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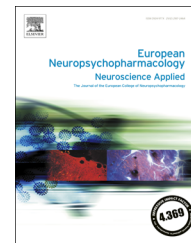
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International trends in antipsychotic use: A study in 16 countries, 2005–2014

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Abstract

The objective of this study was to assess international trends in antipsychotic use, using a standardised methodology. A repeated cross-sectional design was applied to data extracts from the years 2005 to 2014 from 16 countries worldwide. During the study period, the overall prevalence of antipsychotic use increased in 10 of the 16 studied countries. In 2014, the overall prevalence of antipsychotic use was highest in Taiwan (78.2/1000 persons), and lowest in Colombia (3.2/1000). In children and adolescents (0-19 years), antipsychotic use ranged from 0.5/1000 (Lithuania) to 30.8/1000 (Taiwan). In adults (20-64 years), the range was 2.8/1000 (Colombia) to 78.9/1000 (publicly insured US population), and in older adults (65+ years), antipsychotic use ranged from 19.0/1000 (Colombia) to 149.0/1000 (Taiwan). Atypical antipsychotic use increased in all populations (range of atypical/typical ratio: 0.7 (Taiwan) to 6.1 (New Zealand, Australia)). Quetiapine, risperidone, and olanzapine were most frequently prescribed. Prevalence and patterns of antipsychotic use varied markedly between countries. In the majority of populations, antipsychotic utilisation and especially the use of atypical antipsychotics increased over time. The high rates of antipsychotic prescriptions in older adults and in youths in some countries merit further investigation and systematic pharmacoepidemiologic monitoring. © 2017 Elsevier B.V. and ECNP. All rights reserved.

1. Introduction

The term “antipsychotics” denotes a heterogeneous group of pharmaceutical substances with antipsychotic and tranquilising properties. Traditionally, antipsychotics have been classified into typical antipsychotics (syn. “first generation antipsychotics”) versus atypical antipsychotics (syn. “second generation antipsychotics”), according to the extent of perceived extrapyramidal adverse effects (Leucht et al., 2013).

The indications for treatment with antipsychotics are numerous, including e.g. schizophrenia spectrum disorder, bipolar disorder, tic disorder, agitation, and sleeping problems. In recent years, antipsychotics have also been increasingly used in the treatment of patients with anxiety disorders, attention-deficit/hyperactivity disorder (ADHD), major depression, personality disorders, disruptive disorders, and dementia (Bachmann et al., 2014; Comer et al., 2011; Reus et al., 2016; Toteja et al., 2014).

Adverse effect profiles of typical and atypical antipsychotics differ, with atypical antipsychotics regularly having

more pronounced metabolic adverse effects, and typical antipsychotics often carrying more extrapyramidal adverse effects (e.g. dyskinesia) (Correll et al., 2015; Leucht et al., 2013; Vancampfort et al., 2015). Despite only some atypical antipsychotics being more effective for the treatment of psychosis than typical antipsychotics (Leucht et al., 2013, 2009), atypical antipsychotics are often accredited with higher efficacy than typical antipsychotics (Jauhar et al., 2012).

In addition to potential adverse effects, several other issues may arise with the use of antipsychotics. Firstly, long-term safety and/or effectiveness data are lacking, especially for children and elderly people (Nesvag et al., 2016; Persico et al., 2015; Schröder et al., 2017; Seida et al., 2012). Secondly, antipsychotics are often prescribed for other disorders than their licensed indication, leading to off-label use rates of sometimes up to 93% (Carton et al., 2015). Thirdly, a significant portion of patients of all ages is treated with antipsychotic polypharmacy (≥ 2 concurrent antipsychotic substances), which can lead to increased rates of adverse effects (Campos Mendes et al., 2016; Fontanella

et al., 2014; James et al., 2017; Norgaard et al., 2017; Westaway et al., 2016).

