ORIGINAL RESEARCH

Estimated prevalence and incidence of diagnosed ADHD and health care utilization in adults in Sweden – a longitudinal population-based register study

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Background: Although the worldwide prevalence of attention-deficit/hyperactivity disorder (ADHD) in adults is estimated to be between 2% and 5%, it is considered to be underdiagnosed. This register study explored the prevalence of diagnosed ADHD and incidence of newly diagnosed ADHD in Swedish adults over time, and assessed comorbidities and pharmacologic treatment.

Methods: National Patient Register data were used to estimate the overall prevalence of adults (≥18 years) with a registered ADHD diagnosis from 2006 to 2011, and the incidence of newly registered diagnoses from 2007 to 2011. Data from the Prescribed Drug Register were used to estimate the mean dose of the most frequently prescribed ADHD medication.

Results: The estimated annual prevalence (N=44,364) of diagnosed ADHD increased from 0.58 per 1,000 persons in 2006 to 3.54 per 1,000 persons in 2011. The estimated annual incidence of newly diagnosed ADHD (N=24,921) increased from 0.39 per 1,000 persons to 0.90 per 1,000 persons between 2007 and 2011. At least one comorbidity was diagnosed in 52.6% of adults with ADHD (54.0% of newly diagnosed adults), with anxiety, substance use disorders, and depression being the most common. Among all adults with ADHD, 78.9% (65.7% of newly diagnosed adults) were prescribed ADHD medication and one-third were prescribed more than one add-on medication. Osmotic release oral system methylphenidate was the most commonly used medication. The mean daily dose was 51.5 mg, and was significantly higher in males, patients with substance use disorders, patients with drug holidays, and patients with at least one add-on medication. The most frequent concomitant medications were anxiolytics and hypnotics.

Conclusion: In Sweden, the number of adults diagnosed with ADHD increased between 2006 and 2011, and the majority of patients were prescribed ADHD-specific medication. Over one-half of patients had psychiatric comorbidities; one-third were prescribed more than one add-on medication. Consumption of pharmacologic ADHD medication was high in specific patient subpopulations.

Keywords: prevalence, attention-deficit/hyperactivity disorder, adult, register analysis, daily dose, methylphenidate, comorbidity, concomitant medication, treatment dosing

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Introduction

Attention-deficit/hyperactivity disorder (ADHD) is a heterogeneous neurodevelopmental disorder characterized by core symptoms of inattention, hyperactivity, and impulsivity, with childhood onset and at least partial persistence into adulthood in the majority of cases.[1–3] The worldwide prevalence of ADHD in adults is estimated to be between 2%

and 5%.[4–8] In Sweden, ADHD in adults has been reported to account for 2.7% of all psychiatric diagnoses.[9] In general, it is thought that <20% of patients with ADHD are formally diagnosed, and only a small proportion receive pharmacologic treatment for their condition.[8,10] A study conducted in the USA, based on a national survey and follow-up interviews, revealed that only 10.9% of adults with ADHD received pharmacologic treatment in the year prior to the interview.[6]

Diagnosis of ADHD requires a comprehensive review of symptoms and related functional impairments. Criteria routinely used for diagnosis of children and adults with ADHD are the American Psychiatric Association's *Diagnostic and Statistical Manual of Mental Disorders* – 5th Edition (DSM-5),[11] which replaced the previous version (*Diagnostic and Statistical Manual of Mental Disorders* – 4th Edition [DSM-IV])[12] in 2013, and the International Statistical Classification of Diseases and Related Health Problems, Tenth Revision (ICD-10).[13] Both the DSM-5 and ICD-10 focus on describing the behavioral problems associated with ADHD, but differences exist in the diagnostic approach; for example, the DSM-5 divides symptoms into 2 groups, inattention and hyperactivity-impulsivity, which the ICD-10 does not. Neither of these diagnostic instruments, however, addresses adult ADHD symptoms comprehensively, with some symptoms of adult ADHD absent from the diagnostic criteria, such as emotional dysregulation.[11,13–15] The diagnostic procedure in Sweden includes a clinical diagnostic interview with the patient and significant others (usually parents or spouses) to assess the patient's developmental and current medical history. Assessment of comorbid disorders, physical examination, and tests for cognitive and executive functioning are also performed.[16] DSM-5 criteria are most commonly used for diagnosis in clinical practice in Sweden (and may be converted into an ICD-10 diagnosis using the DSM converter).[17]

ADHD in adulthood is an important health issue both for the individual and at a societal level.[10] ADHD affects the working and social life of patients and is linked to unemployment.[18] Furthermore, ADHD is associated with higher use of health care services; for example, due to increased risk of injuries and transport accidents, criminality, smoking, and substance use disorders (SUDs).[6,19–21] In general, ADHD frequently coexists with other psychiatric disorders and social problems. It has been reported that ~80% of individuals with ADHD (both children and adults) have at least one registered psychiatric comorbidity,[22] such as depression, anxiety, SUD, bipolar disorder, antisocial personality disorder, and impulse control disorders.[6,10,23,24] Consequently, in addition to ADHD-specific pharmacologic treatment, many patients

with ADHD also use psychotropic medications,[25] such as antidepressants, antipsychotics, hypnotics, or sedatives, or medications used to treat addiction disorders.[3,22,25]

During the period of the current study (2006–2011), no registered pharmaceuticals were approved for treatment of ADHD in adults. Since then, osmotic release oral system methylphenidate (OROS-MPH) has been approved for continued treatment in adulthood in 2011, atomoxetine (ATX) for adults in 2013, and methylphenidate extended release in 2014 for adults newly diagnosed with ADHD. In Sweden, psychiatry specialists and trained pediatric neurologists can initiate pharmacologic treatment with MPH in patients with ADHD, while the authority to prescribe ATX is not restricted to psychiatry specialists.[17] During the period studied, amphetamines (amphetamine and dexamphetamine) were recommended in Sweden as the last treatment option and were only available on a named-patient basis.[17] Since December 2013, the long-acting prodrug lisdexamfetamine (LDX) has been available in Sweden: it was initially approved for treatment of ADHD in children and adolescents (6–17 years) when response to previous MPH treatment was considered clinically inadequate.[26] Since March 2015, LDX has also been approved for the treatment of ADHD in adults.[26]

In Nordic countries including Sweden, awareness of ADHD appears to be increasing, with higher reported rates of diagnosis and treatment in recent years,[3,22,25,27] and an increase in ADHD prescriptions over time, for both sexes and irrespective of age.[3,28] Despite such increases, adults with ADHD may still be undertreated, and rates of treatment discontinuation in adolescents and young adults are higher than expected considering the persistence of the disorder in later life.[28] A comprehensive overview of the prevalence and treatment of ADHD in adults in Sweden is needed to inform clinicians and aid resource planning for patient management in the future.

