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ORIGINAL ARTICLE

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Trends in utilization and dosing of antipsychotic drugs in Scandinavia: Comparison of 2006 and 2016

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Aims: The aim of this study was to investigate time trends in dosing and prevalence of antipsychotic prescriptions in Scandinavia.

Methods: We retrieved data on antipsychotic use between 2006 and 2016 from Danish, Norwegian and Swedish national prescription registers. For each antipsychotic, we calculated prevalence of use and mean doses, overall and for specific age groups (young, adults and elderly).

Results: Antipsychotic use in Scandinavia increased from 16.5 to 17.2 users/1000 inhabitants between 2006 and 2016 (+2.4%, annual change: 0.07 users/1000 inhabitants/year, 95% CI: 0.02–0.20, $P = 0.02$). In 2006, chlorprothixene and levomepromazine were the most commonly used antipsychotics. By 2016, quetiapine was the most used antipsychotic in all three countries and across all age groups, with an overall 1-year prevalence of 4.05–9.97 users/1000 inhabitants (annual change: 0.57 users/1000 inhabitants/year, 95% CI: 0.54–0.60, $P < 0.001$). Quetiapine showed a marked decrease in mean doses during the 11-year study period (0.46–0.28 defined daily doses (DDD)/user/day: 39.1%, −0.02 DDD/user/day/year, 95% CI: −0.020 to −0.015, $P < 0.001$). In 2016, the highest mean doses were seen for clozapine (0.90–1.07 DDD/user/day) and olanzapine (0.66–0.88 DDD/user/day).

Conclusions: There is an increased prevalence of antipsychotic prescriptions that coincides with low and/or decreasing mean doses of the majority of commonly used antipsychotics in Scandinavia. Of all antipsychotics, this development was most pronounced for quetiapine. Reasons for and consequences of increased antipsychotic use that lasts shorter periods of time requires further study.

KEYWORDS

antipsychotics, drug utilization, pharmacoepidemiology, psychopharmacology

1 | INTRODUCTION

Antipsychotic drugs are approved primarily for the treatment of severe psychiatric disorders, such as schizophrenia and bipolar mania.[1,2] Furthermore, antipsychotic drugs are also used for a range of other psychiatric disorders, including major depressive disorder, substance abuse, anxiety disorders, sleep disturbance and behavioural symptoms of dementia.[3-5] However, there is significant variation in the evidence of efficacy for the treatment of these conditions.[2,6] The overall prevalence of antipsychotic use has been increasing,[7] and population studies have found the use of antipsychotic drugs in non-psychotic disorders such as depression, anxiety, autism spectrum disorders to be common.[4,5,8-11] In Norway, increasing use of the second-generation antipsychotic quetiapine was found to coincide

with decreasing mean doses and increased prescribing for non-psychotic disorders, indicating increasing off-label use.[8] Among incident users of antipsychotic drugs in Denmark, the most common psychiatric diagnosis was 'Reaction to severe stress and adjustment disorders' followed by major depressive episode and organic mental disorders.[4] Widespread use of antipsychotic drugs might constitute a challenge to public health, as exposure to antipsychotic drugs has been associated with the potential for a range of serious adverse events, ranging from fatal arrhythmias[12] over metabolic disturbances and cardiovascular risk factors[13] to incident diabetes.[14] This study investigates whether the relationship between the time trends in the dosing and prevalence of quetiapine prescriptions found in Norway[8] is present in other countries and, possibly, also for other antipsychotic drugs as part of a more general phenomenon. To guide future initiatives on the rational use of antipsychotic drugs, there is a need for detailed information on current practice and trends in the utilization of this drug class.

What is already known about this subject

- The number of antipsychotic users has been increasing, mainly due to increasing use of antipsychotic drugs in non-psychotic disorders such as depression, anxiety and autism spectrum disorders.
- Increasing use of quetiapine has been found to coincide with decreasing mean doses and increased prescribing for non-psychotic disorders among Norwegian patients.
- We do not know if the development in Norway is seen in other countries and for other antipsychotics as part of a general trend in antipsychotic prescribing.

What this study adds

- Mean doses have been low or decreasing for the majority of commonly used antipsychotic drugs, except for olanzapine and clozapine.
- The use of quetiapine has been increasing in all Nordic countries, and this development coincides with a decrease in its mean doses.
- Five of the ten most prevalent prescribed antipsychotic drugs in 2016 were first-generation antipsychotic drugs, which are generally not recommended in psychiatric guidelines.