In this light, systematic monitoring of antipsychotic utilisation is of major public health importance. Many countries have reported increasing antipsychotic utilisation rates over recent years (Bachmann et al., 2014; Comer et al., 2011; Olfson et al., 2014, 2015a; Verdoux et al., 2010), but comparison and interpretation of these data is hampered by marked differences in study designs. While ADHD drug and antidepressant utilisation have previously been assessed across countries, multi-national studies with comparable data on antipsychotic use are scarce (Abbing-Karahagopian et al., 2014; Bachmann et al., 2016; Karlstad et al., 2016; Lewer et al., 2015; Raschi et al., 2013). Such a knowledge of antipsychotic utilisation patterns across different populations and geographical areas is an important help to inform health policy and decision-making, in order to ensure rational use of these drugs.

The aim of this study was to describe trends in the prevalence of antipsychotic use in children adolescents, adults, and old adults in 16 countries in Europe, Asia, North America, South America, and Oceania, using standardised criteria for data analysis. and

2. Experimental procedures

2.1. Data sources

We used data from national or regional administrative databases from the following countries: Australia, Colombia, Denmark, Finland, France, Germany, Iceland, Japan, Lithuania, the Netherlands, New Zealand, Norway, Spain, Sweden, Taiwan, and the USA. The Netherlands and Lithuania contributed data for the analysis of general antipsychotic utilisation, but data on typical and atypical antipsychotic use along with the top five most used substances were unavailable from these two countries. The characteristics of the underlying databases are described in Table 1.

2.2. Data analysis

We included individuals who were registered continuously for each calendar year from 2005 (2006 for data from Australia, Colombia, Sweden and France, 2009 for data from Japan, 2011 for data from Spain) to 2014 (2010 for data from the publicly insured US population, 2013 for data from Taiwan). Annual prevalence was defined as the proportion of individuals per calendar year with one or more prescription or dispensing of an antipsychotic (code N05A (with lithium (N05AN01) excluded) within the Anatomical Therapeutic Chemical (ATC) drug classification system employed by the WHO (WHO Collaborating Centre for Drug Statistics Methodology, 2015).

For each of the data extracts, we determined the annual antipsychotic use prevalence per 1000 persons, stratified by sex and age group: 0-19 years (children and adolescents), 20-64 years (adults), and 65+ years (older adults (World Health Organisation, 2015)). Furthermore, we reported the prevalence (per 1000 persons) of antipsychotic use in 2005 and 2014 (or first and last available data years) stratified by antipsychotic type (typical versus atypical), sex and age group. The following antipsychotic substances were defined as atypical in the analysis: amisulpride, aripiprazole, asenapine, brexpiprazole, cariprazine, clozapine, iloperidone, levosulpride, lurasidone, mosapramine, olanzapine, paliperidone, quetiapine, sertindole, sulpiride, sultopride, remoxipride, risperidone, ziprasidone, and zotepine. The following antipsychotics were defined as typical: acepromazine, acetophenazine, benperidol, bromperidol,

butaperazine, chlorproethazine, chlorpromazine, chlophenthixol, chlorprothixene, clotiapine, cyamemazine, dixyrazine, droperidol, fluanisone, flupentixol, fluphenazine, fluspirilene, haloperidol, levomepromazine, loxapine, melperone, mesoridazine, molindone, moperone, oxypertine, penfluridol, perazine, periciazine, perphenazine, pimozide, pipamperone, pipotiazine, prochlorperazine, promazine, prothipendyl, thiopropazate, thioproperazine, tiapride, trifluoperazine, triflupromazine, thioridazine, trifluoperidol, tiotixene, veralipride, and zuclopenthixol.

To assess antipsychotic use by sex, we calculated the male to female prevalence ratio by dividing the prevalence of use among males by the prevalence among females by population and age group in 2014 (or last available data year). Similarly, we calculated the overall atypical to typical antipsychotic prevalence ratio in each population in 2014. To assess relative change in antipsychotic use across calendar years, we calculated the prevalence ratio between the first and last study year by population and age group, expressed as prevalence ratio with accompanying 95% confidence intervals (CI) and *p*-value.

