British Journal of Clinical Pharmacology

ORIGINAL ARTICLE

Use of attention-deficit/hyperactivity disorder medication among older adults in Denmark

Correspondence Lotte Rasmussen, Clinical Pharmacology and Pharmacy, University of Southern Denmark, JB Winsløwsvej 19, 2, DK-5000 Odense C, Denmark. Tel.: +45 65507194; E-mail: lorasmussen@health.sdu.dk

Received 29 September 2017; **Revised** 13 February 2018; **Accepted** 15 February 2018

Stina Schultz Ormhøj[1], Anton Pottegård[1], Christiane Gasse[2,3,4] and Lotte Rasmussen[1]

[1]Clinical Pharmacology and Pharmacy, Department of Public Health, University of Southern Denmark, DK-5000 Odense C, Denmark, [2]National Centre for Register-based Research, Aarhus University, Aarhus, Denmark, [3]The Lundbeck Foundation Initiative for Integrative Psychiatric Research (iPSYCH), Denmark, and [4]Centre for Integrated Register-Based Research at Aarhus University (CIRRAU), Aarhus, Denmark

Keywords aged, attention deficit disorder with hyperactivity, drug utilization, methylphenidate, off-label use

AIMS

Knowledge on the use of attention-deficit/hyperactivity disorder (ADHD) medication among older adults is limited. We hypothesized that ADHD medication is used off-label in adults aged ≥50 years as part of palliative care in e.g. cancer patients. The aim of this study was to describe the use of ADHD medication among adults aged ≥50 years in Denmark.

METHODS

Using the Danish health registries, we identified new users ≥50 years of ADHD medication during 2000–2012. We estimated the annual incidence of ADHD medication use and ADHD diagnoses. We described new users of ADHD medication according to co-medication, comorbidities and assessed the 1-year cumulative mortality rate. A *posthoc* analysis allowed us to include new users until 2015.

RESULTS

We identified 6690 new users of ADHD medication from 2000 to 2012. From 2000 to 2015 we observed an increase in the incidence of ADHD medication use from 12.5 to 30.3 per 100 000 person-years. However, the incidence rate decreased from 2010 to 2015. Throughout the study period, the incidence rate of ADHD diagnoses was low (overall prevalence among new users ≤2%). Opioids were the most frequent comedication used (used by 54%), while cancer was the most frequent diagnosis preceding treatment (prevalence of 52%). The 1-year cumulative mortality was 50%, primarily driven by patients with a preceding cancer diagnosis.

CONCLUSION

There was an increase in the incidence of ADHD medication use in adults aged ≥50 years from 2000–2010 and a decreasing incidence from 2010–2015. Our results suggest that ADHD medication is used off-label in older adults as part of palliative care.

DOI:10.1111/bcp.13569

WHAT IS ALREADY KNOWN ABOUT THIS SUBJECT

- The use of attention-deficit/hyperactivity disorder (ADHD) medication in adults has increased; however, knowledge on the use of ADHD medication in older adults is limited.
- Based on a previous study, we hypothesized that ADHD medication is used off-label in adults aged ≥50 years as part of palliative care.

WHAT THIS STUDY ADDS

- Overall, the use of ADHD medication in older adults increased from 2000 to 2015, however, between 2010 and 2015 the use was decreasing.
- ADHD medication seems to be used off-label in adults aged ≥50 years as part of palliative care, especially in patients with cancer.
- Researchers should be cautious when relying only on prescription data to identify older adults with ADHD.

Introduction

Over recent decades, the use of medication against attention-deficit/hyperactivity disorder (ADHD) in adults has increased worldwide [1–6]. In Denmark, use of ADHD medication in adults has raised concern due to the risk profile of these medications, such as the risk of cardiovascular diseases [7]. Treatment guidelines and approved medications for adults with ADHD have been missing [7]. However, since 2008, **atomoxetine**, a nonstimulant drug used for ADHD, has been approved for newly diagnosed ADHD in adults [8, 9]. Furthermore, since 2011, specific formulations of **methylphenidate** have been approved for the treatment of ADHD in adults aged <65 years [10, 11].

Recently, a Danish study [12] found a surprisingly high mortality among new users of ADHD medication aged >50 years compared to new users aged <50 years. Given that the incidence of ADHD in this population is reported to be low [7, 13], this finding might indicate off-label use of ADHD medication. Literature suggests that the potential off-label use of ADHD medication in older patients may be linked to the treatment of symptoms such as opioid induced sedation, fatigue and cognitive dysfunction in terminally ill patients, such as with cancer [14–16].

