Received Date: 14-Jan-2014

Accepted Date: 19-Mar-2014

Article Type: Original Article

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

Running title: ADHD drug use: adult population study

Drifa Palin Geirs[1], Anton Pottegård[2 & 3], Matthías Halldórsson[4] and Helga Zoëga[1]

1) Centre of Public Health Sciences, Faculty of Medicine, University of Iceland, Reykjavík, Iceland
2) Clinical Pharmacology, Institute of Public Health, University of Southern Denmark, Odense, Denmark.
3) Department of Clinical Chemistry & Pharmacology, Odense University Hospital, Odense, Denmark.
4) Department of Psychiatry, Landspitali University Hospital, Hringbraut, Reykjavík, Iceland.

Author for correspondence: Drifa Palin Geirs, Centre of Public Health Sciences, University of Iceland. Stapi v/Hringbraut, 101 Reykjavík, Iceland (email: dpg1@hi.is).

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.

This article has been accepted for publication and undergone full peer review but has not been through the copyediting, typesetting, pagination and proofreading process, which may lead to differences between this version and the Version of Record. Please cite this article as doi: 10.1111/bcpt.12243

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, i.e., 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 amongst 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 on patients and 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 name, formulation, package and volume). The Medicines Registry does not hold information on the underlying indication

for the prescribed drugs. Table 1 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: *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 1,000 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 1,000 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 1) [39]; 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 & Hallas [40] that is based on the waiting time distribution [41]. 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 1,000 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 by 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, i.e. 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 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 amongst those who had long pauses between prescriptions.

All calculations were performed using 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 5,292 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, 33,389 prescriptions for instant release formulations), followed by amphetamine (10,221 prescriptions) and atomoxetine (5,384 prescriptions).

The 1-year period prevalence for ADHD drug use in Iceland increased over the study period, from 2.9 per 1,000 in 2003 to 12.2 per 1,000 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 1,000 young females and 2.7 to 24.0 per 1,000 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-fold (table 2), 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 1,000) and lowest among adults 50 years and older (from 0.6 to 1.5 per 1,000). Specialists in psychiatry initiated ADHD 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 4,069 individual users were eligible to assess treatment duration. The proportion of ADHD drug users still receiving treatment after one 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-fold increase in use of ADHD 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 three 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 ten years [32] allows us to interpret our results with confidence. Given the conflicting messages of treatment options for adult ADHD and on-going 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, 42, 43]. Whereas ADHD is more commonly diagnosed among boys than 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, 42, 43]. 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, 42, 43]. However, the estimated utilization in Iceland is indeed higher than what has been reported for adults in Sweden in 2009, 3.6 per 1,000 (22-45 years) [9]; Denmark in 2011, 7-11 per 1,000 (18-24 years), 4-5 per 1,000 (25-49 years) [12]; and the UK in 2008, 1.1 per 1,000 (18-24 years), <1 per 1,000 (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, though, 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 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 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, 45]. According to both European [14, 15, 26] and Icelandic [35] clinical guidelines, adult ADHD diagnosis is based on careful and systematic assessment of a lifetime 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, 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 treatments 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 International Narcotics Control Board [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, 46-48], while discontinuation patterns among individuals who start treatment in adulthood have been documented to a lesser extent. We found that one 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 eight (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 three 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 three years of ADHD drug treatment, 24%, 34%, 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 three 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, 42, 43], 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 has no conflict of interest to declare in general or in relation to this study.

Helga Zoëga has no conflict of interest to declare in general or in relation to this study.

Matthias Halldorsson has 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.

References

1. Wilens TE, Morrison NR, Prince J. An update on the pharmacotherapy of attention-deficit/hyperactivity disorder in adults. Expert Rev Neurother 2011;**11**:1443-65.

2. Scheffler RM, Hinshaw SP, Modrek S, Levine P. The global market for ADHD medications. Health Aff (Millwood) 2007;**26**:450-7.

3. Zoega H., Baldursson G., Halldorsson M. [Use of methylphenidate among children in Iceland 1989-2006]. Laeknabladid 2007;**93**:825-32.

4. Zoëga H, Furu K, Halldórsson M, Thomsen PH, Sourander A, Martikainen J. Use of ADHD drugs in the Nordic countries: a population-based comparison study. Acta Psychiatr Scand 2011;**123**:360-7.

5. Donker GA, Groenhof F, van der Veen WJ. [Increasing trend in prescription of methylphenidate in general practices in the north-east of The Netherlands, 1998-2003]. Ned Tijdschr Geneeskd 2005;**149**:1742-7.