Additionally, we described the five most commonly used substances in each participating population in 2005 and 2014, measured as prevalence per 1000 persons, stratified by age group. When determining the most frequently used substances across all participating populations, we ranked the top five substances within each country and each age group on a point scale from 1 to 5, where the most commonly used substance received 5 points and the fifth most commonly used substance received 1 point. The total sum of points was then used to determine the relative position of each substance and the top five most commonly used substances overall.

Finally, the overall antipsychotic use prevalence in each population was directly age-standardised to the WHO world standard population (Ahmad et al., 2001) to account for potential differences in the age composition of the underlying populations.

2.3. Ethical approvals

The study was approved by the following country specific institutional review boards:

Australia: The New South Wales Population and Health Services Research Ethics Committee (CINSW HREC Approval no. 2013/11/494). The Australian Department of Human Services External Request Evaluation Committee approved access to the data.

Iceland: The National Bioethics Committee in Iceland, Reference no. VSN-16-117.

Japan: The ethical committee of Kyoto University Graduate School of Medicine (Reference no. R0780).

New Zealand: The "Human Ethics Committee (Health) Departmental Conditional Approval of Projects using Health Information", University of Otago (Reference no. HD 16/034).

Sweden: The regional ethics review board in Stockholm.

Taiwan: The Institutional Review Board (IRB) of the Chang Gung Memorial Hospital (Reference no.: 103-0637B).

USA: The Institutional Review Board of Brigham and Women's Hospital, which granted a waiver of informed consent.

In the remaining participating countries, according to their respective regulations, no ethical approval was necessary for this study.

3. Results

3.1. Trends in antipsychotic use between 2005 and 2014

Figure 1 shows how the overall prevalence of antipsychotic use evolved over time during the study period in all participating countries.

Table 1 Database characteristics.

Country	Database	Regional (R) or nationwide (N) data	or Nationally representative data	Population under risk (in 2014 or most recent year available)	% of population covered
Asia					
Japan	Database from three large nation-wide pharmacy companies (Kraft Inc, AIN HOLDINGS INC, Sogo Medical Inc), containing reimbursed outpatient prescriptions	N	NO	3.3 m	2.6
Taiwan	National Health Insurance Research Database (NHIRD-TW) (prescriptions from outpatient care claims, pharmacy claims, or hospital care claims)	N	YES	23 m (cohort: 1 m random sample of population under risk)	100
Europe					
Denmark	Danish Registry of Medicinal Products Statistics (national database with all outpatient prescriptions/dispensings)	N	YES (total population)	5.6 m	100
Finland	Finnish Prescription Registry (all reimbursed outpatient prescriptions/dispensings)	N	YES (total population)	5.5 m	100
France	French insurance healthcare system (all reimbursed outpatient prescriptions/dispensings)	N	YES	52.7 m (cohort: 1/97 random sample of population under risk)	100
Germany	BARMER GEK public health insurance funds (all reimbursed outpatient prescriptions)	N	NO	8.6 m	10.6
Iceland	Icelandic Medicines Registry (all outpatient prescription dispensings, since 2011 also including nursing homes)	N	YES (total population)	0.3 m	100
Lithuania	National Health Insurance Fund database (reimbursed outpatient prescriptions)	N	YES (total population)	2.9 m	100
Netherlands	IADB.nl (all outpatient dispensings database from community pharmacies in northern and eastern parts of the Netherlands)	R	NO	0.6 m	3.6
Norway	Norwegian Prescription Database (NorPD) (national database with all outpatient prescriptions/dispensings)	N	YES (total population)	5.2 m	100
Spain	CatSalut database (all outpatient prescription dispensings from the public health care system in the autonomous community of Catalonia)	R	NO	7.6 m	16.2
Sweden	Swedish Prescribed Drug Register (national database with all outpatient prescriptions/dispensings)	N	YES (total population)	9.7 m	100
Oceania					
Australia	Pharmaceutical Benefits Scheme (PBS) database (all dispensed PBS-listed medicines attracting a government subsidy)	N	YES	23.1 m (cohort: 10% random sample of population under risk)	100