The objectives of this study were to explore over time the overall prevalence of diagnosed ADHD between 2006 and 2011, and the incidence of newly registered ADHD diagnoses between 2007 and 2011 in Swedish adults, and to assess comorbidities and pharmacologic treatment use in this population.

Methods

This was a retrospective, longitudinal, observational, register study in Sweden of all adults with a registered diagnosis of ADHD between 2006 and 2011, and adults newly diagnosed with ADHD between 2007 and 2011. Data were derived through the linkage of two national population-based registers (using unique personal identification

numbers): the National Patient Register (NPR) and the Prescribed Drug Register (PDR), both held by the National Board of Health and Welfare (Stockholm, Sweden).[29] The NPR has nationwide coverage of about 75% for psychiatric outpatient care since 2001 and includes information on patient characteristics such as age and sex, date of the visit, primary discharge diagnosis, and up to 7 secondary diagnoses assigned by the treating medical doctor in accordance with ICD-10.[13] The PDR provides information on all prescribed medications since 2005, with identity data for more than 99.7% of patients.[30] Data were unidentified when analyzed, and the study was approved by the Regional Ethical Review Board (protocol reference number: 2012/1315-31/3) in Stockholm. As this was a retrospective register study, informed consent by participants was not sought and the Regional Ethical Review Board deemed this ethically acceptable.

Patients

Through the NPR, adults (18 years and above) with a diagnosis of ADHD or hyperkinetic disorder defined by the ICD-10 codes F90.0–F90.9 and F98.8, either as the primary or secondary diagnosis, were identified. The F98.8 code was included to minimize the risk of missing any ADHD cases, as this code was used for ADHD without hyperactivity during this time period in some regions of Sweden. Data on age, sex, and the comorbid diagnoses (ICD codes are listed in Table 1) of autism, atypical autism, anxiety, Asperger syndrome, bipolar disorder, depression, eating disorder, impulse control disorder, personality disorder, oppositional defiant disorder, schizophrenia, and SUD were obtained. The PDR provided data (including dispensing date) on ADHD medications, including OROS-MPH, immediate-release methylphenidate (MPH-IR), modified-release methylphenidate (MPH-MR), ATX, amphetamine, dexamphetamine, and modafinil. Medications with the Anatomical Therapeutic Chemical (ATC) code substring "N06BA" were considered to be ADHD medications.[31] Although ATX and OROS-MPH were not approved for use in adults at the time of the study, both were approved for use in children and adolescents, and were used off-label for adults with ADHD. Modafinil is not indicated for use in ADHD but is prescribed off-label for this indication.[32] Information on concomitant medications was also obtained through the PDR. The categories of psychotropic medications used were anxiolytics, hypnotics, selective serotonin reuptake inhibitors (SSRIs), serotonin–norepinephrine reuptake inhibitors (SNRIs), antipsychotics, non-selective antidepressants, and other antidepressants; the ATC codes for the medications within each of these categories are listed in Table 1.

A cross-sectional dataset included information from January 1, 2006 through December 31, 2011, to estimate the prevalence of diagnosed ADHD. A longitudinal dataset was created, including data from January 1, 2007 through December 31, 2011, to estimate the rate of newly diagnosed adult ADHD and to analyze pharmacologic treatment patterns. For patients to be included in the longitudinal dataset, a 12-month period prior to their first appearance in the NPR with defined ADHD diagnosis, during which no ADHD medication (stimulants or non-stimulants) was dispensed, was required. Each patient was followed for a maximum of 5 years after the index date (until December 31, 2011).

Measures
Estimated prevalence of diagnosed ADHD and estimated incidence of newly diagnosed ADHD

In Sweden, assessment of ADHD in adults is performed at outpatient clinics by multi-professional teams, including a psychiatrist and a psychologist, and often an occupational therapist and a nurse. Detailed recommendations regarding ADHD diagnostic assessments are published by the Swedish National Board of Health and Welfare.[16] DSM-5 criteria are commonly used for diagnosing ADHD, and the diagnosis must be reported in the NPR using an ICD-10 code; DSM codes may be translated to an ICD code using a specific code key.

The estimated prevalence rate of ADHD was calculated by dividing the total number of patients with a registered diagnosis of ADHD in the cross-sectional data set per year by the population statistics for Sweden per year overall and by age group (18–21 years, 22–64 years, ≥65 years).[33] It was assumed that the size of the population in Sweden was stable during the year and equal to the value measured on November 1 of each year.

The estimated incidence of newly diagnosed ADHD was calculated by dividing the number of newly diagnosed patients in the longitudinal dataset per year by the population statistics for Sweden per year, overall and by age group.

The proportions of patients according to sex and age group, and median and mean (SD) age, were calculated for both the cross-sectional and longitudinal datasets to generate yearly rates.