6. Asheim H, Nilsen KB, Johansen K, Furu K. [Prescribing of stimulants for ADHD in Nordland County]. Tidsskr Nor Laegeforen 2007;**127**:2360-2.

7. Lillemoen PK, Kjosavik SR, Hunskar S, Ruths S. Prescriptions for ADHD medication, 2004-08. Tidsskr Nor Laegeforen 2012;**132**:1856-60.

8. van den Ban E, Souverein P, Swaab H, van Engeland H, Heerdink R, Egberts T. Trends in incidence and characteristics of children, adolescents, and adults initiating immediate- or extended-release methylphenidate or atomoxetine in the Netherlands during 2001-2006. J Child Adolesc Psychopharmacol 2010;**20**:55-61.

9. Zetterqvist J, Asherson P, Halldner L, Langstrom N, Larsson H. Stimulant and non-stimulant attention deficit/hyperactivity disorder drug use: total population study of trends and discontinuation patterns 2006-2009. Acta Psychiatr Scand 2013;**128**:70-7.

10. Volkow ND, Swanson JM. Clinical practice: Adult attention deficit-hyperactivity disorder. N Engl J Med 2013;**369**:1935-44.

11. Moriyama TS, Polanczyk GV, Terzi FS, Faria KM, Rohde LA. Psychopharmacology and psychotherapy for the treatment of adults with ADHD-a systematic review of available meta-analyses. CNS Spectr 2013;**18**:296-306.

12. Pottegard A, Bjerregaard BK, Glintborg D, Hallas J, Moreno SI. The use of medication against attention deficit hyperactivity disorder in Denmark: a drug use study from a national perspective. Eur J Clin Pharmacol 2012;**68**:1443-50.

13. Pottegard A, Bjerregaard BK, Glintborg D, Kortegaard LS, Hallas J, Moreno SI. The use of medication against attention deficit/hyperactivity disorder in Denmark: a drug use study from a patient perspective. Eur J Clin Pharmacol 2013;**69**:589-98.

14. National Institute for Health and Clinical Excellence (NICE). Attention deficit hyperactivity disorder: Diagnosis and management of ADHD in children, young people and adults 2008 [updated 27 March 2013; cited 2013 May 15]. Clinical guidelines CG72:[Available from: http://www.nice.org.uk/nicemedia/live/12061/42059/42059.pdf.

15. Kooij SJ, Bejerot S, Blackwell A, Caci H, Casas-Brugue M, Carpentier PJ, et al. European consensus statement on diagnosis and treatment of adult ADHD: The European Network Adult ADHD. BMC Psychiatry 2010;**10**:67.

16. Huss M, Ginsberg Y, Tvedten T, Arngrim T, Philipsen A, Carter K, et al. Methylphenidate hydrochloride modified-release in adults with attention deficit hyperactivity disorder: a randomized double-blind placebo-controlled trial. Adv Ther 2014;**31**:44-65.

17. European Medicines Agency makes recommendations for safer use of Ritalin and other methylphenidate-containing medicines in the EU [press release]. London: EMEA, January 22 2009.

18. Ramos-Quiroga JA, Montoya A, Kutzelnigg A, Deberdt W, Sobanski E. Attention deficit hyperactivity disorder in the European adult population: prevalence, disease awareness, and treatment guidelines. Curr Med Res Opin 2013;**29**:1093-104.

19. Medice. Medice receives first German authorisation for treatment of adult ADHD. Iserlohn, Deutschland: Medice; 2011 [cited 2014 Feb. 24]. Available from: http://www.medice.de/service-en/news/medice-receives-first-german-authorisation-for-treatment-of-adult-adhd.

20. McKee S. UK licenses first therapy for adults diagnosed with ADHD 2013 Jun 3 [cited 2013 Sept 27]. Available from: http://www.pharmatimes.com/article/13-06-03/UK_licenses_first_therapy_for_adults_diagnosed_with_ADHD.aspx.

21. Medicines and Healthcare Products Regulatory Agency (MHRA). Public assessment report, decentralised procedure: Strattera 80mg hard capsules, Strattera 100mg hard capsules. . 2013.

22. Institut for Rationel Farmakoterapi. Strattera (atomoxetin): IRF; 2013 [updated Sept 23; cited 2013 Sept 30]. Available from: http://irf.dk/dk/nyheder/strattera_atomoxetin.htm.