2 | METHODS

We conducted a multinational drug utilization study on antipsychotic prescriptions covering the populations of Denmark, Norway and Sweden over an 11-year period, from 2006 to 2016.

2.1 | Data sources

We obtained data from national medicinal product statistics registers: The Danish Register of Medicinal Product Statistics (DRMPS),[15,16] the Norwegian Prescription Database (NorPD)[17] and the Swedish Prescribed Drug Register (SPDR).[18] DRMPS covers the entire Danish population (5.7 million inhabitants in 2016) and holds information on all prescriptions dispensed at pharmacies since 1995.[19] NorPD covers the entire Norwegian population (5.2 million inhabitants in 2016) and holds information on all prescriptions dispensed at pharmacies since 2004.[20] SPDR covers the entire Swedish population (9.9 million inhabitants in 2016) and holds information on all prescriptions dispensed at pharmacies since July 2005.[21] In all three study countries, the health services are publicly funded and available to all citizens regardless of socioeconomic status. Prescription drugs, including antipsychotics, are fully or partially reimbursed, and their dispensing for outpatient care is recorded at pharmacies providing nationwide data from these sources.[22] It is possible to extract population-level statistics from all three registers, regarding the number of users and doses for any specific drug, age group and geographical region, and, generally, 98–99% of prescriptions are identifiable on an individual level resulting in valid estimates of, e.g., age-specific data.[19-21]

2.2 | Antipsychotic drugs

We extracted data on all prescriptions within the Anatomical Therapeutic Chemical (ATC)-group N05A (antipsychotics), but excluded lithium (ATC: N05AN01), which is not a dopamine-antagonist as the remaining drug class. Furthermore, we excluded acepromazine, prochlorperazine and droperidol (ATC: N05AA04, AB04 and AD08) from further analyses, as they are approved, or primarily used, as antiemetics. Defined daily dose (DDD) is the assumed average maintenance dose per day for a drug used for its main indication in adults, and is used for each substance according to the WHO ATC/DDD index.[23]

2.3 | Analysis

One-year prevalence and mean doses were calculated for all marketed antipsychotic drugs. Further, specific analyses were carried out for the 10 most commonly used antipsychotic drugs regarding overall prevalence for Scandinavia. For main analyses, prescriptions were stratified by age group: youth (< 20 years), adults (20–64 years) and elderly (> 64 years). Additionally, for exploratory analyses, further age groups where applied: children (0–14 years), adolescents (15–19 years), young adults (20–44 years), older adults (45–64 years), elderly (65–74 years) and very old (75+ years).

One-year prevalence [users per 1000 inhabitants] was defined as the number of individuals with one or more prescriptions of antipsychotic drugs within a specific calendar year, divided by the number of inhabitants in thousands. We subtracted the number of individuals

with prescriptions of acepromazine, prochlorperazine, droperidol and lithium (ATC N05AA03, AB04, AD08 and AN01) from the number of individuals with prescriptions within the N05A group before calculation of overall prevalence of antipsychotic use. For calculation of age-group specific prevalence, we extracted age-group-specific population statistics from national statistical bureaus.[24-26]

Mean doses (MD) [DDD per users per day] was defined and calculated as total number of DDDs per year of the specific drug, divided by the total number of users per year of this substance, divided by 365 days per year.

Country-specific data were extracted directly from the national databases. Calculation of prevalence and mean doses for Scandinavia as a whole was done by extracting and adding national data on DDD and number of users for the specific subgroup before further calculations were carried out as described above. This means that all values of prevalence and mean doses for Scandinavia are weighted with regard to the country-specific values.

Changes in prevalence and mean doses were calculated as percentages and absolute changes. Time trends were assessed by linear regression reporting values for changes with 95% confidence intervals (95% CI) and associated *P*-values for the hypothesis of the change not being different from zero. All calculations were carried out with GraphPad Prism version 7.0c (GraphPad Software, La Jolla, CA, USA) and STATA release 14.2 (StataCorp, College Station, TX, USA).

De-identified medicinal product statistical data, as well as population data, were publicly available, and therefore no approval from data protection agency or ethical committees were required for this study.