Due to the worldwide increase in the use of ADHD medication in the adult population, and the potential for off-label use, we sought to describe the use of ADHD medication in adults aged ≥50 years in Denmark during the period 2000–2012. We specifically aimed to describe the incidence of ADHD medication use, the incidence of ADHD diagnoses and to describe the clinical characteristics of the population in terms of comorbidities and comedications.

Methods

Using the Danish national health registries, we conducted a drug utilization study identifying new users of ADHD medication aged ≥50 years in Denmark during 2000–2012. We described the use of ADHD medication, the clinical characteristics of this population and the mortality rate.

Data sources

We retrieved data from the Danish National Prescription Registry [17], which contains information on filled prescriptions at outpatient pharmacies from 1995 and onwards for all Danish residents. Thus, we did not have information on in-patient drug use. We extracted information on somatic and psychiatric diagnoses from the Danish National Patient Register [18] and the Danish Psychiatric Central Research Register [19]. The registries contain information on all in-patient contacts since 1977 and 1969, respectively, and all outpatient and emergency room contacts from 1995. Diagnoses made by general practitioners and private psychiatrists are not covered by these registries. Coding is based on the International Classification of Diseases, 8th revision (ICD-8) codes until 1994 and ICD-10 codes thereafter. We identified deaths and migrations from the Danish Civil Registration System [20].

Study population and study drugs

The definition of our study population was based on filling of an ADHD medication. We included all individuals ≥50 years who redeemed their first-ever prescription since 1995 for methylphenidate (Anatomical Therapeutic Chemical (ATC) code [21]: N06BA04) or atomoxetine (ATC: N06BA09) during the study period from 1 January 2000 to 31 December 2012. The date of filling the first prescription marked the index date. Individuals were excluded if they had redeemed a prescription for any ADHD medication (also including **amphetamine** (ATC: N06BA01) and **dexamphetamine** (ATC: N06BA02) prior to the index date and after 1995. As such, all patients had at least a 5-year run-in period with no ADHD drug use. Amphetamine and dexamphetamine were only available as magistral preparations during the study period and not completely covered by our registry. Based on publicly available sales data [22], the use of these drugs in patients above 40 years of age was low (medstat.dk). We excluded individuals who used **modafinil** (ATC: N06BA07) prior to index date because the main indication for modafinil is narcolepsy and patients initiating modafinil before methylphenidate or atomoxetine most likely have narcolepsy. These patients were excluded as we were only interested in patients using ADHD medications for ADHD or other off-label indications. Furthermore, to ensure full coverage of our study population we excluded individuals with a migration history any time before and up to 1 year after index date. For individuals included later than July 2012, we did not have data on migration for 1 full year after index date.

Data analysis

Incidence rates of ADHD medication use. We calculated the annual incidence rates [per 100 000 person-years (py)] of ADHD medication use from 2000–2012, stratified into age categories (50–64 years, 65–79 years and 80+ years). We used the number of new users in the relevant age strata as the numerator and the entire Danish population aged ≥50 years by 1 January in the relevant age strata as the denominator [22] as the number of prevalent users is negligible. A *posthoc* analysis allowed us to assess the incidence of ADHD medication use from 2013–2015, but with no data available on migration from July 2013 and onwards.

Incidence rates of ADHD diagnoses. To calculate the annual incidence rates (per 100 000 py) of ADHD diagnoses from 2000–2012, stratified into age categories (50–64 years, 65–79 years and 80+ years), we identified all Danes aged ≥50 years with at least one record of an ADHD diagnosis in our registries. We excluded those that did not receive their first diagnosis within the study period. As such, all patients had a run-in period of at least 5 years. We used the number of Danes with a new ADHD diagnosis in the relevant age strata as the numerator and the entire Danish population aged ≥50 years by 1 January in the relevant age strata as the denominator [22] as the number of patients with an ADHD diagnosis is negligible.

Characteristics of the study population. We described our study population of new ADHD medication users according to a number of characteristics, including age at index date, sex, index medication, use of selected comedications and comorbidities (see Appendix 1) prior to index date. Characteristics of the study population were stratified into age categories as specified above. Use of selected comedications was defined as having filled at least one prescription within 6 months prior to index date. Comorbidities were assessed within 1 year prior to index date, and any time prior to index date as a sensitivity analysis. The presence of an ADHD diagnosis was assessed any time prior to index date (see Appendix 1).

Mortality. For each age category, we calculated the 1-year cumulative mortality rate, specified by calendar year of the index prescription. Estimates were standardized by age and sex, using the study population in 2012 as the reference population. Further, we performed a Kaplan–Meier survival analysis to depict the cumulative mortality occurring during the first year after index date. As we did not have data on death in 2013, these analyses were restricted to new users starting medication in the period 2000–2011.