Comorbidities

All unique adults with diagnosed ADHD in the cross-sectional dataset with registered comorbidities (secondary diagnoses translated from DSM codes to ICD-10 criteria) during the study period were identified. The proportion of patients with at least one registered comorbid disorder was

Table 1 Independent variables used in multiple linear regression with PDD as response variable

Variable	Value	Definition	Comment
Age	≥18 years	n/a	Age was used as a continuous variable
Sex	0= female, 1= male	n/a	
Drug holiday	0= no, 1= yes	Gap between observations for a patient in the PDR that exceeds 90 days (ie, the grace period, associated with the common maximum prescription length in Sweden)	
Expedition year	Starting year: 2006		
ADHD diagnosis[a]	Disturbance of activity and attention (F90.0); DAMP (F90.0A); ADHD (F90.0B); activity and attention disturbance (F90.0C); activity and attention disturbance, unspecified (F90.0X); hyperkinetic conduct disorders (F90.1); other hyperkinetic disorders (F90.8); ADHD, unspecified type (F90.9); other specified emotional disorders with an onset in childhood or adolescence (F98.8)	Presence of diagnosis code in the NPR	All patients will, by definition, have at least one of the diagnoses
Region	Stockholm, west Sweden, south Sweden, mid-Sweden, north Sweden	Region where the patient lived during the study period	
Comorbidity[a]	Autism (F84.0); atypical autism (F84.9); anxiety (F41.2–F41.9); Asperger syndrome (F84.5); bipolar disorder (F31.0–F31.9); depression (F33.0–F33.9); eating disorders (F50.8–F50.9); impulse control disorders (F63.8–F63.9); personality disorders (F60.0–F60.9); oppositional defiant disorders (F91.3); schizophrenia (F20.0–F23.2); substance use disorders (F10.2–F19.2)	Presence of any defined comorbidity	
Add-on ADHD medication[b]	0= no, 1= yes	Has received any other ADHD medication during the time period of OROS-MPH use	Amphetamine (N06BA01); dexamphetamine (N06BA02); atomoxetine (N06BA09); methylphenidate (OROS-MPH, MPH-IR, MPH-MR; N06BA04); modafinil (N06BA07)
Concomitant medications[b]	Antidepressants (N06AA02, N06AA04, N06AA06, N06AA09, N06AA10, N06AA21); antipsychotics (N05A-); anxiolytics (N05BA-, N05BB-); hypnotics (N05CC-, N05CD-, N05CF-, N05CH01); SSRIs (N06AB03, N06AB04, N06AB05, N06AB06, N06AB08, N06AB10); SNRIs (N06AX16, N06AX21); other (N06AX02, N06AX03, N06AX06, N06AX11, N06AX12, NO6AX18, NO6AX22)	Presence of any defined concomitant medication	

Notes: [a]Defined by code from International Statistical Classification of Diseases and Related Health Problems, Tenth Revision.[13] [b]Defined by codes from anatomic therapeutic chemical classification system.[31]
Abbreviations: ADHD, attention-deficit/hyperactivity disorder; DAMP, deficits in attention, motor control, and perception; MPH-IR, immediate-release methylphenidate; MPH-MR, modified-release methylphenidate; n/a, not applicable; NPR, National Patient Register; OROS-MPH, osmotic release oral system methylphenidate; PDD, dispensed patient daily dose; PDR, Prescribed Drug Register; SNRI, serotonin–norepinephrine reuptake inhibitor; SSRI, selective serotonin reuptake inhibitor.

estimated, and the total number of each type of comorbidity was divided by: 1) the total number of all comorbid diagnoses; 2) the total number of patients with at least one comorbid diagnosis; and 3) the complete dataset, to determine the frequency of each of the comorbidities. The same procedure was conducted for the longitudinal dataset to describe the most frequently occurring comorbidities in adults newly diagnosed with ADHD.

Pharmacologic treatment

All patients from the cross-sectional and longitudinal datasets who received ADHD medication at any point during the study period following the patients' index hospital stay or visit were identified and categorized by sex and age group. For patients in the cross-sectional dataset, age group categorization was based on the age of the patient when first registered to be dispensed ADHD medication. The total numbers of

non-medicated patients and newly diagnosed patients were also estimated and presented by age group and sex.

Pharmacologic treatment patterns

The longitudinal dataset was used to analyze pharmacologic treatment patterns for patients diagnosed during the study period. Only one substance or product was followed per patient; if patients were dispensed more than one first-line ADHD medication on the same day, as different medications or different formulations of the same medication, the medication with the highest number of defined daily doses (DDDs) was assumed to be the main first-line treatment for that patient.

To estimate the most frequently dispensed first-line formulations, the number of newly diagnosed patients receiving each type of formulation as first-line treatment was divided by the total number of newly diagnosed patients receiving pharmacologic treatment.

Second-line treatments were estimated in the longitudinal dataset by identifying treatment switches. After the addition of a second dispensed ADHD medication, the patient was followed for a 90-day period (the maximum time period for a prescription in Sweden) to ensure no reappearance of the first-line ADHD medication. To identify the most frequently dispensed second-line ADHD medications, the total number of newly diagnosed patients receiving each type of formulation as second-line treatment was divided by the total number of newly diagnosed patients receiving second-line treatment.

Add-on medication was defined as ADHD medication dispensed in addition to the first-line medication (but not constituting a medication switch within the 90-day review period). The number of newly diagnosed patients treated with 1, 2, 3, or more than 3 ADHD medications at the same time was divided by the total number of newly diagnosed patients receiving ADHD medication.

Concomitant medication was defined as an entry during the same time period as the main first-line ADHD medication. The number of newly diagnosed patients with concomitant medication was divided by the total number of newly diagnosed patients receiving ADHD pharmacologic treatment.

Mean dose of the most frequently prescribed ADHD medication

The average dispensed patient daily dose (PDD) of the most frequently prescribed ADHD medication was identified using the variable "DDD" in the PDR. The number of dispensed PDDs was multiplied by the DDD assigned by the World Health Organization (WHO)[31] and divided by the number of

days included in the study as a proxy for days on treatment. The mean PDD of the medication (presented as DDDs) was calculated using the cross-sectional dataset to represent the mean dose for all adults registered with an ADHD diagnosis, as well as in the longitudinal dataset to describe the mean dose used in newly diagnosed patients.

As more than one observation may exist for each patient in the cross-sectional dataset, potentially captured in different age groups and including different prescribed doses, all patient observations were considered in the analysis. The mean PDD, mean DDD, and distribution of DDDs were calculated separately for males and females, as well as for each age group. The independent t-test and analysis of variance were used to identify potential statistical differences in the mean dose between sexes and age groups, respectively.