3 | RESULTS

We identified 315 982 individuals who redeemed one or more prescriptions of antipsychotic drugs in Scandinavia during 2006, representing a prevalence of 16.5 users per 1000 inhabitants. In 2016, this number was 375 354 individuals, representing a prevalence of 17.2 users per 1000 inhabitants (annual change: 0.07 users/1000 inhabitants/year, 95% CI: 0.02–0.20, $P = 0.02$). In 2016, the total number of users of antipsychotic drugs was 117 473 in Denmark, 103 383 in Norway and 136 498 in Sweden, representing increases of 18.4%, 26.9% and 0.9% from the number of users in 2006. Of the Scandinavian countries, Denmark had the highest 1-year prevalence in 2016 with 20.6 users/1000 inhabitants, followed by Norway with 19.7 users/1000 inhabitants, and Sweden with 13.9 users/1000 inhabitants.

3.1 | One-year prevalence of specific drugs

Table 1 presents 1-year prevalence for the 10 most used antipsychotic drugs in Scandinavia in 2006 and 2016. For Scandinavia as a whole, levomepromazine and chlorprothixene were the most commonly prescribed first-generation antipsychotic drugs, whereas quetiapine and olanzapine were the most commonly prescribed second-generation antipsychotic drugs. Quetiapine had the highest increase in prevalence during the study period with 397% (from 1.40 to 6.95 users/1000 inhabitants for Scandinavia, +0.57 users/1000 inhabitants/year, 95% CI: 0.54–0.60), followed by aripiprazole (220%; from 0.58 to 1.74 users/1000 inhabitants for Scandinavia, +0.12 users/1000 inhabitants/year, 95% CI: 0.11–0.13). One-year prevalence for other antipsychotic drugs in 2006 and 2016 can be found in Table S1.

3.2 | Mean doses of specific drugs

Table 1 presents mean doses for the 10 most used antipsychotic drugs for 2006 and 2016 in Scandinavia and each of the countries. In 2016, for Scandinavia as a whole, fluphenazine treatment had the highest MD (Scandinavia, 2016) (1.72 DDD/user/day), followed by ziprasidone (0.97 DDD/user/day), clozapine (0.94 DDD/user/day), perphenazine (0.87 DDD/user/day) and sertindole (0.78 DDD/user/day). Levomepromazine treatment had the lowest MD (0.08 DDD/user/day), followed by chlorprothixene (0.12 DDD/user/day), melperone (0.13 DDD/user/day), flupenthixol (0.25 DDD/user/day) and haloperidol (0.26 DDD/user/day). Of these, haloperidol had the most pronounced difference between countries: 0.16 DDD/user/day for Norway and 0.30 DDD/user/day for Sweden (see Table S2).

Overall, quetiapine had the most pronounced decrease in MD (−39.1%, −0.02 DDD/user/day/year, 95% CI: −0.020 to −0.015) among commonly used antipsychotic drugs from 2006 to 2016, followed by haloperidol (−16.1%, −0.006 DDD/user/day/year, 95% CI: −0.008 to −0.004), and chlorprothixene (−14.3%, −0.002 DDD/user/day/year, 95% CI: −0.003 to −0.001). MDs for levomepromazine, clozapine, olanzapine and risperidone remained relatively stable with changes between 0% and 3.7%, whereas MDs increased for zuclopenthixol (+17.3%, 0.009 DDD/user/day/year, 95% CI: 0.008–0.01) and flupenthixol (+36.1%, 0.007 DDD/user/day/year, 95% CI: 0.006–0.007) (see Table 1).

Figures 1 and 2 presents changes in 1-year prevalence and MD by country and age group for the two most used second-generation antipsychotic drugs in 2016: olanzapine (Figure 1) and quetiapine (Figure 2). Graphical representation of 1year prevalence and MD by country and age group for the 10 most commonly used antipsychotic drugs in 2016 can be found in Figures S1–S10. Among the oldest patients (≥75 years), we found high prevalence and low mean doses of haloperidol, risperidone and quetiapine use. However, there were differences between the studied countries: Haloperidol use increased in Denmark from 2006 to 2016 (4.5 to 8.2 users/1000 inhabitants), but decreased in Norway and Sweden during the same period (from 6.2 and 11.2 to 4.4 and 7.1 users/1000 inhabitants, respectively) (see Figure S2). Risperidone use was considerably higher among the oldest subjects in 2016 in Sweden (19 users/1000 inhabitants) than in Denmark and Norway (9.2 and 4.0 users/1000 inhabitants, respectively) (see Figure S9).