Supplementary analyses

We performed several supplementary analyses. First, we stratified the incidence of ADHD medication use by the five regions of Denmark (i.e. Capital Region of Denmark, Region Zealand, Region of Southern Denmark, Central Denmark Region, and North Denmark Region). We did this to assess whether there were any regional differences in ADHD medication use during the period 2008–2012. Second, to assess differences by sex, we stratified our main analysis by this parameter. Lastly, to test our hypothesis of use of ADHD medication in palliative care, we stratified our main analysis by the presence of cancer 1 year before index date, as well as death within 1 year after index date (for those starting medication in the period 2000–2011).

Statistical analysis

To test for trends over time, we performed a linear regression analysis of the incidence rate as a function of index year. Likewise, we performed a linear regression analysis of the mortality rate as a function of index year. We used the slope and the corresponding confidence intervals to interpret on the trends over time. If the confidence interval of the slope did not contain zero, we interpreted this as a statistically significant trend (positive or negative) over time. We reported the *P*-values for the *t*-test of coefficients in the linear regression model. We reported confidence intervals for incidence rates of ADHD medication use and ADHD diagnoses. The significance level was set to 0.05. Data analysis was performed using STATA Release 14.2 (StataCorp, College Station, Texas, USA).

Ethical approval

The study was approved by the Danish Data Protection Agency and Statistics Denmark's Scientific Board. Ethical approval was not needed for this study according to Danish legislation [23].

Nomenclature of targets and ligands

Key protein targets and ligands in this article are hyperlinked to corresponding entries in http://www.guidetopharmacology.org, the common portal for data from the IUPHAR/BPS Guide to PHARMACOLOGY [24], and are permanently archived in the Concise Guide to PHARMACOLOGY 2017/18.

Results

A total of 6705 new users of ADHD medication aged ≥50 years were identified between 2000 and 2012. After excluding 15 individuals due to migration, the final study was based on data from 6690 individuals.

From 2000 to 2012, we observed a significant increase in the overall incidence rate of new ADHD medication use ($P < 0.001$); from 2000 to 2010, we observed an increase from 12.5 to 49.3 per 100 000 py, and from 2010 to 2012 we observed a decrease from 49.3 to 38.0 per 100 000 py (see age stratified incidence rates in Figure 1 and Supporting Table S1). We observed similar trends between the different age groups; however, we observed the largest increase among 50–64-year-olds (Figure 1). The *posthoc* analysis showed a slight decrease in the incidence rate, reaching 30.3 per 100 000 py in 2015 (Supporting Figure 1 and Supporting Table S1).

We observed regional variations in the incidence of ADHD medication use, most pronounced among the 50–79-year-olds; the incidence was highest in Region Zealand (2012: around 54 per 100 000 py) and in the Capital Region of Denmark (2012: around 61 per 100 000 py), and lowest in

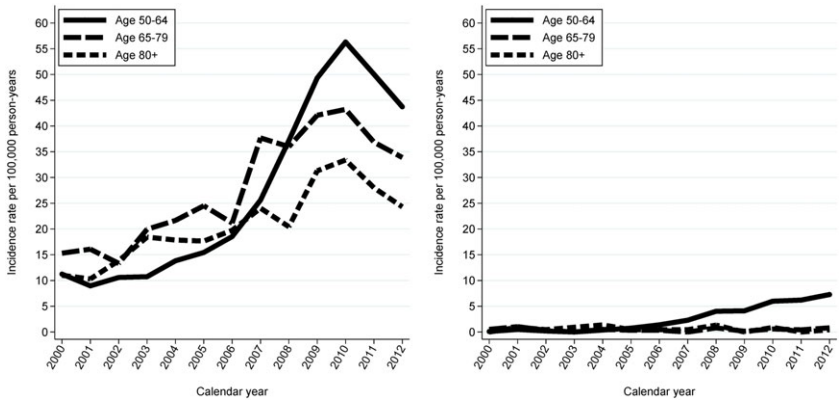

Figure 1

Incidence rates (per 100 000 person-years) of new users of attention-deficit/hyperactivity disorder medication (left graph) and incidence rates of attention-deficit/hyperactivity disorder diagnoses (right graph) per calendar year (2000–2012). Stratified by age

the region of Southern Denmark (2012: 20 per 100 000 py; Supporting Figure S2).

The incidence rate of new ADHD diagnoses was low throughout the study period, and increased only among users aged 50–64 years (0.1 to 7.3 per 100 000 py, $P < 0.001$; Figure 1 and Table S1).