The influence of individual characteristics on the PDD was explored using linear regression analysis with PDD as the continuous response variable. The selected patient characteristics for the starting model are presented in Table 1. Dummy variables were used for qualitative independent variables (eg, presence of certain comorbidities). Variables in <5% of patients were excluded from the analysis. Variable selection was based on a forward selection process with a significance level of 10% selected for variable exclusion to minimize the risk of including variables by chance. The PDD was transformed through the natural logarithm, and the regression coefficients are presented as percentage change in PDD. The final model was selected based on R^2 adjusted for number of coefficients and model interpretation (validity of variable and regression coefficient).

SAS Version 9.3 (SAS Institute Inc., Cary, NC, USA) was used in all statistical analyses. If not stated otherwise, the two-sided t-test (5% level of significance) was used for comparisons of means. The p-values presented are descriptive and are uncorrected for multiple comparisons and should be interpreted as non-inferential.

Results
Estimated prevalence of diagnosed ADHD

The cross-sectional dataset included 44,364 patients, aged 18 years and older, registered with an ADHD diagnosis during the study period (2006–2011). Over time, the estimated prevalence of diagnosed ADHD increased from 4,149 patients in 2006 to 26,820 patients in 2011, an increase in the total estimated prevalence from 0.58 per 1,000 persons in 2006 to 3.54 per 1,000 persons in 2011 (Table 2). The mean (SD) age

Table 2 Estimated prevalence[a] of diagnosed ADHD in adults, and characteristics of adult patients with an ADHD diagnosis, 2006–2011

	2006 (n=4,149)	2007 (n=6,888)	2008 (n=11,085)	2009 (n=15,414)	2010 (n=21,389)	2011 (n=26,820)
Age in years, mean (SD); median	30.8 (10.8); 29.0	31.1 (10.8); 29.0	31.5 (11.0); 29.0	31.5 (11.1); 29.0	31.9 (12.2); 29.0	31.7 (11.6); 29.0
Sex, n (%)						
Male	2,592 (62.5)	4,208 (61.1)	6,529 (58.9)	8,903 (57.8)	12,015 (56.2)	14,808 (55.2)
Female	1,557 (37.5)	2,680 (38.9)	4,556 (41.1)	6,511 (42.2)	9,374 (43.8)	12,012 (44.8)
Age group, n (%)						
18–21 years	1,109 (26.7)	1,738 (25.2)	2,690 (24.3)	3,797 (24.6)	5,380 (25.2)	6,678 (24.9)
22–64 years	3,026 (72.9)	5,131 (74.5)	8,361 (75.4)	11,572 (75.1)	15,745 (73.6)	20,000 (74.6)
≥65 years	14 (0.3)	19 (0.3)	34 (0.3)	45 (0.3)	264 (1.2)	142 (0.5)
Estimated prevalence per 1,000 persons, by age group	0.58	0.95	1.51	2.07	2.85	3.54
18–21 years	2.42	3.65	5.40	7.33	10.20	12.67
22–64 years	0.59	0.99	1.61	2.22	3.01	3.81
≥65 years	0.01	0.01	0.02	0.03	0.15	0.08

Notes: [a]Swedish population from November 2006–2011: Total, 2006: 7,190,792; 2007: 7,261,025; 2008: 7,342,036; 2009: 7,429,061; 2010: 7,507,516; 2011: 7,574,814; age 18–21 years, 2006: 457,478; 2007: 475,707; 2008: 497,843; 2009: 517,732; 2010: 527,248; 2011: 527,133; age 22–64 years, 2006: 5,138,439; 2007: 5,163,520; 2008: 5,185,548; 2009: 5,207,670; 2010: 5,229,188; 2011: 5,249,647; age ≥65 years, 2006: 1,594,875; 2007: 1,621,798; 2008: 1,658,645; 2009: 1,703,659; 2010: 1,751,080; 2011: 1,798,034.[33]
Abbreviation: ADHD, attention-deficit/hyperactivity disorder.

increased from 30.8 (10.8) years in 2006 to 31.7 (11.6) years in 2011, and the proportion of males decreased from 62.5% in 2006 to 55.2% in 2011 (Table 2).

Estimated incidence of newly diagnosed ADHD

The longitudinal dataset included 24,921 adults newly diagnosed with ADHD between 2007 and 2011. The yearly number increased from 2,809 in 2007 to 6,816 in 2011, translating to estimated incidence rate for newly diagnosed patients of 0.39 per 1,000 persons in 2007 and 0.90 per 1,000 persons in 2011 (Table 3). The mean (SD) age increased from 31.4 (10.7) years in 2007 to 32.4 (11.9) years

in 2011, and the proportion of male patients decreased from 60.3% in 2007 to 53.1% in 2011.

Comorbidities

In the cross-sectional dataset, 23,344/44,364 (52.6%) adults with diagnosed ADHD were diagnosed with at least one comorbidity during the study period. In the longitudinal dataset (13,447/24,921 [54.0%]), patients newly diagnosed with ADHD had 1 or more comorbidities. In both groups of patients, the comorbidities most commonly observed were anxiety, SUD, and depression, and the least commonly observed comorbidities were impulse control disorder and oppositional defiant disorder (Table 4).

Table 3 Estimated incidence[a] and characteristics of newly diagnosed adult patients, 2007–2011

	2007 (n=2,809)	2008 (n=4,083)	2009 (n=4,831)	2010 (n=6,382)	2011 (n=6,816)
Age in years, mean (SD); median	31.4 (10.7); 29.0	31.7 (10.8); 30.0	31.8 (11.0); 29.0	33.4 (14.0); 30.0	32.4 (11.9); 30.0
Sex, n (%)					
Male	1,695 (60.3)	2,345 (57.4)	2,726 (56.4)	3,442 (53.9)	3,621 (53.1)
Female	1,114 (39.7)	1,738 (42.6)	2,105 (43.6)	2,940 (46.1)	3,195 (46.9)
Age group, n (%)					
18–21 years	625 (22.2)	868 (21.3)	997 (20.6)	1,353 (21.2)	1,431 (21.0)
22–64 years	2,176 (77.5)	3,203 (78.4)	3,815 (79.0)	4,811 (75.4)	5,315 (78.0)
≥65 years	8 (0.3)	12 (0.3)	19 (0.4)	218 (3.4)	70 (1.0)
Estimated incidence per 1,000 persons, by age group	0.39	0.56	0.65	0.85	0.90
18–21 years	1.31	1.74	1.93	2.57	2.71
22–64 years	0.42	0.62	0.73	0.92	1.01
≥65 years	<0.01	0.01	0.01	0.12	0.04