Table 1 (continued)

Country	Database	Regional (R) or nationwide (N) data	Nationally representative data	Population under risk (in 2014 or most recent year available)	% of population covered
New Zealand	Pharms database, Ministry of Health (all outpatient community pharmacy dispensings)	N	YES (total population)	4.5 m	100
North and South America					
Colombia	Two health insurance funds of the National Health Insurance System (outpatient prescription dispensings)	N	NO	2.7 m	5.7
USA (privately insured population)	United Health database (outpatient prescription dispensings)	N	NO	9.9 m	3.1
USA (publicly insured population)	Medicaid Analytic eXtract (MAX) (outpatient prescription dispensings from the majority of US federal states)	N	YES	33.4 m	10.5

Between 2005 and 2014, the overall prevalence of anti-psychotic use increased in 11 of the 17 studied populations. The relative increase ranged from 2.6% (publicly insured US population) to 91.2% (Colombia) during the study period. In five populations, the overall antipsychotic use decreased, ranging from a 2.4% relative decrease (Taiwan) to a 32.6% relative decrease (Japan). The relative change in prevalence over time (first vs. last study year) was statistically significant in all populations and across all age groups (Table 2).

3.2. Antipsychotic use by country population

In 2014, overall antipsychotic use across all ages was highest in Taiwan (78.2 per 1000 persons) and in the publicly insured US population (40.0 per 1000 persons), and lowest in Colombia (3.2 per 1000 persons) and Lithuania (11.9 per 1000 persons), resulting in up to a 25-fold difference in overall prevalence of antipsychotic use between populations. After standardising the populations by age, the pattern of highest and lowest use prevalence remained the same (Table 2).

3.3. Antipsychotic use by age and sex

In all studied populations, except for the Japanese and the publicly insured in the USA, the overall prevalence of anti-psychotic use in 2014 was highest in older adults, ranging from 19.0 per 1000 persons (Colombia) to 149.0 per 1000 persons (Taiwan) (Table 2/Figure 1d). In adults, the prevalence ranged from 3.3 per 1000 persons (Colombia) to 81.5 per 1000 persons (Taiwan), yielding a 25-fold difference between populations. In children and adolescents, the prevalence ranged from 0.5 per 1000 persons (Lithuania) to 30.8 per 1000 persons (Taiwan), resulting in up to a 62-fold difference in prevalence between populations. This pattern of antipsychotic use by age group was similar for males and females.

In 2014, the overall male/female prevalence ratio ranged from 0.7 (Germany, Lithuania, and Taiwan) to 1.4 (Colombia) across populations, with a median value of 0.9. The median sex ratio differed by age group, ranging from 1.5 in children and adolescents and 1.0 in adults to 0.7 in older adults.

3.4. Antipsychotic drug use by type

The prevalence of typical vs. atypical antipsychotic use for each population in 2005 and 2014 is shown in Figure 2.

For atypical antipsychotics, the prevalence ranged from 1.3 (Colombia) to 37.1 (publicly insured US population) per 1000 persons in 2005, and from 2.7 (Colombia) to 55.3 (New Zealand) per 1000 persons in 2014. For typical antipsychotics, the prevalence ranged from 2.0 (Colombia) to 44.8 (Taiwan) per 1000 persons in 2005, and from 1.7 (Colombia) to 41.8 (Taiwan) per 1000 in 2014.

Over the study period, the prevalence of atypical antipsychotic use increased in all of the studied populations. The highest relative increase was observed in Japan (217.6%) and Finland (179.2%). The prevalence of typical antipsychotic use decreased in nearly all studied populations, except for Japan, New Zealand, and the privately insured US population.

In 2014 (or the last available data year), the atypical/typical antipsychotic prevalence ratio ranged from 0.7 (Taiwan) to 6.1 (New Zealand and Australia), with a median of 2.1.