The characteristics of the study population are shown in Table 1. The median age was 62 years (interquartile range, 55–71 years), and 52% were male. The majority used methylphenidate (98%) with immediate release (91%) being the most common formulation. Use of other psychotropic drugs was common; opioids (used by 54%), antidepressants (45%) and hypnotic and sedatives (34%) were the most frequently used comedications prior to index date (Table 1). Stratification revealed variations between the different age categories (Table 1). Among individuals ≥65 years, use of opioids, loop-diuretics and antithrombotic agents was more common compared to individuals below 65 years (Table 1). Cancer was the most common diagnosis among new users of ADHD medication (52%, Table 1). We found the highest prevalence of cancer in individuals ≥65 years (up to 70%; Table 1), and in individuals dying within 1 year after index date (93%; Supporting Table S2). Use of other psychotropic drugs, especially opioids (84%), was more common in patients with cancer compared to patients without cancer (Supporting Table S2). The prevalence of other comorbidities, including psychiatric disorders, was generally low (≤8%; Table 1). The same patterns were observed when assessing comorbidity any time prior to index date. The prevalence of ADHD diagnoses in the study population was low (2%) and an ADHD diagnosis was only observed among individuals younger than 65 years (4%; Table 1).

We observed variations in the 1-year mortality rate over time between the different age groups (Supporting Figure S3). Throughout the study period, the 1-year mortality rate declined for those aged 50–64 years (from around 53% to 23%, $P < 0.001$; Supporting Figure S3). For individuals aged ≥65 years, the mortality rate was slightly increasing (Supporting Figure S3). The overall standardized 1-year mortality rate during the study period was 50%. Figure 2 shows the survival analysis stratified by age. Stratification revealed that around 88% of individuals with cancer died within 1 year after index date compared to around 7% of individuals without cancer (Supporting Figure S4).

We performed a *posthoc* analysis investigating the top ten most frequent diagnoses in the study population 1 year and any time prior to index date. We did this to capture relevant diagnoses not specified beforehand as potential off-label use. Pain was the most frequently registered diagnosis in this analysis (1-year analysis: 29%; Supporting Table S3). Other identified diagnoses included malaise and fatigue, nausea and vomiting, other functional intestinal disorders, sleep disorders, and essential hypertension.

Throughout all analyses, we observed no differences when stratifying by sex (data not shown).

Discussion

We document a marked increase in ADHD medication use in adults aged ≥50 years during the period 2000–2010 and a decrease from 2010 and onwards while observing a low incidence of ADHD diagnoses. Among old new users of ADHD medication, a cancer diagnosis was common and the 1-year mortality was high. Together, this indicates off-label use of ADHD medication (e.g. as part of palliative care in cancer patients).

The incidence of ADHD medication use increased from 2000–2010, with some regional variations from 2008–2012. The increase in the use of ADHD medication in older adults is supported by observations from other countries between 1994 and 2012 [1–3]. In 2010, a Danish report underlined the increased use of methylphenidate in adults and raised concern about the risk profile [7]. This may have contributed to the decline in the use of ADHD medication observed between 2010 and 2015 [7].

Our results generally support our hypothesis that ADHD medication is used off-label in older adults as part of palliative care. First, the incidence and prevalence of ADHD diagnoses was low, and cancer was by far the most prevalent diagnosis preceding treatment initiation. Second, our *posthoc* analysis revealed common diagnoses preceding treatment initiation

Table 1

Characteristics of new users of attention-deficit/hyperactivity disorder medication aged ≥50 years, 1 January 2000 to 31 December 2012