Notes: [a]Swedish population from November 2007–2011: Total, 2007: 7,261,025; 2008: 7,342,036; 2009: 7,429,061; 2010: 7,507,516; 2011: 7,574,814; age 18–21 years; 2007: 475,707; 2008: 497,843; 2009: 517,732; 2010: 527,248; 2011: 527,133; age 22–64 years; 2007: 5,163,520; 2008: 5,185,548; 2009: 5,207,670; 2010: 5,229,188; 2011: 5,249,647; age ≥65 years; 2007: 1,621,798; 2008: 1,658,645; 2009: 1,703,659; 2010: 1,751,080; 2011: 1,798,034.[33]
Abbreviation: ADHD, attention-deficit/hyperactivity disorder.

Table 4 Most common comorbidities in adult patients with an ADHD diagnosis from 2006 to 2011 (cross-sectional dataset, N=44,364) and in newly diagnosed adult patients from 2007 to 2011 (longitudinal dataset, N=24,921)

Comorbidity, n (%)	All patients with ADHD and ≥1 comorbidity (n=23,344)				Newly diagnosed patients with ≥1 comorbidity (n=13,447)			
	N	% by comorbidity[a]	% by patients with ≥1 comorbidity[b]	% by complete dataset[c]	N	% by comorbidity[a]	% by patients with ≥1 comorbidity[b]	% by complete dataset[c]
Anxiety	9,109	25.3	39.0	20.5	5,467	26.5	40.7	21.9
Substance use disorder	6,905	19.2	29.6	15.6	3,873	18.8	28.8	15.5
Depression	6,184	17.2	26.5	13.9	3,628	17.6	27.0	14.6
Personality disorder	3,835	10.6	16.4	8.6	2,262	11.0	16.8	9.1
Asperger syndrome	3,587	10.0	15.4	8.1	1,900	9.2	14.1	7.6
Bipolar disorder	3,349	9.3	14.3	7.5	1,981	9.6	14.7	7.9
Autism[d]	1,248	3.5	5.3	2.8	569	2.8	4.2	2.3
Schizophrenia	1,112	3.1	4.8	2.5	559	2.7	4.2	2.2
Eating disorder	611	1.7	2.6	1.4	365	1.8	2.7	1.5
Impulse control disorder	60	0.2	0.3	0.1	28	0.1	0.2	0.1
Oppositional defiant disorder	43	0.1	0.2	0.1	7	<0.1	<0.1	<0.1

Notes: [a]Denominator for percentages is the total number of comorbidities (n=36,043 [all patients], n=20,639 [newly diagnosed patients]). [b]Denominator for percentages is the total number of patients with ADHD and ≥1 comorbidity (n=23,344 [all patients], n=13,447 [newly diagnosed patients]). [c]Denominator for percentages is the total number of patients in the dataset (n=44,364 [all patients], n=24,921 [newly diagnosed patients]). [d]Includes atypical autism.
Abbreviation: ADHD, attention-deficit/hyperactivity disorder.

Pharmacologic treatment

In the cross-sectional dataset, 78.9% of adults with diagnosed ADHD were dispensed ADHD medication at some point during the study period, while in the longitudinal dataset, only 65.7% of newly diagnosed patients received ADHD medication. ADHD medication was dispensed less frequently among elderly patients (≥65 years of age; 28.4% of adults with ADHD and 12.2% of newly diagnosed adults) than in younger adults (22–64 years of age; 80.0% of adults with ADHD and 67.2% of newly diagnosed adults; Table 5).

Pharmacologic treatment patterns

Treatment patterns are reported for the longitudinal dataset (2007–2011) comprising adults newly diagnosed with ADHD.

First-line ADHD medication

OROS-MPH was the most frequently dispensed first-line ADHD medication. In 2011, 69.3% of treated patients between 18 and 21 years of age received OROS-MPH, 15.7% received MPH-MR, and 11.0% received ATX. For patients between 22 and 64 years of age, the corresponding proportions were 65.0%, 16.7%, and 13.0%, respectively (data not shown). For adults ≥65 years of age, the proportions were 81.8%, 0.0%, and 18.2%, respectively.

Second-line ADHD medication

In patients who experienced a treatment switch, MPH-MR was the most commonly used second-line medication; 39.4% of treatment-switched patients received MPH-MR,

Table 5 Characteristics of pharmacologically treated and non-pharmacologically treated adult patients with ADHD

	All patients with diagnosed ADHD		Newly diagnosed ADHD patients	
	Pharmacologically treated	No treatment	Pharmacologically treated	No treatment
Share of total, n (%)	34,987 (78.9)	9,377 (21.1)	16,365 (65.7)	8,556 (34.3)
Sex, n (%)				
Male	19,989 (78.4)[a]	5,510 (21.6)[a]	8,891 (64.3)[b]	4,938 (35.7)[b]
Female	14,998 (79.5)[c]	3,867 (20.5)[c]	7,474 (67.4)[d]	3,618 (32.6)[d]
Age group, n (%)				
18–21 years	11,270 (77.8)[e]	3,214 (22.2)[e]	3,349 (63.5)[f]	1,925 (36.5)[f]
22–64 years	23,611 (80.0)[e]	5,896 (20.0)[e]	12,976 (67.2)[f]	6,344 (32.8)[f]
≥65 years	106 (28.4)[e]	267 (71.6)[e]	40 (12.2)[f]	287 (87.8)[f]

Notes: [a]Denominator is the total number of males (with or without treatment) for all patients. [b]Denominator is the total number of males (with or without treatment) for newly diagnosed patients. [c]Denominator is the total number of females (with or without treatment) for all patients. [d]Denominator is the total number of females (with or without treatment) for newly diagnosed patients. [e]Denominator is the total number in the age group (with or without treatment) for all patients. [f]Denominator is the total number in the age group (with or without treatment) for newly diagnosed patients.
Abbreviation: ADHD, attention-deficit/hyperactivity disorder.