Among young individuals (<20 years) quetiapine, risperidone and aripiprazole were the most commonly used drugs. MD was generally low (≤0.42 DDD/user/day), except for clozapine treatment (0.61–

TABLE 1 Total number of users, 1-year prevalence (Prev.) (users per 1000 inhabitants), total dose (1000 DDDs) and mean doses (MD) (DDD per user per day) and change in MD from 2006 to 2016 for the 10 most used antipsychotic drugs in total for Scandinavia and for each of the three countries in 2006 and 2016

Active substance	Users	Prev.	Dose	MD	Active substance	Users	Prev.	Dose	MD	Change
Scandinavia										
2006					**2016**					
Risperidone	69,529	3.63	6,940	0.27	Quetiapine	144,543	6.95	14,972	0.28	−39.1%
Levomepromazine	60,453	3.16	1,760	0.08	Olanzapine	71,567	3.44	19,016	0.73	+0%
Olanzapine	57,969	3.03	15,537	0.73	Risperidone	60,779	2.92	6,111	0.28	+3.7%
Chlorprothixene	37,908	1.98	1,870	0.14	Aripiprazole	36,086	1.74	7,345	0.56	−6.6%
Haloperidol	26,808	1.40	3,047	0.31	Levomepromazine	34,467	1.66	973	0.08	+0%
Quetiapine	26,744	1.40	4,476	0.46	Chlorprothixene	33,834	1.63	1,467	0.12	−14.3%
Flupenthixol	26,308	1.37	1,870	0.19	Haloperidol	23,748	1.14	2,221	0.26	−16.1%
Zuclopenthixol	22,747	1.19	4,291	0.52	Flupenthixol	14,330	0.69	1,294	0.25	+31.6%
Dixyrazine	20,291	1.06	1,760	0.24	Zuclopenthixol	14,174	0.68	3,175	0.61	+17.3%
Perphenazine	17,795	0.93	3,480	0.54	Clozapine	12,190	0.59	4,168	0.94	−2.1%
Denmark										
2006					**2016**					
Chlorprothixene	21,656	3.99	1,099	0.14	Quetiapine	56,916	9.97	5,811	0.28	−33.3%
Risperidone	18,733	3.45	2,356	0.34	Chlorprothixene	17,424	3.05	749	0.12	−14.3%
Olanzapine	18,416	3.39	5,647	0.84	Olanzapine	16,860	2.95	5,385	0.88	+4.8%
Levomepromazine	15,858	2.92	558	0.10	Risperidone	16,674	2.92	2,015	0.33	−2.9%
Quetiapine	14,069	2.59	2,144	0.42	Aripiprazole	11,029	1.93	2,528	0.63	−10.0%
Flupenthixol	10,961	2.02	633	0.16	Haloperidol	6,663	1.17	553	0.23	−52.1%
Zuclopenthixol	9,731	1.79	1,549	0.44	Levomepromazine	5,177	0.91	155	0.08	−20.0%
Aripiprazole	4,795	0.88	1,233	0.70	Flupenthixol	4,762	0.83	337	0.19	+18.8%
Haloperidol	4,450	0.82	772	0.48	Zuclopenthixol	4,679	0.82	846	0.50	+13.6%
Perphenazine	4,111	0.76	1,054	0.70	Clozapine	3,315	0.58	1,103	0.91	−5.2%
Norway										
2006					**2016**					
Levomepromazine	25,296	5.43	518	0.06	Quetiapine	47,724	9.11	4,451	0.26	−52.7%
Olanzapine	14,913	3.20	3,843	0.71	Olanzapine	16,940	3.23	4,536	0.73	+2.8%
Chlorprothixene	14,612	3.13	673	0.13	Levomepromazine	16,298	3.11	310	0.05	−16.7%
Risperidone	7,812	1.68	1,003	0.35	Chlorprothixene	14,483	2.77	626	0.12	−7.7%
Chlorpromazine	6,646	1.43	269	0.11	Risperidone	8,295	1.58	1,012	0.33	−5.7%
Quetiapine	6,622	1.42	1,318	0.55	Aripiprazole	5,904	1.13	1,285	0.60	+20.0%
Perphenazine	6,343	1.36	945	0.41	Haloperidol	3,984	0.76	237	0.16	−38.5%
Flupenthixol	5,595	1.20	433	0.21	Flupenthixol	3,743	0.71	357	0.26	+23.8%
Haloperidol	4,786	1.03	452	0.26	Clozapine	2,609	0.50	971	1.02	−4.7%
Zuclopenthixol	3,336	0.72	612	0.50	Zuclopenthixol	2,560	0.49	577	0.62	+24.0%
Sweden										
2006					**2016**					
Risperidone	42,984	4.75	3,581	0.23	Quetiapine	39,903	4.05	4,710	0.32	−30.4%
Olanzapine	24,640	2.72	6,047	0.67	Olanzapine	37,767	3.83	9,096	0.66	−1.5%
Levomepromazine	19,299	2.13	684	0.10	Risperidone	35,810	3.64	3,084	0.24	+4.3%
Dixyrazine	18,476	2.04	1,484	0.22	Aripiprazole	19,153	1.94	3,533	0.51	−1.9%