	All (*n* = 6690)	Age 50–64 years (*n* = 3781)	Age 65–79 years) (*n* = 2305)	Age 80+ years (*n* = 604)
Median age at index date, years (IQR)[a]	62 (55–71)	56 (52–60)	71 (67–75)	83 (81–86)
Sex, *n* (%)				
Male	3451 (52)	1919 (51)	1234 (54)	298 (49)
Female	3239 (48)	1862 (49)	1071 (46)	306 (51)
Index medication, *n* (%)				
Methylphenidate	6571 (98)	3674 (97)	2295 (100)	602 (100)
Atomoxetine	119 (2)	107 (3)	10 (0)	*n* < 5
ADHD diagnosis any time before index date, *n* (%)	156 (2)	151 (4)	*n* < 5	*n* < 5
Comedication 6 months before index date, *n* (%)				
Opioids	3588 (54)	1661 (44)	1556 (68)	371 (61)
Antiepileptics	1249 (19)	760 (20)	417 (18)	72 (12)
Antipsychotics	1016 (15)	626 (17)	324 (14)	66 (11)
Anxiolytics	1917 (29)	1037 (27)	723 (31)	157 (26)
Hypnotics and sedatives	2251 (34)	1112 (29)	916 (40)	223 (37)
Antidepressants	3018 (45)	1776 (47)	994 (43)	248 (41)
Drugs used in addictive disorders	613 (9)	404 (11)	183 (8)	26 (4)
High-ceiling diuretics (loop-diuretics)	1014 (15)	355 (9)	486 (21)	173 (29)
Beta-blocking agents	763 (11)	330 (9)	344 (15)	89 (15)
Lipid-modifying agents, plain	933 (14)	442 (12)	403 (17)	88 (15)
Antithrombotic agents	1539 (23)	535 (14)	729 (32)	275 (46)
Comorbidities 1 year before index date, *n* (%)				
Hypertensive heart disease	14 (0)	*n* < 5	7 (0)	*n* < 5
Hypertensive renal disease	*n* < 5	*n* < 5	*n* < 5	*n* < 5
Angina pectoris	111 (2)	46 (1)	52 (2)	13 (2)
Acute myocardial infarction	38 (1)	13 (0)	15 (1)	10 (2)
Atrial fibrillation and flutter	200 (3)	50 (1)	105 (5)	45 (7)
Heart failure	101 (2)	22 (1)	53 (2)	26 (4)
Intracerebral haemorrhage	33 (0)	14 (0)	19 (1)	*n* < 5
Cerebral infarction	68 (1)	21 (1)	30 (1)	17 (3)
Atherosclerosis	52 (1)	14 (0)	25 (1)	13 (2)
Type 2 diabetes mellitus	532 (8)	226 (6)	247 (11)	59 (10)
Other chronic obstructive pulmonary disease	247 (4)	75 (2)	137 (6)	35 (6)
Parkinson's disease	33 (0)	*n* < 5	20 (1)	9 (1)
Any malignant neoplasms (cancer)[b]	3446 (52)	1431 (38)	1621 (70)	394 (65)
Malignant neoplasm of colon	424 (6)	164 (4)	195 (8)	65 (11)
Malignant neoplasm of bronchus and lung	710 (11)	291 (8)	356 (15)	63 (10)
Malignant neoplasm of breast	438 (7)	212 (6)	182 (8)	44 (7)
Malignant neoplasm of prostate	453 (7)	109 (3)	268 (12)	76 (13)
Malignant neoplasms of brain	63 (1)	37 (1)	20 (1)	*n* < 5
Any psychiatric diagnoses[c]	337 (5)	257 (7)	60 (3)	20 (3)

[a]IQR; interquartile range (Q25–Q75)
[b]Except nonmelanoma skin cancer
[c]F00–F98 except F90 and F98.8

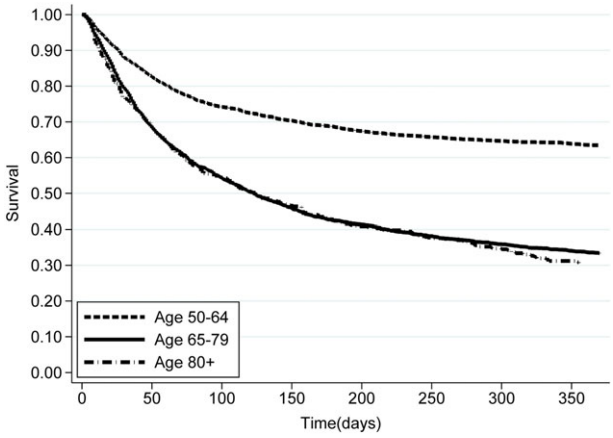

Figure 2

Kaplan–Meier plot of survival probability of new users of attention-deficit/hyperactivity disorder medication initiating treatment between 2000 and 2011. Stratified by age

that could potentially be related to cancer or the treatment of cancer (e.g. pain, fatigue, nausea and vomiting). Third, 93% of new users of ADHD medication who died within 1 year after treatment initiation had a diagnosis of cancer. Use of methylphenidate in cancer patients as part of palliative care has been described in two previous studies [25, 26]. During the terminal stage of cancer, methylphenidate has been found to alleviate the following symptoms: opioid induced sedation [15, 27–29]; fatigue [15, 16, 30, 31]; depression [28, 32, 33]; loss of appetite [32, 34]; and cognitive dysfunction [15, 30].

A hospital diagnosis of cancer was registered in 93% of people dying within 1 year after initiating treatment. Among the remaining 7% of individuals dying within the 1st year, we found more frequent use of loop-diuretics and antithrombotic agents as a possible indicator of frailty [35, 36].

While the 1-year mortality rate increased slightly for individuals aged ≥65 years during the study period, it decreased for individuals aged 50–64 years. This decrease in mortality rate might be explained by a dilution effect due to increased on-label use of ADHD medication within this age stratum. This is supported by the observed increase in the incidence of ADHD diagnoses among 50–64-year-olds for whom some formulations of ADHD medication have been approved [9, 10].