23. Asherson P, Adamou M, Bolea B, Muller U, Morua SD, Pitts M, et al. Is ADHD a valid diagnosis in adults? Yes. BMJ 2010;**340**:c549.

24. Moss A. Europe regulators not yet on board with adult ADHD due to concerns regarding diagnosis methods [Online]. London: Financial Times; 2013 May 9 [cited 2013 Sept 15]. Available from: http://www.ft.com/cms/s/2/8b721a20-b8e9-11e2-a6ae-00144feabdc0.html#axzz2leqzwEQd.

25. Moncrieff J, Timimi S. Is ADHD a valid diagnosis in adults? No. BMJ 2010;**340**:c547.

26. Nutt DJ, Fone K, Asherson P, Bramble D, Hill P, Matthews K, et al. Evidence-based guidelines for management of attention-deficit/hyperactivity disorder in adolescents in transition to adult services and in adults: recommendations from the British Association for Psychopharmacology. J Psychopharmacol 2007;**21**:10-41.

27. Steinhausen HC. Attention-deficit hyperactivity disorder in a life perspective. Acta Psychiatr Scand 2003;**107**:321-2.

28. Ramos-Quiroga JA, Ochoa Sagüés M. Adult ADHD: an area lacking in clinical research? Clinical Investigation 2013;**3**:803-5.

29. International Narcotics Control Board. Report of the International Narcotics Control Board on the Availability of Internationally Controlled Drugs: Ensuring Adequate Access for Medical and Scientific Purposes Vienna: United Nations: International Narcotics Control Board, 2011.

30. Zuvekas SH, Vitiello B. Stimulant medication use in children: a 12-year perspective. Am J Psychiatry 2012;**169**:160-6.

31. McCarthy S, Wilton L, Murray ML, Hodgkins P, Asherson P, Wong IC. The epidemiology of pharmacologically treated attention deficit hyperactivity disorder (ADHD) in children, adolescents and adults in UK primary care. BMC Pediatr 2012;**12**:78.

32. Directorate of Health Iceland. Icelandic Medicine Registry. Reykjavik, 2013.

33. Furu K, Wettermark B, Andersen M, Martikainen JE, Almarsdottir AB, Sorensen HT. The Nordic countries as a cohort for pharmacoepidemiological research. Basic Clin Pharmacol Toxicol 2010;**106**:86-94.

34. Statistics Iceland. Population by sex and age 1841-2013. 2013 [cited 2013 June 24]. Available from: http://www.statice.is/Statistics/Population/Overview.

35. Baldursson G, Magnusson P, Haraldsson HM, Halldorsson M. [ADHD - Guidelines for diagnosis and treatment of attention deficit hyperactivity disorder] Reykjavik, Iceland: Directorate of Health; 2012 [cited 2013 March 21]. Available from: http://www.landlaeknir.is/utgefid-efni/skjal/item14259/.

36. Icelandic Medicine Agency. Summaries of product characteristics (SmPC). Reykjavik: Icelandic Medicine Agency; 2010-2013.

37. World Health Organization. WHO collaborating centre for drug statistics methodology: ATC/DDD index 2013 Oslo: World Health Organization; 2013 [cited 2013 14.03]. Available from: http://www.whocc.no/atc_ddd_index/.

38. The Icelandic Health Insurance. [Modiodal - guidelines for reimbursement] Modiodal - Lyfjaskírteini - vinnuregla 2013 [cited 2013 Jul 10]. Available from: http://www.sjukra.is/media/lyfjaskirteini-4.mai-2013/Modiodal-mai-2013_.pdf.

39. Icelandic Medicine Agency. Reykjavik, 2013.

40. Pottegard A, Hallas J. Assigning exposure duration to single prescriptions by use of the waiting time distribution. Pharmacoepidemiol Drug Saf 2013;**22**:803-9.

41. Hallas J, Gaist D, Bjerrum L. The waiting time distribution as a graphical approach to epidemiologic measures of drug utilization. Epidemiology 1997;**8**:666-70.

42. Fayyad J, De Graaf R, Kessler R, Alonso J, Angermeyer M, Demyttenaere K, et al. Cross-national prevalence and correlates of adult attention-deficit hyperactivity disorder. Br J Psychiatry 2007;**190**:402-9.

43. Simon V, Czobor P, Balint S, Meszaros A, Bitter I. Prevalence and correlates of adult attention-deficit hyperactivity disorder: meta-analysis. Br J Psychiatry 2009;**194**:204-11.