(Continues)

TABLE 1 (Continued)

Active substance	Users	Prev.	Dose	MD	Active substance	Users	Prev.	Dose	MD	Change
Haloperidol	17,572	1.94	1,824	0.28	Haloperidol	13,101	1.33	1,431	0.30	+7.1%
Flupenthixol	9,752	1.08	804	0.23	Levomepromazine	12,992	1.32	508	0.11	+10.0%
Zuclopenthixol	9,680	1.07	2,131	0.60	Zuclopenthixol	6,935	0.70	1,752	0.69	+15.0%
Perphenazine	7,341	0.81	1,481	0.55	Clozapine	6,266	0.64	2,094	0.92	+2.2%
Quetiapine	6,053	0.67	1,014	0.46	Flupenthixol	5,825	0.59	600	0.28	+21.7%
Clozapine	5,163	0.57	1,705	0.90	Perphenazine	2,836	0.29	969	0.94	+70.9%

Source: Danish Register of Medicinal Product Statistics, Danish Health Data Authority; Norwegian Prescription Database, The Norwegian Institute of Public Health; Swedish Prescribed Drug Register, National Board of Health and Welfare.

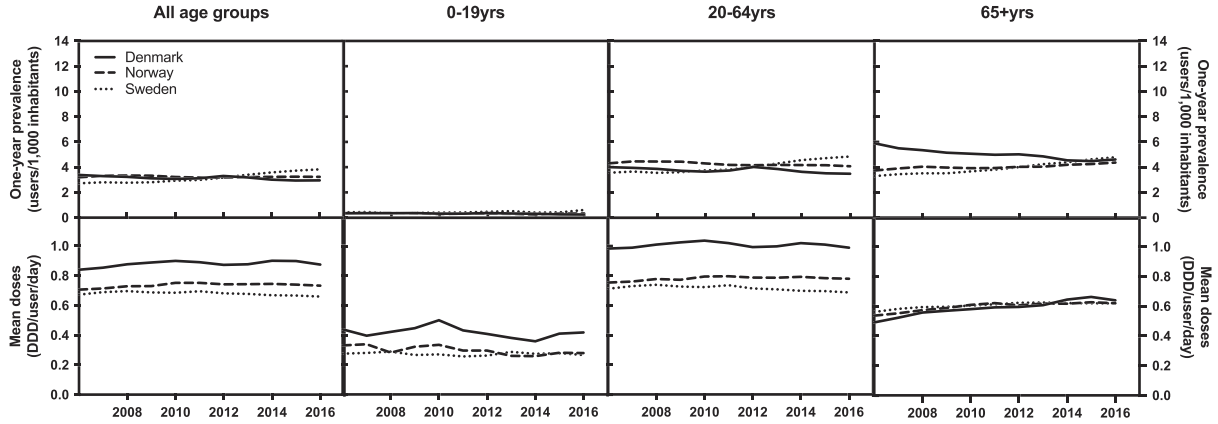

FIGURE 1 Country-specific time trends in one-year prevalence (upper half) and mean doses (lower half) for olanzapine from 2006 to 2016 overall and by age groups (DDD for olanzapine is 10 mg). Data from Danish register of medicinal product statistics, Danish health data authority; Norwegian prescription database, the Norwegian Institute of Public Health; Swedish prescribed drug register, National Board of Health and Welfare