Data on the use of ADHD medication from dispensing data are often subject to uncertainty about clinical indications. Our study shows that researchers should be cautious when relying only on dispensing data to define patients with ADHD above the age of 50 years. Furthermore, researchers analyzing use of ADHD medication in adults should be aware of use that may not represent on-label use in their interpretation of results.

Our study has several strengths. First, we used data from the Danish nationwide health registries, described to have complete registration and high validity [17–20]. Further, data from the Danish National Prescription Registry were available since 1995, ensuring correct classification of new users of ADHD medication.

Our study also has some limitations. First, the indication for treatment with ADHD medication was not available from the Danish National Prescription Registry. ADHD medication might be used in the treatment of narcolepsy in an adult population, however, the prevalence of this disorder is generally low (0.05%) [37]. Our *posthoc* analysis showed a prevalence of 8% for sleep disorders including narcolepsy. Although narcolepsy only accounts for a fraction of this, we cannot rule out that a few people of our study population were treated with ADHD medication due to a diagnosis of narcolepsy. Second, the prevalence of ADHD diagnoses could only be based on hospital discharge diagnosis data. As adult patients might receive ADHD diagnoses outside the hospital setting (e.g. from general practitioners or psychiatrists), we might underestimate the true prevalence of ADHD in this population.

In conclusion, our study revealed an increase in the incident use of ADHD medication in adults aged ≥50 years during 2000–2010, however decreasing from 2010 and onwards. While we cannot rule out the possibility of a small fraction of on-label use in our population, due to ADHD in individuals aged <65 years or narcolepsy for examples, ADHD medication seems to be primarily used off-label as part of palliative care, especially in patients with cancer.

Competing Interests

There are no competing interests to declare.

Contributors

All authors contributed to the design of the study. L.R. and A.P. performed the data analysis. All authors contributed to the interpretation of data. S.S.O. and L.R. drafted the first version of the paper, and all authors were involved in critically revising the text. All authors read and approved the final version of the paper.

Appendix 1

Use of drugs (6 months prior to index date)		
Opioids	*ATC code*	N02A
Antiepileptics	*ATC code*	N03A
Antipsychotics	*ATC code*	N05A
Anxiolytics	*ATC code*	N05B
Hypnotics and sedatives	*ATC code*	N05C
Antidepressants	*ATC code*	N06A
Drugs used in addictive disorders	*ATC code*	N07B
High-ceiling diuretics (loop-diuretics)	*ATC code*	C03C
Beta-blocking agents	*ATC code*	C07A

(continues)

(Continued)

Use of drugs (6 months prior to index date)		
Lipid-modifying agents, plain	*ATC code*	C10A
Antithrombotic agents	*ATC code*	B01A
Diagnoses (12 months prior to index date)		
Hypertensive heart disease	*ICD-10*	I11
Hypertensive renal disease	*ICD-10*	I12
Angina pectoris	*ICD-10*	I20
Acute myocardial infarction	*ICD-10*	I21
Atrial fibrillation and flutter	*ICD-10*	I48
Heart failure	*ICD-10*	I50
Intracerebral haemorrhage	*ICD-10*	I61
Cerebral infarction	*ICD-10*	I63
Atherosclerosis	*ICD-10*	I70
Type 2 diabetes mellitus[a]	*ICD-10*	E11
Other chronic obstructive pulmonary disease	*ICD-10*	J44
Parkinson's disease	*ICD-10*	G20
Any malignant neoplasms (cancer), except nonmelanoma skin cancer	*ICD-10*	C00-C97, except C44
Malignant neoplasms of colon	*ICD-10*	C18
Malignant neoplasms of bronchus and lung	*ICD-10*	C34
Malignant neoplasms of breast	*ICD-10*	C50
Malignant neoplasms of prostate	*ICD-10*	C61
Malignant neoplasms of brain	*ICD-10*	C71
Organic, including symptomatic, mental disorders	*ICD-10*	F00-F09
Dementia in Alzheimer's disease	*ICD-10*	F00
Vascular dementia	*ICD-10*	F01
Mental and behavioral disorders due to psychoactive substance abuse	*ICD-10*	F10-F19

(continues)

(Continued)