20.5% were switched to OROS-MPH, 19.1% to MPH-IR, and 14.5% to ATX.

Add-on ADHD medication

Among newly diagnosed patients treated with ADHD medication (n=16,365), 64.7% received no add-on ADHD medication, while 35.3% received at least one add-on medication. A quarter (25.3%) of the newly diagnosed patients who were treated with ADHD medication received one add-on ADHD medication, and 8.0% received 2 add-on medications. The most frequent add-on formulation was MPH-IR (44.0%) followed by MPH-MR (29.4%). The proportions of patients receiving 1, 2, 3, or more than 3 products were similar across age groups (data not shown).

Concomitant medication

A total of 7,323 (22.5%) patients were dispensed concomitant treatment with anxiolytics, 6,677 (20.5%) with hypnotics, and 6,015 (18.5%) with SSRIs. Fewer patients received antipsychotics (4,184, 12.8%), SNRIs (3,087, 9.5%), non-selective antidepressants (989, 3.0%), and other antidepressants (4,304, 13.2%).

Mean dose of OROS-MPH

In the cross-sectional dataset, the mean (SD) PDD of OROS-MPH in adults with diagnosed ADHD was 51.5 (31.0) mg, which corresponds to ~1.72 DDDs when applying the WHO recommendation of DDD = 30 mg. As presented in Table 6,

the mean (SD) PDD for males (54.4 mg [33.3]; 1.81 DDDs) was significantly higher ($p<0.05$) than for females (47.9 mg [27.7]; 1.60 DDDs). Furthermore, the mean PDD was significantly lower ($p<0.05$) for patients aged 18–21 years than for those aged 22–64 and ≥65 years (Table 6).

A quarter (25.0%; 5,476) of adults treated with OROS-MPH received a mean dose of <1 DDD, while 9,951 (45.4%) received 1–2 DDDs and 6,499 (29.6%) received ≥2 DDDs (Table 7). A mean dose of <1 DDD was most common in those aged 18–21 years (29.7%), and a dose of ≥2 DDDs was most common (33.1%) in those aged 22–64 years. In the longitudinal dataset, the mean PDD of OROS-MPH received by newly diagnosed adults with ADHD was 48.4 mg (~1.61 DDDs). The mean PDD was higher for males (50.9 mg [1.70 DDDs]) than for females (45.5 mg [1.52 DDDs]). The mean (SD) PDD of OROS-MPH varied across age groups: 18–21 years, 40.7 mg (21.4); 22–64 years, 50.5 mg (30.3); and ≥65 years, 45.6 mg (26.5) (data not shown).

Predictors of OROS-MPH dose level

The regression analysis of individual parameters influencing the PDD of OROS-MPH suggested that the presence of at least one add-on medication, comorbid SUD, drug holiday (gap between observations for a patient in the PDR exceeding 90 days), and male sex were the strongest predictors of an increase in PDD (ie, higher mean dose) of OROS-MPH (all $p<0.0001$; Table 8). In addition, a later expedition year (ie, year when the medication was dispensed), concomitant treatment with an antipsychotic, comorbid personality disorder, concomitant treatment with hypnotics, concomitant treatment with an SNRI, ADHD of combined subtype, and

Table 6 Patient daily dose and defined daily dose of OROS-MPH among all adult patients with diagnosed ADHD treated with OROS-MPH during the study period (cross-sectional dataset; 2006–2011)

	Mean (SD) patient daily dose, mg	Defined daily dose, mg	95% confidence limits (mg)
Total (n=21,926)	51.5 (31.0)	1.72	51.1, 51.9
Males (n=12,025)	54.4 (33.3)[a]	1.81	53.8, 55.0
Females (n=9,901)	47.9 (27.7)	1.60	47.4, 48.5
Age group			
18–21 years (n=4,942)	42.9 (21.5)[b]	1.43	42.3, 43.5
22–64 years (n=16,930)	53.9 (32.9)	1.80	53.5, 54.4
≥65 years (n=54)	53.5 (34.9)	1.78	44.0, 63.1

Notes: [a]$p<0.05$ for comparison with females. [b]$p<0.05$ for comparisons with 22–64 years and ≥65 years. The patient daily dose is the average daily amount of a drug that is actually prescribed. The defined daily dose is the assumed average maintenance dose per day for a drug used for its main indication in adults.[31] The independent t-test was used to identify potential statistical differences in the mean dose between sexes, and analysis of variance was used to identify potential statistical differences in the mean dose between age groups.
Abbreviations: ADHD, attention-deficit/hyperactivity disorder; OROS-MPH, osmotic release oral system methylphenidate.

Table 7 Proportions of patients receiving OROS-MPH <1 DDD, 1–2 DDDs, and ≥2 DDDs during the study period (cross-sectional dataset)

	<1 DDD	1–2 DDDs	≥2 DDDs
N (%) of adults with diagnosed ADHD who reported use of OROS-MPH treatment[a]	5,476 (25.0)	9,951 (45.4)	6,499 (29.6)
Males[b]	2,716 (49.6)	5,326 (53.5)	3,983 (61.3)
Females[b]	2,760 (50.4)	4,625 (46.5)	2,516 (38.7)
Age group, n (%)[a]			
18–21 years	1,470 (29.7)	2,587 (52.3)	885 (17.9)
22–64 years	3,992 (23.6)	7,339 (43.3)	5,599 (33.1)
≥65 years	14 (26.0)	25 (46.3)	15 (27.8)

Notes: 1 DDD[31] =30 mg MPH. [a]Denominators for percentages in this row are the total number of patients included in the row. [b]Denominators for percentages in this row are the total number of patients per DDD group (<1 DDD, 1–2 DDDs, ≥2 DDDs).
Abbreviations: ADHD, attention-deficit/hyperactivity disorder; DDD, defined daily dose; OROS-MPH, osmotic release oral system methylphenidate.