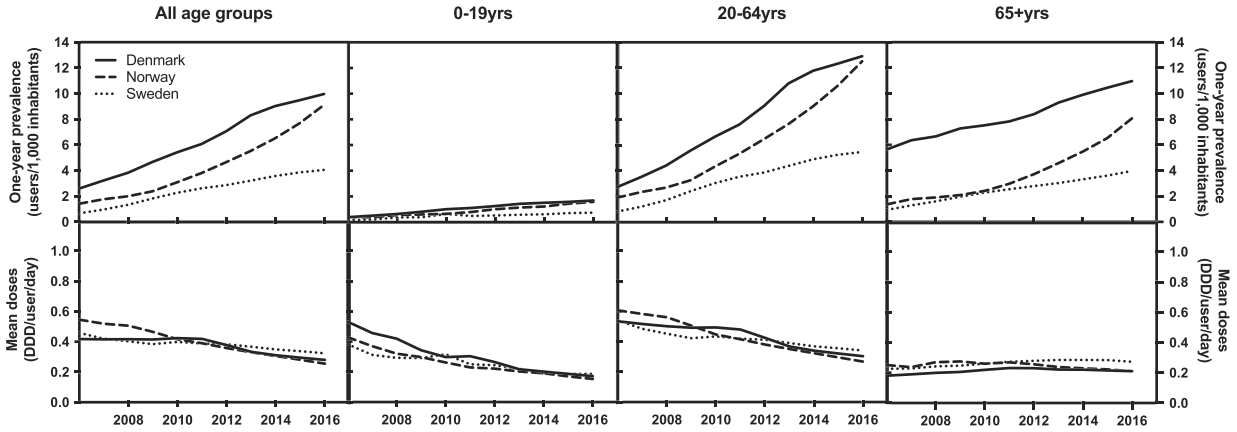

FIGURE 2 Country-specific time trends in one-year prevalence (upper half) and mean doses (lower half) for quetiapine from 2006 to 2016 overall and by age groups (DDD for quetiapine is 400 mg). Data from Danish register of medicinal product statistics, Danish health data authority; Norwegian prescription database, the Norwegian Institute of Public Health; Swedish prescribed drug register, National Board of Health and Welfare

0.73 DDD/user/day). Among adults (20–64 years), chlorprothixene, olanzapine and quetiapine were the most used drugs, but there were remarkable differences in prevalence between countries. MD was lowest for levomepromazine and chlorprothixene treatment (≤0.11 and ≤0.12 DDD/user/day) and highest for clozapine and olanzapine treatment (≥0.98 and ≥0.78 DDD/user/day). In the elderly (> 64 years), haloperidol, quetiapine and risperidone were the most commonly used drugs, and MD was generally low, but with some variation: levomepromazine (≤0.09 DDD/user/day) and olanzapine (≥0.62 DDD/user/day) (see Tables S3 and S4).

4 | DISCUSSION

In this study of nationwide prescription data from the three Scandinavian countries, we found low or decreasing mean doses in 7 of 10 of the most commonly used antipsychotic drugs. Use of second-generation antipsychotic drugs is increasingly prevalent, with quetiapine being the most used antipsychotic drug. We also found a considerable use of first-generation antipsychotic drugs, including levomepromazine, chlorprothixene and flupenthixol.

We found increasing prevalence of antipsychotic use in Denmark and Norway, but not in Sweden. This finding is in contrast with Hálfdánarson and colleagues[7] who found increasing prevalence of antipsychotic prescriptions in Denmark, but decreasing prevalence in Norway and Sweden during a similar period (2005–2014). However, this difference might be due to methodological differences, as these authors only excluded prescriptions of lithium (N05AN01) and not dopamine antagonists primarily used as antiemetics, as in the present study. In Norway and Sweden, the use of dixyrazine and prochlorperazine was substantial in 2006 but has decreased considerably by 2016. These drugs have commonly been used as antiemetics during pregnancy,[27] and our exclusion of these drugs could have led to the observed difference in prevalence trends in comparison with Hálfdánarson and colleagues.[7]

