólfur Þórlindsson og Grétar Sigurbergsson teljast vera ábyrgðaraðilar vinnslunnar í skilningi 4. tölul. 2. gr. laga nr. 77/2000 og jafnframt handhafar leyfis þessa (hér eftir nefndir „leyfishafar"). Fer Helga Zoega, 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 leyfisskilmálar*
a. Þegar leyfishafar fara þess á leit við ábyrgðarmenn sjúkraskráa, sbr. 12. tölul. 3. gr. laga nr. 55/2009 um sjúkraskrár, að fá aðgang að viðkomandi sjúkraskrám, ber þeim að framvísa leyfi þessu.
b. Leyfi þetta er bundið því skilyrði að ábyrgðarmenn umræddra sjúkraskráa hafi lýst því yfir að þeir séu því samþykkir fyrir sitt leyti að leyfishafi fái aðgang að þeim.
c. Leyfi þetta er bundið því skilyrði að siðanefnd, eða eftir atvikum vísindasiðanefnd, hafi lagt mat á rannsóknina og látið í té skriflegt álit sitt þess efnis að hvorki vísindaleg né siðfræðileg sjónarmið mæli gegn framkvæmd hennar, sbr. 3. mgr. 15. gr. laga nr. 74/1997, sbr. 4. mgr. 2. gr. sömu laga.

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. Farið skal með upplýsingar sem skráðar eru vegna rannsóknarinnar, í samræmi við lög nr. 77/2000, lög nr. 74/1997 og læknalög nr. 53/1988. Hvílir þagnarskylda á leyfishöfum og öðrum þeim sem koma að rannsókninni um heilsufarsupplýsingar sem unnið er með, sbr. 15. gr. laga nr. 53/1988. Þagnarskylda helst þótt látið sé af störfum við rannsóknina.
c. Taki háskólanemar eða aðrir, sem ekki teljast til löggiltra heilbrigðisstétta, þátt í framkvæmd rannsóknarinnar skulu þeir undirrita sérstaka þagnarskylduyfirlýsingu, þar sem þeir m.a. ábyrgjast að tilkynna leyfishöfum ef í rannsóknargögnum eru viðkvæmar persónuupplýsingar um þá sem eru eða hafa verið maki viðkomandi, skyldir eða mægðir honum í beinan legg eða að öðrum lið til hliðar eða tengdir honum með sama hætti vegna ættleiðingar. Er viðkomandi þá óheimilt að kynna sér gögn um þá einstaklinga. Matthíasi Halldórssyni eða fulltrúa hans ber að votta rétta undirskrift hlutaðeigandi og dagsetningu slíkrar yfirlýsingar og koma henni til Persónuverndar innan tveggja vikna frá útgáfu leyfis þessa eða frá því að viðkomandi hefur störf við rannsóknina. Þagnarskyldan er byggð á 3. mgr. 35. gr. laga nr. 77/2000. Á heimasíðu Persónuverndar er að finna staðlað eyðublað fyrir þagnarskylduyfirlýsingu. Ef þagnarskylduyfirlýsingum er ekki skilað innan tilskilins frests getur Persónuvernd afturkallað leyfi þetta.
d. Leyfi þetta heimilar einvörðungu að safnað verði þeim heilsufarsupplýsingum sem gildi hafa fyrir rannsókn leyfishafa og samrýmast markmiðum hennar.

4. Auðkenning rannsóknargagna

a. Í rannsóknargögn má skrá upplýsingar um fæðingarmánuð, fæðingarár og kyn hvers sjúklings.
b. Óheimilt er að skrá í rannsóknargögn upplýsingar um nöfn sjúklinga, nafnnúmer, heimilisföng, símanúmer, fax-númer, tölvupóstföng eða annað sambærilegt.
c. Öll gögn úr Lyfjagagnagrunni verða dulkóðuð þegar rannsakendur fá gögn í hendur en hver einstaklingur verður merktur sérstöku rannsóknarnúmeri til auðkenningar. Á endu stigi máls munu rannsakendur hafa undir höndum upplýsingar um nöfn, kennitölur eða nákvæma búsetu einstaklinga. Í ljósi þessa er heimilt við framkvæmd rannsóknar þessarar að skrá og varðveita *tímabundið* sérstaka skrá, greiningarlykil, sem tengir saman upplýsingar um kennitölur einstaklinga og rannsóknarnúmer á meðan verið er að undirbúa rannsóknargögn. Slíka skrá/greiningarlykil skal ávallt varðveita aðskilda frá öðrum rannsóknargögnum. Þegar rannsókn er lokið, og eigi síðar en við lok gildistíma leyfis þessa, skal greiningarlykli eytt.
d. Þegar þær heilbrigðisupplýsingar, sem leyfi þetta tekur til, hafa verið skráðar í rannsóknargögn, og eftir atvikum verið staðreynt að þær séu réttar, og gögnin að öðru leyti verið fullgerð, skal tryggja að þar liggi ekki fyrir auðkenning á því frá hvaða einstaklingi upplýsingarnar stafa, s.s. með eyðingu kennitalna.

5. Öryggi við vinnslu persónuupplýsinga

Leyfishöfum 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 m.a. áskilið að:

a. 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. 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.