Diagnoses (12 months prior to index date)		
Schizophrenia and related disorders	*ICD-10*	F20-F29
Mood disorders	*ICD-10*	F30-F39
Neurotic, stress-relates, and somatoform disorders	*ICD-10*	F40-F48
Behavioral syndromes associated with psychological disturbances and physical factors	*ICD-10*	F50-F59
Eating disorders	*ICD-10*	F50
Disorders of adult personality and behavior	*ICD-10*	F60-F69
Specific personality disorders	*ICD-10*	F60
Mental retardation	*ICD-10*	F70-F79
Disorders of psychological development	*ICD-10*	F80-F89
Behavioral and emotional disorders with unset occurring in childhood and adolescence	*ICD-10*	F90-F98, except F90, F98.8
Diagnosis (any time prior to index time)		
Attention-deficit/ hyperactivity disorder	*ICD-8*	308.01
Attention-deficit/ hyperactivity disorder	*ICD-10*	F90, F98.8

[a]Diabetes mellitus is defined as having filled at least one prescription within 1 year prior to index date or having a diagnosis 1 year prior to index date

ICD, International Classification of Disease; ATC, Anatomical Therapeutic Chemical

References

1 Geirs DP, Pottegård A, Halldorsson M, Zoega H. A nationwide study of attention-deficit/hyperactivity disorder drug use among adults in Iceland 2003-2012. Basic Clin Pharmacol Toxicol 2014; 115: 417–22.

2 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.

3 Olfson M, Blanco C, Wang S, Greenhill LL. Trends in office-based treatment of adults with stimulants in the United States. J Clin Psychiatry 2013; 74: 43–50.

4 Pottegård 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.

5 Pottegård 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.

6 Karlstad O, Zoega H, Furu K, Bahmanyar S, Martikainen JE, Kieler H, *et al*. Use of drugs for ADHD among adults-a multinational study among 15.8 million adults in the Nordic countries. Eur J Clin Pharmacol 2016; 72: 1507–14.

7 The Danish Health and Medicines Authority. [Assessment of the safety by use of methylphenidate]. 2010. Available at: https://laegemiddelstyrelsen.dk/da/udgivelser/2010/~/media/853DB0D8B52942CDA24484E8DF9E1DAB.ashx (last accessed 1 February 2016).

8 The Ministry of Health and Medicine. [Health and Prevention Comittee, regular part 2013–2014: questions and answers]. 2014. Available at http://www.ft.dk/samling/20131/almdel/suu/spm/1148/index.htm (last accessed 19 February 2016).

9 Danish Health and Medicines Authority. [Strattera – Summary of Product Characteristics]. 2015. Available at: www.produktresume.dk (last accessed 3 March 2016).

10 Danish Health and Medicines Authority. [Ritalin Uno – Summary of Product Characteristics]. 2015. Available at: www.produktresume.dk (last accessed 4 April 2016).

11 The Danish Health and Medicines Authority. [Concerta – Summary of Product Characteristics]. Available at: www.produktresume.dk (last accessed 24 March 2016).

12 Rasmussen L, Zoega H, Hallas J, Pottegård A. Deviant patterns of methylphenidate use in adults: a Danish nationwide registry-based drug utilization study. Pharmacoepidemiol Drug Saf 2015; 24: 1189–96.

13 Pedersen CB, Mors O, Bertelsen A, Waltoft BL, Agerbo E, McGrath JJ, *et al*. A comprehensive nationwide study of the incidence rate and lifetime risk for treated mental disorders. JAMA Psychiat 2014; 71: 573–81.

14 Rozans M, Dreisbach A, Lertora JJ, Kahn MJ. Palliative uses of methylphenidate in patients with cancer: a review. J Clin Oncol 2002; 20: 335–9.

15 Kaminski M, Sjøgren P. The use of psychostimulants in palliative and supportive treatment of cancer patients. Adv Palliat Med 2007; 6: 23–31.

16 Hardy SE. Methylphenidate for the treatment of depressive symptoms, including fatigue and apathy, in medically ill older adults and terminally ill adults. Am J Geriatr Pharmacother 2009; 7: 34–59.

17 Pottegård A, Schmidt SA, Wallach-Kildemoes H, Sorensen HT, Hallas J, Schmidt M. Data resource profile: the Danish National Prescription Registry. Int J Epidemiol 2017; 46: 798–8f.

18 Schmidt M, Schmidt SA, Sandegaard JL, Ehrenstein V, Pedersen L, Sorensen HT. The Danish National Patient Registry: a review of content, data quality, and research potential. Clin Epidemiol 2015; 7: 449–90.

19 Mors O, Perto GP, Mortensen PB. The Danish Psychiatric Central Research Register. Scand J Public Health 2011; 39: 54–7.

20 Schmidt M, Pedersen L, Sorensen HT. The Danish Civil Registration System as a tool in epidemiology. Eur J Epidemiol 2014; 29: 541–9.