44. The Icelandic Health Insurance. [Health care contracts] Samningar um heilbrigðisþjónustu 2013 [cited 2013 Oct 9]. Available from: http://www.sjukra.is/heilbrigdisstarfsfolk/samningar-um-heilbrigdisthjonustu/.

45. Asherson P, Chen W, Craddock B, Taylor E. Adult attention-deficit hyperactivity disorder: recognition and treatment in general adult psychiatry. Br J Psychiatry 2007;**190**:4-5.

46. Banaschewski T, Coghill D, Santosh P, Zuddas A, Asherson P, Buitelaar J, et al. Long-acting medications for the hyperkinetic disorders. A systematic review and European treatment guideline. Eur Child Adolesc Psychiatry 2006;**15**:476-95.

47. van den Ban E, Souverein PC, Swaab H, van Engeland H, Egberts TC, Heerdink ER. Less discontinuation of ADHD drug use since the availability of long-acting ADHD medication in children, adolescents and adults under the age of 45 years in the Netherlands. Atten Defic Hyperact Disord 2010;**2**:213-20.

48. McCarthy S, Asherson P, Coghill D, Hollis C, Murray M, Potts L, et al. Attention-deficit hyperactivity disorder: treatment discontinuation in adolescents and young adults. Br J Psychiatry 2009;**194**:273-7.

Tables and Figures

Table 1. ADHD drugs with marketing authorization in Iceland 2003-2012

Name	ATC class	DDD (mg)	Adult indication in Iceland (SmPC / Guidelines)[c]	Prescription restrictions	Year of marketing authorization[47]
Amphetamine	N06BA01	15	No / Yes	Controlled substance[d] max dosage 30 days	1991-2011[g]
Methylphenidate	N06BA04	30[a]	No / Yes		
instant release				Controlled substance max dosage 30 days	1965
extended release				Controlled substance max dosage 100 days [e]	2002
Atomoxetine	N06BA09	80[b]	Yes / Yes	Prescriptions by specialists only[f]	2005[h]

a. Same DDD for both immediate-release and long-acting methylphenidate products [37].

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 [37].

c. According to drug package insertion and national clinical guidelines.

d. Categorized as controlled substance by the INCB and prescriptions should be monitored [29, 32]

e. Prior to 2006 the max dosage was 30 days.

f. Reimbursement only available for prescriptions issued by specialists.

g. Original marketing authority in 1991 deregistered in 2011. Current marketing authority under exemption and not registered.

h. Atomoxetine available in Iceland unlicensed from 2003.

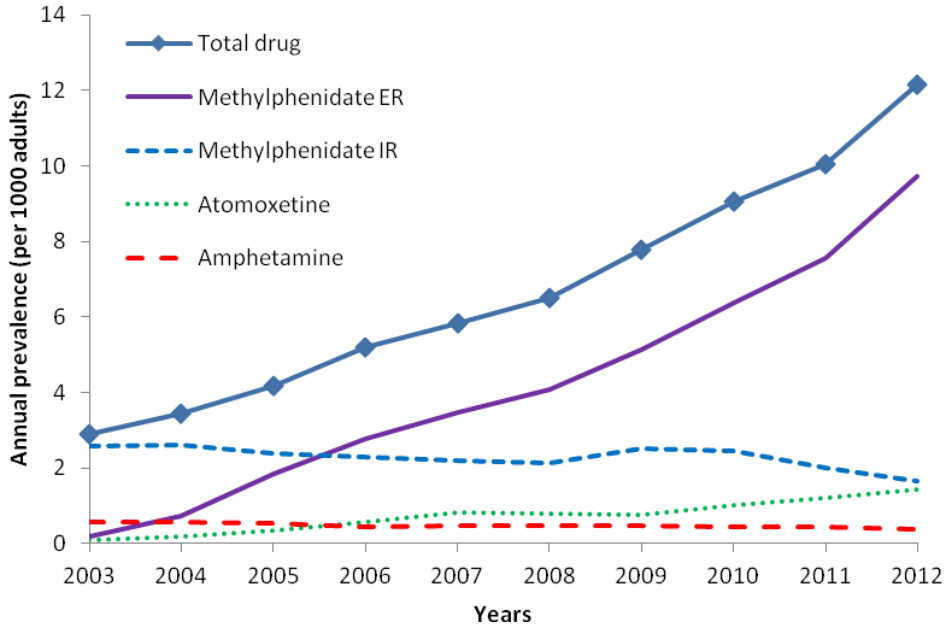

Figure 1. Prevalence* of ADHD drug use among adults (19 years and older) in Iceland 2003-2012

*Prevalence (prev.) proportions are expressed as number of adults per 1000 adults in the population filling at least one prescription in the relevant year.