In our analysis of specific antipsychotic drugs, quetiapine and olanzapine were most commonly used (Table 1). This finding is in line with other drug utilization studies,[5,28] where increases in the prevalence of antipsychotic prescriptions were primarily attributable to increases in quetiapine use.[5,8,28,29] We observed a similar trend in Scandinavia, where quetiapine use increased most dramatically during the 10-year study period by 397%. The extension of licensed indications during the study period might explain this increase. Quetiapine was first approved for mania in all three Scandinavian countries during 2008 and 2009, and later for further indications, such as bipolar depression, maintenance treatment in bipolar disorder, and for major depressive disorder during 2009 and 2010. However, this might not be the only cause of the observed increase, as a significant proportion of quetiapine users, ranging from 57–70%, did not have diagnoses of severe mental illness (schizophrenia or bipolar disorder).[5,8,9,30,31] Data have suggested that low-dose quetiapine is frequently used for anxiety and sleep disorders.[5,9,28] In affective disorders, the extend release formulation of quetiapine is generally used in lower doses (50–300 mg/day ~ 0.125–0.75 DDD/day). Therefore, increased utilization in this indication might have contributed to decreasing mean doses in quetiapine in general. In this context, we observed a similar association between decreasing mean doses and increasing prevalence for quetiapine use in both youth and adults in Denmark and Sweden (Figure 2), as Gjerden and colleagues[8] did in Norway.

Prevalence of clozapine and olanzapine use and associated mean doses did not change considerably during the study period, and the mean doses of both drugs were among the highest for commonly used antipsychotic drugs (Table 1, Tables S2–S4, Figure 2 and Figure S6). This finding might suggest that olanzapine and clozapine are primarily used in the treatment of severe mental illnesses. In the UK, 62% of patients on olanzapine had diagnoses of severe mental illness, in comparison with quetiapine users where only 36% had diagnoses of severe mental illness, and there were significant differences in median dose of olanzapine between severe mental illness and non-severe mental illness treatment (12 mg/day *vs.* 6 mg/day).[5] The considerable use of olanzapine might be problematic, besides its propensity to lead to metabolic side effects,[13] as high cumulative doses of olanzapine have also been associated with a slightly increased risk of breast cancer in a recent case–control study.[32] Bachmann and colleagues also found similar stable or slightly increasing prevalence of clozapine use in the Scandinavian countries as well as other countries, suggesting that clozapine is reserved for treatment of severe mental illness.[33]

We found a considerable use of first-generation antipsychotic drugs in all three countries. However, prevalences were generally decreasing and highest among the elderly (65+ years). Other prescription surveys have found decreasing utilization of first-generation antipsychotic drugs.[5,7,34] The prevalent use of first-generation antipsychotic drugs, despite their higher risk of extrapyramidal side effects in comparison with second-generation antipsychotic drugs,[35,36] might be because of use in other medical specialties such as neurology, oncology and palliative care: for example, levomepromazine (methotrimeprazine) is used in the treatment of medication-overuse headache as supportive treatment during detoxification[37] and for nausea or delirium in palliative care.[38] Haloperidol is recommended for the pharmacological intervention in delirium and nausea as part of palliative care[39,40] and is, together with zuclopenthixol, recommended as third-line treatment in schizophrenia in Denmark[41] due to a lower risk of orthostasis and the related risk of falls in comparison with second-generation antipsychotics, especially clozapine, quetiapine and risperidone.[42] We found a slight increase in the use of haloperidol in Denmark, driven by increasing use among the oldest patients (Figure S2). Considerable and increasing use of haloperidol has also been found in other European countries, despite the association with potentially fatal cardiac arrhythmias.[43] Chlorprothixene is still widely used in both Denmark and Norway, but not in Sweden (Table 1 and Figure S4). We found mean doses of 0.12 DDD/user/day in both countries, suggesting a considerable use for indications other than schizophrenia. Chlorprothixene is approved for the treatment of psychotic conditions in all three countries,[44-46] and in Norway also specifically for the treatment of anxiety and withdrawal symptoms.[45]

The present study details the findings of Hálfdánarson and colleagues,[7] as it investigates prevalence trends for the 10 most commonly used antipsychotic drugs, and is the first study to evaluate changes in mean doses. The low or decreasing MDs for the majority of commonly used antipsychotic drugs might represent a signal of disseminated use outside main indications. This possible development prompts further investigation of the indications for initiating treatment with antipsychotic drugs and the risks associated with antipsychotic drug treatment. Disseminated use of second-generation antipsychotic drugs might affect public health as it is associated with metabolic disturbances and cardiac adverse events.[13,47-52]