3.5. Most commonly used antipsychotic substances

In 2005 (or the last available data year), the antipsychotic substances appearing most frequently in the top 5 of the studied populations were risperidone, olanzapine and quetiapine (Table 3).

In 2014, the antipsychotic substance used most frequently by most countries across all age groups was quetiapine, followed by risperidone and olanzapine. In children and adolescents, risperidone was the most frequently used antipsychotic (ranking first in 10 countries), followed by quetiapine and aripiprazole. In adults, quetiapine was the most commonly used antipsychotic, with olanzapine and risperidone as runners-up. In older adults, quetiapine was the antipsychotic used in the largest number of countries, followed by risperidone and olanzapine.

Overall, there were 26 different antipsychotic substances within the top 5 between all studied populations.

4. Discussion

The main findings of this study are as follows:

1. In two-thirds of the studied populations, there was an increase in antipsychotic utilisation over the studied period, mainly due to increased use of atypical antipsychotics.
2. The prevalence of antipsychotic use differed markedly between countries, with an up to 25-fold difference in overall antipsychotic use prevalence.
3. In people aged 65 years and older, the prevalence of antipsychotic use was up to 15% (150 per 1000 persons).

4.1. Trends in antipsychotic use between 2005 and 2014

The above-mentioned increase in antipsychotic use is in line with the findings of other studies on this topic, e.g. the analysis of antipsychotic prescriptions in European countries for the period 2005-2010 by Raschi et al. (2013), who found an increased utilisation in all 12 studied countries, especially pronounced in central and eastern Europe. Nevertheless, it should not be overlooked that a decreasing prevalence of antipsychotic use across time was apparent in some of the populations in our data, e.g. in Taiwan and Japan. While this trend was generally less pronounced, it may be an indicator of a “ceiling effect” (i.e. a saturation