Table 2. New users of ADHD drugs among adults (19 years and older) in Iceland 2004-2012

		Incidence[a] (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 (1,085)
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

a. Incidence defined as the number of individuals per 1,000 in the population who filled their first prescription for an ADHD drug in the relevant calendar year

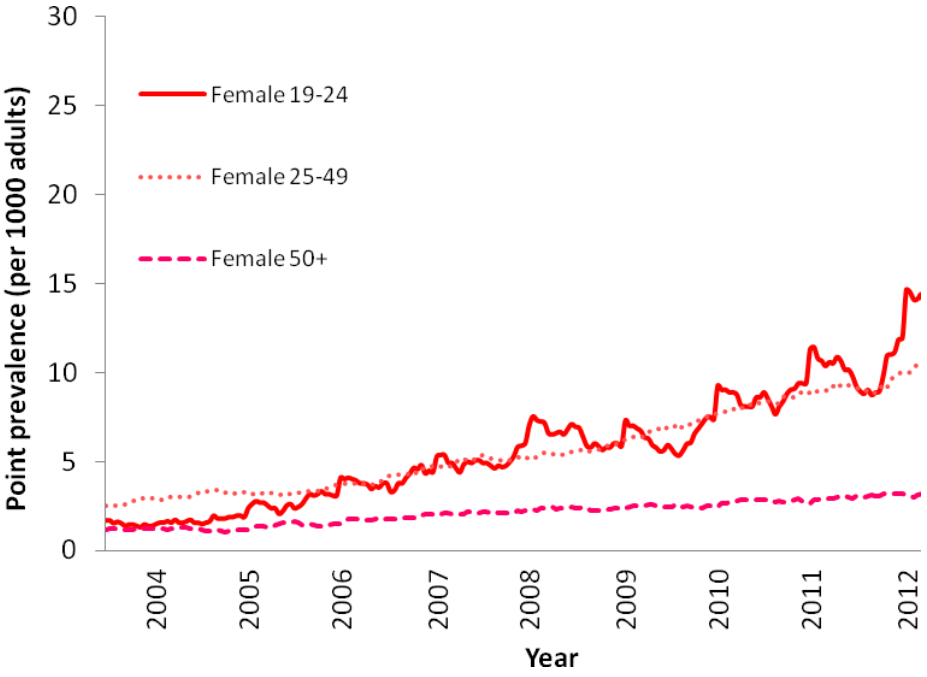

Figure 2a Point prevalence* of ADHD drug use among females (19 years and older) in Iceland 2003-2012

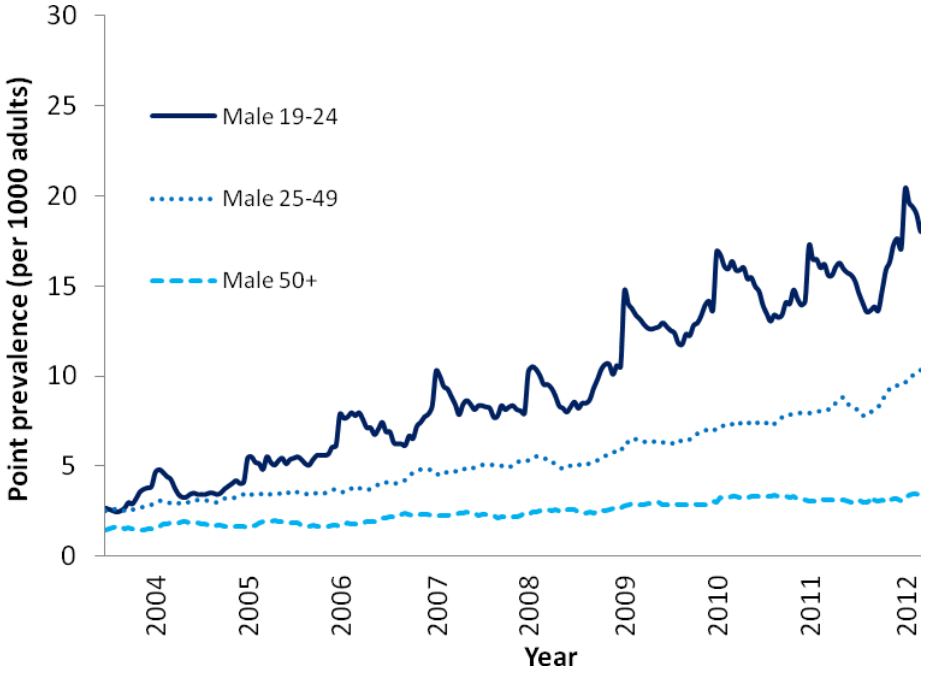

Figure 2b Point prevalence* of ADHD drug use among males (19 years and older) in Iceland 2003-2012