The findings of this study need to be interpreted within its strengths and limitations. A major strength of the present analysis is

its large sample size, covering a population of approximately 20 million people from three neighbouring countries for 11 years, based on prescription registers of high validity (98–99% identifiable on an individual level).[22] Moreover, the analysis of time trends in use and dosing can be informative. However, there are some limitations concerning the present analysis: First, our use of aggregate data on antipsychotic use did not allow us to describe trends on an individual level. This means that we were not able to estimate the incidence of antipsychotic use, nor duration of treatment episodes or to connect this use with diagnostic information to assess the indications for initiating treatment with antipsychotic drugs. This means we are not able to separate off-label treatment from treatment in approved indications, but merely to describe use on a more general level. Second, antipsychotic doses may vary considerably between drugs and individuals. Therefore, we cannot assume average doses above or below 1 DDD to represent either on- or off-label treatment. However, we still consider DDD a relevant measure to quantify changes in mean doses over time. The prescription data used in this study describes the annual number of users and the annual amount dispensed of each drug. We are therefore not able to separate episodic from chronic use. This means that low mean doses might reflect both episodic use of high doses as well as chronic use of low doses. Also, the use of aggregate data did not allow us to determine if the increases in prevalence of antipsychotic use was a result of a higher incidence of antipsychotic prescription or a result of longer duration of treatment.

Third, our analysis only covers prescriptions redeemed at community pharmacies and does not cover in-hospital use. In Denmark, antipsychotic medication for patients with first episode psychosis is distributed free of charge from out-patient facilities and therefore also not covered by the present study. Despite this fact, only 17% of the total turnover of antipsychotic drugs occurs in hospital settings in Denmark,[16] and we do not expect this to interfere with our analysis systematically, as most patients will redeem prescriptions at pharmacies after discharge from psychiatric hospitals.

Fourthly, our estimation of prevalence might underestimate the true number of antipsychotic users, as some of the individuals subtracted might have had prescriptions of both lithium and/or antiemetics and the antipsychotic drugs of interest to this analysis. A recent Australian cohort study[53] on psychotropic polypharmacy found same-class (ATC N05A) polypharmacy in 5.9% to 7.3% of patients with antipsychotic prescriptions, suggesting that it is likely that only a negligible portion of relevant users is excluded from our study by this subtraction. However, the total proportion of individuals with prescriptions of the subtracted drugs are generally <10% of the total number of individuals with prescriptions from the N05A group. Lastly, we were not able to control for migration from the study population, as prescription data were not identifiable on an individual level.

In conclusion, we found an increase in the overall use of antipsychotic drugs in Scandinavia in two of three countries during the past decade. This increase coincided with low or decreasing mean doses of the majority of commonly used antipsychotic drugs. Second-generation antipsychotic drugs were the most commonly used drugs, but first-generation antipsychotic drugs were still utilized to a considerable extent in 2016. Our findings seem to represent a signal of disseminated use of antipsychotic drugs outside of severe mental illness indications.

COMPETING INTERESTS

M.H., E.J., R.A.K. and P.M. report no potential conflicts of interest. A.P. reports participation in research projects funded by Alcon, Almirall, Astellas, Astra-Zeneca, Boehringer-Ingelheim, Novo Nordisk, Servier and LEO Pharma, all with funds paid to the institution where he was employed (no personal fees) and with no relation to the work reported in this paper. J.R. is employed at the Centre for Pharmacoepidemiolgy which receives grants from several entities (pharmaceutical companies, regulatory authorities, contract research organizations) for the performance of drug utilization and safety studies. C.U.C. has been a consultant and/or advisor to or has received honoraria from: Alkermes, Allergan, Angelini, Gerson Lehrman Group, IntraCellular Therapies, Janssen/J&J, LB Pharma, Lundbeck, Medavante, Medscape, Merck, Neurocrine, Otsuka, Pfizer, ROVI, Servier, Sunovion, Takeda, and Teva. He has provided expert testimony for Bristol-Myers Squibb, Janssen, and Otsuka. He served on a Data Safety Monitoring Board for Lundbeck, ROVI and Teva. He received royalties from UpToDate and grant support from Janssen and Takeda. He is also a shareholder of LB Pharma.

CONTRIBUTORS

All authors were responsible for the study concept and design, and also the interpretation of the data. M.H. was responsible for data acquisition and statistical analysis of the data. M.H. had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis. The manuscript was drafted by M.H., A.P. and J.R. All the authors critically revised the manuscript for important intellectual content.

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SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section at the end of the article.

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