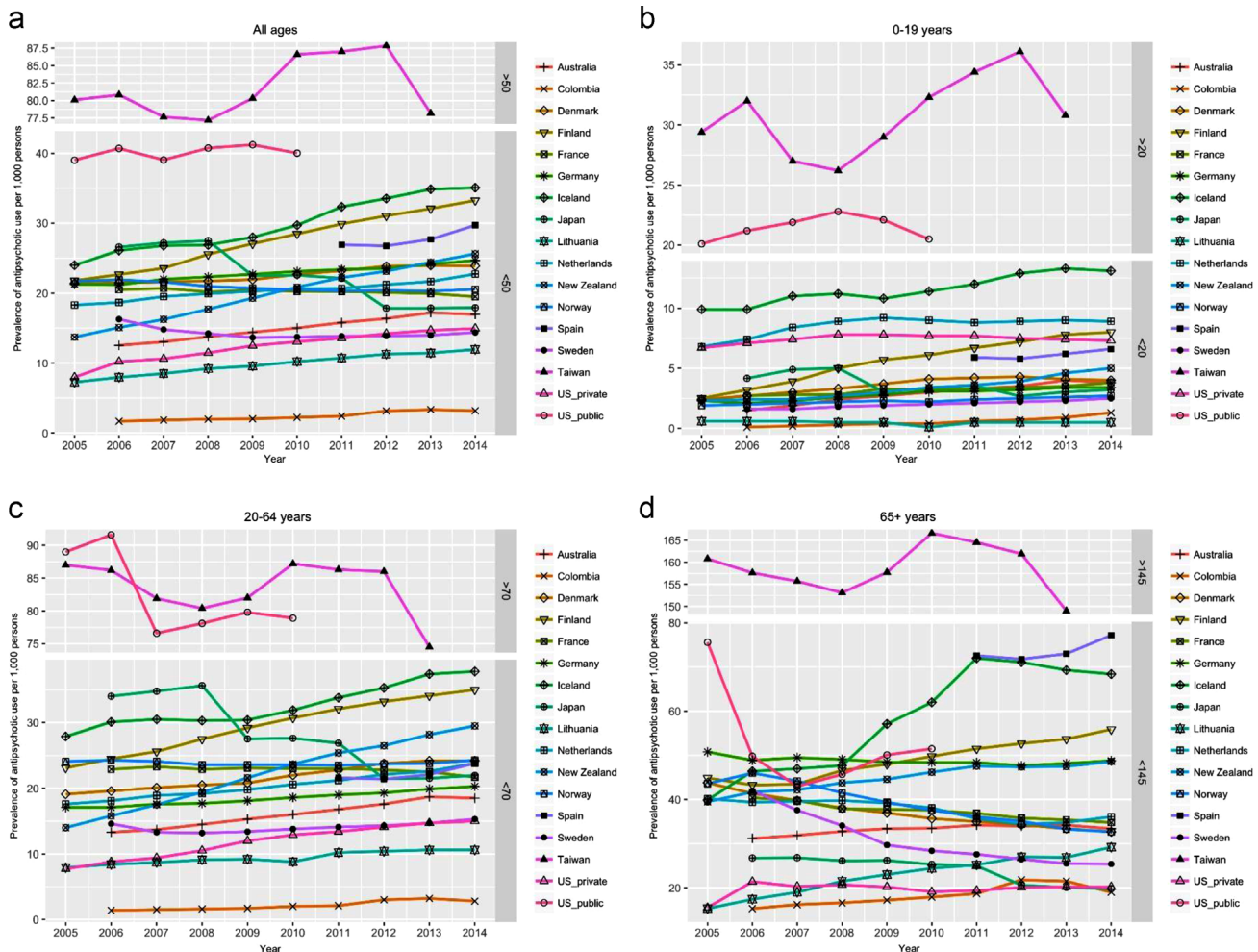


Figure 1 Overall prevalence of antipsychotic use in populations from 16 countries, 2005-2014 (per 1000 persons). (a) All ages, (b) 0-19 years, (c) 20-64 years, (d) 65+ years.

Table 2 Prevalence of antipsychotic use per 1000 persons in 2014 (or most recent year available), by population, age group and sex.