Table 8 Estimates of coefficients for the estimated change in PDD of OROS-MPH (final regression model)

Variable	Change in PDD of OROS-MPH (%)[a]	95% CI (%)[a]		p-value
Age at current prescription	0.587	0.527	0.647	<0.0001
Male sex	10.783	9.453	12.113	<0.0001
Expedition year	6.545	6.032	7.057	<0.0001
Drug holiday[b]	15.165	13.814	16.515	<0.0001
ADHD diagnosis F90.0B	4.037	2.663	5.412	<0.0001
ADHD diagnosis F90.0C	−4.795	−6.945	−2.645	<0.0001
Region: Stockholm	−9.866	−11.422	−8.310	<0.0001
Region: West Sweden	−5.046	−6.768	−3.323	<0.0001
Anxiety	−2.115	−3.737	−0.494	0.0106
Depression	−1.931	−3.767	−0.094	0.0394
Bipolar disorder	−5.791	−8.180	−3.402	<0.0001
Personality disorder	4.803	2.549	7.057	<0.0001
Asperger syndrome	−2.840	−5.151	−0.529	0.0160
Substance use disorder	18.010	16.210	19.810	<0.0001
Add-on medication	18.392	16.867	19.917	<0.0001
Concomitant medication: antipsychotics	5.911	4.299	7.523	<0.0001
Concomitant medication: hypnotics	4.514	3.095	5.933	<0.0001
Concomitant medication: SNRI	1.750	0.108	3.393	0.0367

Notes: F90.0B: ADHD; F90.0C: Activity and attention disturbance; F90.0X: Activity and attention disturbance, unspecified. [a]North Sweden and expedition year 2006 used as reference. [b]A gap between observations for a patient in the Prescribed Drug Register exceeding 90 days.
Abbreviations: ADHD, attention-deficit/hyperactivity disorder; OROS-MPH, osmotic release oral system methylphenidate; PDD, dispensed patient daily dose; SNRI, serotonin–norepinephrine reuptake inhibitor.

older age were associated with an increase in PDD (Table 8). The strongest predictors of a decrease in PDD (ie, lower mean dose) were living in Stockholm or west Sweden, presence of comorbid bipolar disorder, and ADHD diagnosis F90.0C (all $p<0.0001$; Table 8).

Discussion

This Swedish population-based study elucidated information regarding the prevalence of diagnosed ADHD and incidence of newly diagnosed ADHD in adults, as well as data on the common comorbidities and patterns of pharmaceutical treatment in this patient population. From 2006 to 2011, there was an increase in the number of adults registered with an ADHD diagnosis in Sweden. The majority of patients with an ADHD diagnosis received both an ADHD medication and a concomitant medication. The most commonly prescribed ADHD medication during the period studied was OROS-MPH. The mean dose of OROS-MPH was heavily influenced by the presence of at least one add-on ADHD medication, comorbid

SUD, drug holidays, and male sex. Psychiatric comorbidities were recorded in more than half of the patients.

The increase in both the number of newly diagnosed adults with ADHD from 2007 to 2011 and the overall estimated prevalence of adults with a registered ADHD diagnosis in Sweden from 2006 to 2011 found in this study is consistent with other Nordic studies,[3,22,24,25,27,28] and may reflect an increased awareness of the manifestations of ADHD over the lifespan of the patient,[8] leading to a higher rate of diagnosis and/or treatment in adults. Such increased recognition of adults with ADHD was found to be a contributing factor to the increased incidence rates of diagnosed ADHD reported in Denmark, as was a general increase in patients seen in psychiatry.[34] In Sweden, access to mental health care services has not changed during the time this study was conducted. However, resources may have been prioritized for certain disorders, including ADHD, which may also have contributed to the increased estimated incidence and prevalence rates seen in the study. Previous studies have reported the "dispensing prevalence", that is, ADHD prevalence irrespective of the registered diagnosis. One study reported that the dispensing prevalence among individuals aged 6–45 years increased from 2.93 per 1,000 in 2006 to 6.98 in 2009, with a larger increase in women than in men.[28] In a Danish register-based study, which included age groups from 0–1 to ≥50 years, the dispensing prevalence for ADHD in the general population increased from 1995 until 2008, but was stable from 2009 until the end of the study period in 2011.[27] This trend for stabilizing prevalence rates was not observed in the current study of Swedish register data, possibly reflecting the inclusion of only adults in the Swedish study population. As ADHD has been studied more extensively in children than in adults, the inclusion of children as well as adults in the Danish study population may have stabilized the prevalence of ADHD. In addition, the increasing awareness of ADHD in adults may have boosted prevalence rates in an adult-only population. In the USA, the incidence and prevalence of diagnosed ADHD also increased over the period between 2006 and 2009.[35]

The estimated prevalence among patients with a registered ADHD diagnosis in Sweden (clinical cases) reported in the present study (3.55 per 1,000 persons in 2011) was lower than the worldwide prevalence estimates of ADHD (between 2% and 5%) that were reported in studies seeking to identify all current ADHD cases, both diagnosed and undiagnosed.[4–8] Biederman et al estimated that only 20% of ADHD cases in adults are diagnosed, which translates to 4 to 8 cases per 1,000 persons, numbers comparable with the results of the current study.[10] Furthermore, differences

in diagnostic procedures might produce different prevalence estimates, with studies using ICD-10 to identify ADHD cases estimating significantly lower prevalence rates than studies based on DSM-IV criteria.[36]

There was no difference in estimated prevalence of ADHD diagnosis between sexes in the present study, which contrasts with the finding of a higher dispensing prevalence in males than in females in a study by Zetterqvist et al.[28] However, the Zetterqvist study evaluated the period between 2006 and 2009, while the present study explored the period from 2006 to 2011, and showed that the proportion of females with ADHD increased over time (from 37.5% in 2006 to 44.8% in 2011).