21 ATC/DDD Index [online]. Available at: http://www.whocc.no/atc_ddd_index/?code=N06BA04 (last accessed 2 April 2016).

22 Schmidt M, Hallas J, Laursen M, Friis S. Data Resource Profile: Danish online drug use statistics (MEDSTAT). Int J Epidemiol 2016; 45: 1401–2g.

23 Thygesen LC, Daasnes C, Thaulow I, Bronnum-Hansen H. Introduction to Danish (nationwide) registers on health and social issues: structure, access, legislation, and archiving. Scand J Public Health 2011; 39: 12–6.

24 Harding SD, Sharman JL, Faccenda E, Southan C, Pawson AJ, Ireland S, *et al*. The IUPHAR/BPS Guide to PHARMACOLOGY in 2018: updates and expansion to encompass the new guide to IMMUNOPHARMACOLOGY. Nucl Acids Res 2018; 46: D1091–106.

25 Ng CG, Dijkstra E, Smeets H, Boks MP, de Wit NJ. Psychiatric comorbidity among terminally ill patients in general practice in the Netherlands: a comparison between patients with cancer and heart failure. Br J Gen Pract 2013; 63: e63–8.

26 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.

27 Medical Services Commission. Palliative care for the patient with incurable cancer or advanced disease. Part 2: pain and symptom management. 2011. Available at: http://www2.gov.bc.ca/gov/content/health/practitioner-professional-resources/bc-guidelines/palliative-pain-management (last accessed 28 April 2016).

28 Chai E. Geriatric palliative care. Oxford: Oxford University Press, 2014; 606.

29 Andersen SF. Symptomkontrol i palliativ medicin: en quick-guide, 5th edn. FADL: Copenhagen, 2012; 120.

30 Prommer E. Methylphenidate: established and expanding roles in symptom management. Am J Hosp Palliat Care 2012; 29: 483–90.

31 Radbruch L, Strasser F, Elsner F, Goncalves JF, Loge J, Kaasa S, *et al*. Fatigue in palliative care patients – an EAPC approach. Palliat Med 2008; 22: 13–32.

32 The Danish Society for General Medicine and The Danish Society for Palliative Medicine. [Clinical guideline - palliation]. 2004. Available at: http://www.dsam.dk/files/9/palliation_2004.pdf (last accessed 5 February 2016).

33 Stiefel F, Die Trill M, Berney A, Olarte JM, Razavi A. Depression in palliative care: a pragmatic report from the Expert Working Group of the European Association for Palliative Care. Support Care Cancer 2001; 9: 477–88.

34 Hanks G. Oxford textbook of palliative medicine, 4th edn. Oxford: Oxford University Press, 2011; 1666.

35 Van Kraaij DJ, Jansen RW, de Gier JJ, Gribnau FW, Hoefnagels WH. Prescription patterns of diuretics in Dutch community-dwelling elderly patients. Br J Clin Pharmacol 1998; 46: 403–7.

36 Wauters M, Elseviers M, Vaes B, Degryse J, Dalleur O, Vander Stichele R, *et al*. Polypharmacy in a Belgian cohort of community-dwelling oldest old (80+). Acta Clin Belg 2016; 71: 158–66.

37 Ohayon MM, Priest RG, Zulley J, Smirne S, Paiva T. Prevalence of narcolepsy symptomatology and diagnosis in the European general population. Neurology 2002; 58: 1826–33.

Supporting Information

Additional Supporting Information may be found online in the supporting information tab for this article.

http://onlinelibrary.wiley.com/doi/10.1111/bcp.13569/suppinfo

Figure S1 Incidence rates (per 100 000 person-years) of new users of attention-deficit/hyperactivity disorder medication per calendar year (2000–2015). Stratified by age

Figure S2 Incidence rates (per 100 000 person-years) of new users of attention-deficit/hyperactivity disorder medication during 2008–2012 across the five Danish Regions. (A) 50–64 years, (B) 65–79 years and (C) shows 80+ years

Figure S3 One-year mortality rate (%) of new users of attention-deficit/hyperactivity disorder medication between 2000 and 2011 stratified by age, standardized to the population in 2012

Figure S4 Kaplan–Meier plot of survival probability of new users of attention-deficit/hyperactivity disorder medication between 2000 and 2011. Stratified by a diagnosis of cancer

Table S1 Incidence rates (per 100 000 person-years) of new users of attention-deficit/hyperactivity disorder medication and attention-deficit/hyperactivity disorder diagnoses per calendar year (2000–2015). Overall and stratified by age

Table S2 Characteristics of new users of attention-deficit/hyperactivity disorder medication ≥50 years, 1 January 2000 to 31 December 2012. Stratified by the presence of cancer and death within 1 year after index date

Table S3 *Posthoc* analysis; the 10 most frequent diagnoses in the study population 1 year prior to index date