Age group	Australia	Colombia	Denmark	Finland	France	Germany	Iceland	Japan	Lithuania	Netherlands	New Zealand	Norway	Spain	Sweden	Taiwan (2013)	USA (publicly insured) (2010)	USA (privately insured)	
0–19																		
Total	3.8 [3.7-3.8]	1.3 [1.2-1.3]	4.0 [3.9-4.1]	8.0 [7.8-8.1]	3.8 [3.4-4.1]	3.4 [3.3-3.5]	13.1 [12.4-13.9]	3.2 [3.1-3.4]	0.5 [0.4-0.5]	8.9 [8.4-9.4]	5.0 [4.9-5.1]	2.7 [2.6-2.8]	6.6 [6.5-6.7]	2.5 [2.4-2.5]	30.8 [29.9-31.7]	20.5 [20.5-20.6]	7.3 [7.2-7.5]	
Male	4.9 [4.9-5.0]	2.0 [1.9-2.1]	4.4 [4.2-4.5]	8.1 [7.9-8.3]	5.3 [4.7-5.8]	4.4 [4.3-4.6]	16.8 [15.7-18.0]	3.8 [3.6-4.0]	0.5 [0.5-0.6]	12.8 [11.9-13.7]	5.0 [4.8-5.2]	2.8 [2.6-2.9]	9.1 [8.9-9.3]	2.8 [2.7-2.9]	29.3 [28.1-30.6]	27.3 [27.2-27.4]	8.8 [8.6-9.0]	
Female	2.5 [2.5-2.6]	0.6 [0.5-0.6]	3.6 [3.5-3.8]	7.8 [7.6-8.1]	2.2 [1.9-2.6]	2.4 [2.3-2.5]	9.3 [8.4-10.3]	2.6 [2.4-2.8]	0.4 [0.3-0.5]	4.8 [4.2-5.4]	5.0 [4.8-5.2]	2.6 [2.5-2.7]	3.9 [3.8-4.1]	2.1 [2.1-2.2]	32.4 [31.0-33.8]	13.6 [13.5-13.6]	5.8 [5.7-6.0]	
Prevalence ratio (time trend)	2.59 [2.52-2.66]	8.77 [6.51-11.82]	1.69 [1.62-1.77]	3.19 [3.05-3.32]	1.38 [1.20-1.58]	1.52 [1.45-1.59]	1.33 [1.22-1.45]	0.77 [0.71-0.84]	0.74 [0.64-0.85]	1.30 [1.19-1.42]	2.18 [2.08-2.28]	1.44 [1.36-1.52]	1.13 [1.10-1.16]	1.57 [1.51-1.64]	1.05 [1.01-1.09]	1.02 [1.02-1.03]	1.11 [1.08-1.13]	
p-value (time trend)	<.0001	<.0001	<.0001	<.0001	<.0001	<.0001	<.0001	<.0001	<.0001	<.0001	<.0001	<.0001	<.0001	<.0001	0.0154	<.0001	<.0001	
20–64																		
Total	18.5 [18.4-18.5]	2.8 [2.8-2.9]	24.2 [24.1-24.4]	35.0 [34.8-35.2]	21.7 [21.2-22.2]	20.3 [20.1-20.4]	37.8 [36.9-38.6]	22.0 [21.7-22.2]	10.6 [10.5-10.8]	23.8 [23.3-24.4]	29.5 [29.3-29.8]	24.3 [24.2-24.5]	23.8 [23.6-23.9]	15.3 [15.2-15.4]	74.5 [73.9-75.1]	78.9 [78.8-79.1]	15.0 [14.9-15.1]	
Male	19.7 [19.6-19.8]	3.2 [3.1-3.3]	24.1 [23.8-24.3]	34.7 [34.4-35.0]	23.9 [23.2-24.7]	19.2 [19.0-19.4]	33.6 [32.5-34.8]	23.6 [23.2-24.0]	10.4 [10.1-10.6]	25.9 [25.1-26.7]	30.0 [29.7-30.3]	22.5 [22.3-22.8]	23.6 [23.4-23.8]	15.2 [15.1-15.3]	59.8 [59.0-60.6]	107.2 [106.8-107.5]	12.4 [12.3-12.6]	
Female	17.2 [17.1-17.3]	2.5 [2.4-2.6]	24.4 [24.2-24.6]	35.4 [35.1-35.7]	19.5 [18.9-20.2]	21.1 [20.9-21.2]	42.0 [40.7-43.3]	20.6 [20.3-20.9]	10.9 [10.7-11.1]	21.7 [21.2-22.6]	29.1 [28.8-29.4]	26.2 [26.0-26.5]	23.9 [23.7-24.1]	15.4 [15.3-15.6]	88.5 [87.6-89.5]	67.2 [67.0-67.4]	17.6 [17.4-17.8]	