The current study found several psychiatric disorders to be comorbid in patients with ADHD, consistent with previous studies.[6,10,24] Kessler et al reported anxiety disorders to be the most common psychiatric comorbidity in adult respondents with ADHD (47.1%), followed by mood disorders (38.3%), impulsive control disorder (19.6%), and any SUD (15.2%).[6] While these prevalence estimates do not fully tally with the proportions obtained in the current study, possibly due to differences in definitions of comorbid disorders, anxiety, SUD, and depression are 3 of the most common psychiatric comorbidities reported in both studies. When assessing comorbidities in patients with ADHD, it is important to consider the risk of ADHD masquerading as the coexisting conditions, for example, ADHD symptoms may be similar to those of anxiety.

In agreement with previous studies that found that MPH was the most commonly used ADHD drug, in the present study, OROS-MPH was the most commonly prescribed pharmacologic treatment for ADHD in adults in Sweden.[22,27,37] The proportion of diagnosed adults treated with ADHD medications (78.9%) from 2006 to 2011 (cross-sectional dataset) was higher than the proportion (57.0%) reported by Lichtenstein et al in 2012, based on the same registers but conducted from 2006 to 2009.[21] This difference may be explained by differences in the definition of ADHD medications between the 2 studies (only MPH and ATX were included in the Lichtenstein study compared with MPH, ATX, amphetamines, and modafinil in the present study), as well as the inclusion of adolescents (aged 15–17 years) in the Lichtenstein study population.

In a study in the USA (n=154), only 10.9% of adults with ADHD reported treatment with ADHD medication in the prior 12-month period;[6] this is markedly lower than the proportion (78.9%) in the current study. Potential explanations for this large discrepancy may be the different methods used, with the Kessler study using DSM-IV ADHD diagnoses in

a survey of a sample of patients, and the current study using ICD-10 diagnoses in a population-based register study.

The PDD analyses demonstrated that the majority of patients were treated with 1–2 DDDs of OROS-MPH, and that the highest doses were found in the group aged 22–64 years. A higher mean dose of OROS-MPH was associated with comorbid SUD, male sex, drug holidays, or the presence of at least one add-on ADHD medication. The positive association between SUD and higher mean dose could result from overuse related to patients abusing their own stimulant medication,[38] or it could also be that patients with ADHD and SUD need higher doses to benefit fully from treatment than do patients without SUD.[39] The association between add-on ADHD medications and higher PDDs suggests that some patients' symptoms are more difficult to address with pharmacologic treatment. The association between drug holidays and higher mean dose could be a consequence of higher impairment due to more severe symptoms, with these patients often requiring higher doses. From the clinical experience of one of the authors (YG), patients with more severe symptoms tend to miss more appointments and fill prescriptions more frequently than patients with lower impairment (who often require comparably lower doses of medication). Drug holidays may occur for numerous reasons, and it is possible that, in this adult population, these are mostly unintended breaks.

The current study was a large population-based study with a 5-year follow-up. Population-based studies, which include all patients with a specific disease instead of only a sample, minimize the possibility that selection bias will have unintended consequences on the study results. The same holds true as potential recall bias can be avoided compared with retrospectively collected data from an interview or survey. Therefore, the results related to estimated prevalence and incidence, patient characteristics, and comorbidities should be representative for all contexts in which the DSM-5 is converted to ICD-10 codes and is subsequently used to provide a diagnosis. Pharmacologic treatment patterns could be influenced by country-specific guidelines and by reimbursement status, which means that the results from those analyses may be less generalizable to other countries.

As with all studies of administrative databases, there are limitations to this current study. As previously stated, the data from this study represent estimated prevalence of diagnosed ADHD and estimated incidence of newly diagnosed ADHD, and this should be noted when making comparisons with other studies, which may present prevalence and incidence based on pharmacotherapy use for ADHD rather than prevalence and incidence of diagnosis. The calculations

were made using information from hospital and outpatient administrative data, which may have contained errors due to inaccurate coding, misdiagnosis, or fraud, and coverage may not have been complete. The coverage of psychiatric health care activities in the NPR was ~75%; therefore, 25% of all visits were not recorded and consequently were not included in the analysis. The results were based on data for diagnosed patients in routine clinical practice, and therefore this study provides valuable real-world evidence. However, such data are less stringent than, for example, data collected in a controlled clinical trial, hence prevalence may have been underestimated due to undiagnosed patients or overestimated due to the inclusion of false positives. There was a high rate (80%) of patients who were prescribed ADHD medication. It is possible that some doctors may have only recorded a diagnosis once they had decided that pharmacotherapy was appropriate.

Furthermore, these analyses assume that all relevant visits would have been to psychiatric specialists in Sweden (rather than ADHD-related visits to general clinics). Also, the PDR does not include the indication for the dispensed treatment, a problem that was partly addressed by ensuring that a diagnosis of ADHD for each patient was present in the NPR. In addition, patients may have been diagnosed with ADHD or received treatment for ADHD prior to 2006, then had a gap in treatment or in health care contacts, and reappeared during the period studied, to be incorrectly included as 'newly diagnosed'.

Finally, as with all observational research, inferential statistics are not subject to the experimental nature of randomized controlled trials, and may therefore be biased by the influence of omitted or immeasurable variables. Causality between the variables and the PDD cannot be concluded.

Conclusion

This study provides important information about adult ADHD in Sweden, including estimated prevalence and incidence, comorbidities, and treatment, a research area in which few recent studies have been performed. Results showed that the number of adults with an ADHD diagnosis increased over time. It also demonstrated that adult ADHD is characterized by high rates of coexistent psychiatric disorders, and that the vast majority of patients are treated pharmacologically with at least one ADHD medication. The high rates of concomitant treatments suggest that current ADHD medications are not sufficient in addressing all symptoms that the adult with ADHD may present with. More resources will be needed for patient management in the future if the rate of diagnosis, and consequently the need for treatment, continue to increase.

Studies monitoring patient-reported symptoms, functioning, and quality of life over a longer term, before and after initiation of treatment, through a national quality register for ADHD, are warranted.

Author contributions

YG, EA, and EM contributed to study design, manuscript development, and final manuscript review. MP contributed to data collection and analysis, manuscript development, and final manuscript review. All authors contributed toward data analysis, drafting and revising the paper and agree to be accountable for all aspects of the work. All authors approved the final version of the manuscript.

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