Leyfishafar bera ábyrgð á því að hver sá er starfar í umboði þeirra og hefur aðgang að persónuupplýsingum vinni aðeins með þær í samræmi við skýr fyrirmæli sem þeir gefa 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. Leyfishafar bera ábyrgð á að farið sé með öll persónuauðkennd gögn sem sjúkragögn í samræmi við lög, reglur og ákvæði þessa leyfis.
b. Leyfishafar skulu ábyrgjast að engir aðrir en þeir fái í hendur persónugreinanleg gögn sem sérstaklega verður aflað í þágu þessarar rannsóknar.
c. Óski leyfishafar þess að hætta rannsókn ber þeim 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.
d. Leyfishöfum 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.
e. Persónuvernd getur látið gera úttekt á því hvort leyfishafar fullnægi skilyrðum laga nr. 77/2000 og reglna sem settar eru samkvæmt þeim eða einstökum fyrirmælum. Getur Persónuvernd ákveðið að þeir skuli greiða þann kostnað sem af því hlýst. Persónuvernd getur einnig ákveðið að leyfishafar 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.

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

Virðingarfyllst

Teitur Skúlason

Helga Grethe Kjartansdóttir

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Reykjavík, 30. maí 2013
Tilvísun: 2013010062HGK/--

Efni: Viðbót við leyfi, dags. 7. mars 2013, vegna rannsóknarinnar „Notkun örvandi lyfja við ADHD (ofvirkni með athyglisbrest) meðal fullorðna á Íslandi 2003-2012“

Persónuvernd hefur borist bréf yðar, dags. 7. maí 2013, þar sem óskað er eftir viðbótarleyfi vegna rannsóknarinnar „Notkun örvandi lyfja við ADHD (ofvirkni með athyglisbrest) meðal fullorðna á Íslandi 2003-2012“. Með bréfi, dags. 7. mars 2013, veitti Persónuvernd yður, Drífu Pálín Geirsdóttur, Matthíasi Halldórssyni, Þórólfi Þórlindssyni og Grétari Sigurbergssyni, leyfi til aðgangs að lyfjagagnagrunni landlæknis vegna framangreindrar rannsóknar. Í erindi yðar segir m.a.:

> „[...Ó]skar undirrituð eftir viðbótarleyfi til þess að rannsaka samhliða lyfjanotkun hjá fullorðnum einstaklingum sem nota *adrenvirk lyf með verkun á miðtaugakerfið* (ATC flokkur N06BA). Óskað er eftir leyfi Persónuverndar til að skoða samhliða úttektir fyrir eftirtalin lyf, sem einnig hafa verkun á miðtaugakerfið, hjá þessum einstaklingum:
>
> - N02 - Verkjalyf
> - N02A - Ópíóíðar
> - N02B - Önnur verkjalyf og hitalækkandi lyf
> - N02C - Mígrenilyf
> - N03 - Flogaveikislyf
> - N04 - Parkinsonlyf
> - N05 - Geðlyf
> - N05A - Geðrofslyf
> - N05B - Róandi og kvíðastillandi lyf
> - N05C - Svefnlyf og róandi lyf
> - N06 - Geðlyf
> - N06A - Þunglyndislyf

- N06C - Geðlyfjablöndur
- N06D - Lyf við heilabilun
- N06BC - Xantínafleiður
- N06BX - Önnur örvandi lyf og lyf sem efla heilastarfsemi

- N07 - Önnur lyf með verkun á taugakerfið

Samhliða lyfjanotkun hjá notendum *adrenvirkra lyfja með verkun á miðtaugakerfið* verður skilgreind þannig að þeir hafi jafnframt leyst út tiltekin lyf sem tilheyra lyfjaflokki N (sbr. upptalningu að framan) einu sinni eða oftar sama árið. Sem og fyrr verða öll persónuauðkenni afmáð [hjá] embætti landlæknis áður en rannsakendur fá rannsóknargögn í hendur. Þess verður jafnframt gætt, eftir sem áður, að flokkun rannsóknarbreyta verði það gróf að með engu móti verði unnt að bera kennsl á notendur lyfjanna.

Með upplýsingum um samhliða lyfjanotkun notenda örvandi lyfja munu rannsakendur greina lyfjanotkunarmynstur út frá s.k. „Lórenz kúrfu" sem gefur vísbendingar um dreifingu daglegra dagskammta (DDD) allra lyfja sem hafa verkun á miðtaugakerfið. Slíkar greiningar geta reynst afar gagnlegar til þess að koma auga á mögulega misnotkun lyfja."

Þá hefur Persónuvernd móttekið undirritaða yfirlýsingu embættis landlæknis, dags. 23. maí 2013, þar sem embættið heimilar fyrir sitt leyti aðgang að framangreindum upplýsingum úr lyfjagagnagrunni landlæknis, til viðbótar þeim upplýsingum úr lyfjagagnagrunni sem vísað er til í leyfi Persónuverndar, dags. 7. mars 2013, í samræmi við 4. mgr. 27. gr. lyfjalaga nr. 93/1994 og f- og m-liði 4. gr. laga um landlækni og lýðheilsu nr. 41/2007.

Það tilkynnist yður hér með að Persónuvernd gerir ekki athugasemdir við fyrirhugaðar breytingar á framkvæmd rannsóknarinnar, þ.e. að einnig verði aflað upplýsinga um úttektir tilgreindra lyfja sem hafa verkun á miðtaugakerfið hjá öllum fullorðnum einstaklingum sem hafa leyst út lyf með ATC flokkun á Íslandi á tímabilinu 2002 til og með 2012, enda verði farið að öllum þeim skilmálum sem kveðið er á um í áður útgefnu leyfi stofnunarinnar, dags. 7. mars 2013, til yðar vegna rannsóknarinnar.

Virðingarfyllst

Helga Grethe Kjartansdóttir

Vigdís Eva Líndal