***** 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

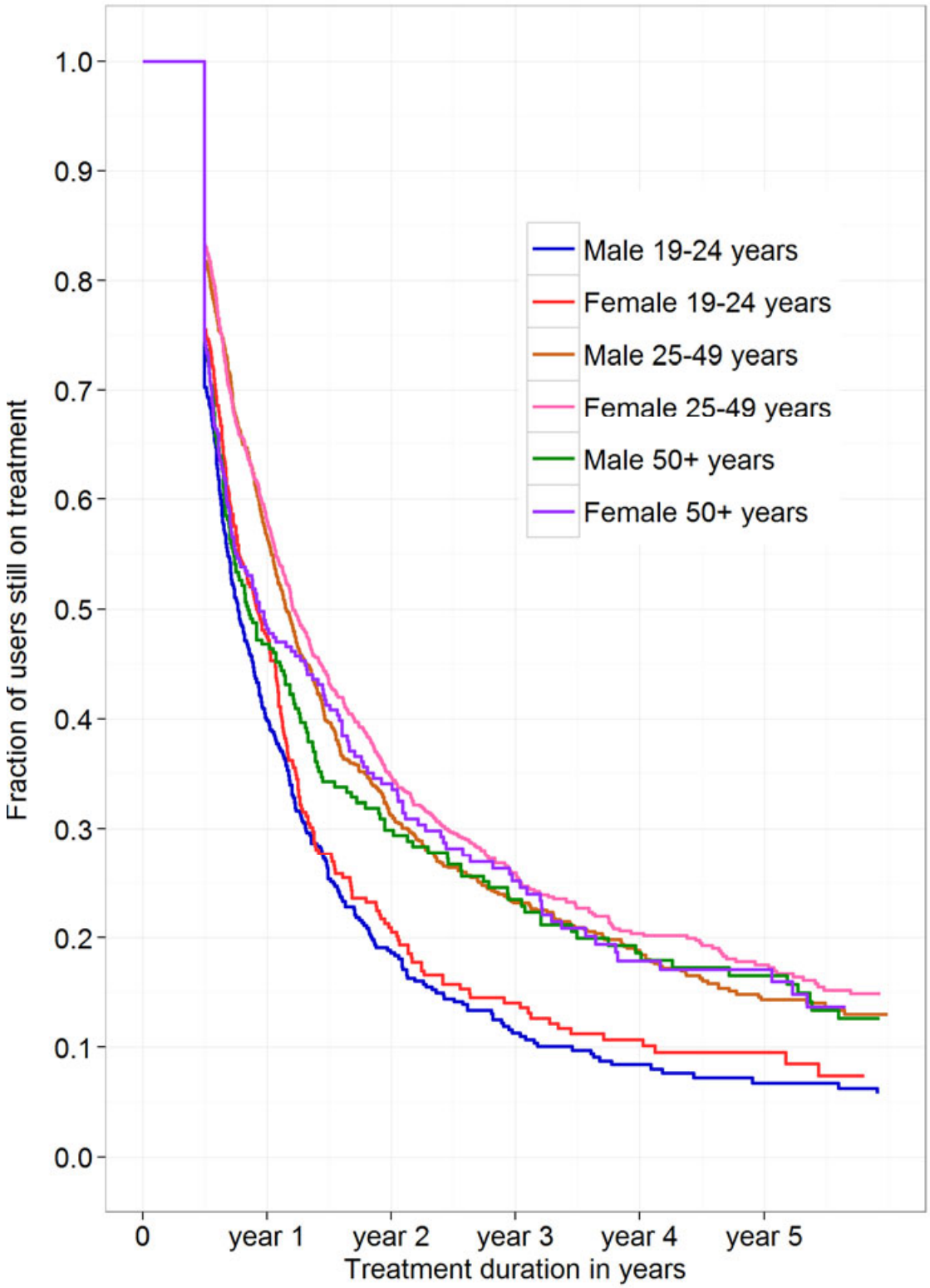

Figure 3. Kaplan-Meier curve of duration* of ADHD drug treatment according to age group and sex.

* Treatment was considered terminated when 180 days had passed without an ADHD prescription fill.