Prevalence ratio (time trend)	1.38 [1.38-1.39]	2.09 [1.97-2.22]	1.27 [1.26-1.28]	1.52 [1.50-1.53]	0.95 [0.92-0.98]	1.18 [1.17-1.19]	1.35 [1.30-1.40]	0.65 [0.63-0.66]	1.35 [1.32-1.38]	1.35 [1.31-1.40]	2.11 [2.09-2.14]	1.01 [1.00-1.02]	1.10 [1.09-1.11]	1.05 [1.04-1.06]	0.86 [0.85-0.87]	0.89 [0.88-0.89]	1.96 [1.93-1.98]	
p-value (time trend)	<.0001	<.0001	<.0001	<.0001	0.0015	<.0001	<.0001	<.0001	<.0001	<.0001	<.0001	0.0371	<.0001	<.0001	<.0001	<.0001	<.0001	
65+																		
Total	33.4 [33.2-33.6]	19.0 [18.2-19.7]	32.7 [32.3-33.0]	55.9 [55.5-56.3]	34.8 [33.6-36.0]	48.8 [48.5-49.1]	68.4 [66.0-70.8]	19.8 [19.6-20.1]	29.2 [28.7-29.6]	36.1 [34.9-37.3]	48.6 [48.1-49.1]	32.7 [32.3-33.1]	77.2 [76.8-77.7]	25.4 [25.2-25.6]	149.0 [147.0-151.0]	51.5 [50.8-52.2]	20.2 [20.0-20.3]	
Male	28.3 [28.0-28.5]	22.0 [20.8-23.2]	26.5 [26.0-27.0]	47.2 [46.6-47.8]	27.7 [26.1-29.4]	36.5 [36.1-37.0]	59.2 [56.0-62.6]	15.3 [14.9-15.6]	22.1 [21.4-22.8]	32.0 [30.4-33.7]	42.3 [41.5-43.0]	25.7 [25.2-26.2]	60.5 [59.9-61.1]	20.7 [20.4-21.0]	122.6 [119.9-125.2]	49.6 [48.5-50.8]	15.1 [14.9-15.3]	
Female	37.8 [37.5-38.1]	16.6 [15.7-17.5]	37.8 [37.3-38.3]	62.5 [61.9-63.1]	39.9 [38.3-41.6]	55.6 [55.2-56.0]	76.4 [73.0-79.9]	23.3 [22.9-23.6]	32.7 [32.2-33.3]	39.4 [37.7-41.1]	54.0 [53.3-54.8]	38.5 [37.9-39.0]	89.6 [88.9-90.2]	29.4 [29.1-29.7]	172.7 [169.8-175.6]	52.5 [51.7-53.3]	24.0 [23.8-24.3]	
Prevalence ratio (time trend)	1.07 [1.06-1.08]	1.2 [1.15-1.33]	0.75 [0.74-0.76]	1.24 [1.23-1.26]	0.86 [0.82-0.90]	0.96 [0.95-0.97]	1.72 [1.61-1.83]	0.74 [0.72-0.76]	1.90 [1.85-1.95]	0.90 [0.86-0.94]	1.23 [1.21-1.25]	0.75 [0.74-0.76]	1.06 [1.05-1.07]	0.61 [0.60-0.61]	0.93 [0.91-0.94]	0.68 [0.67-0.70]	1.30 [1.27-1.33]	
p-value (time trend)	<.0001	<.0001	<.0001	<.0001	<.0001	<.0001	<.0001	<.0001	<.0001	<.0001	<.0001	<.0001	<.0001	<.0001	<.0001	<.0001	<.0001	
All ages (crude values)																		
Total	17.0 [16.9-17.0]	3.2 [3.1-3.3]	21.0 [20.9-21.1]	33.2 [33.1-33.4]	19.5 [19.1-19.9]	24.7 [24.6-24.8]	35.1 [34.4-35.7]	17.9 [17.8-18.1]	11.9 [11.8-12.1]	22.7 [22.4-23.1]	25.6 [25.5-25.8]	20.6 [20.4-20.7]	29.7 [29.6-29.8]	14.4 [14.3-14.5]	78.2 [77.6-78.7]	40.0 [40.0-40.1]	15.0 [14.9-15.0]	
Male	17.1 [17.0-17.1]	3.7 [3.6-3.8]	19.7 [19.5-19.8]	30.8 [30.6-31.0]	19.6 [19.1-20.1]	19.9 [19.8-20.1]	32.1 [31.2-33.0]	16.8 [16.6-17.0]	9.7 [9.5-9.9]	23.9 [23.3-24.5]	24.6 [24.3-24.8]	18.2 [18.0-18.4]	26.2 [26.0-26.3]	13.3 [13.2-13.4]	63.2 [62.5-63.9]	45.1 [45.0-45.2]	12.4 [12.3-12.5]	
Female	16.9 [16.8-16.9]	2.7 [2.6-2.8]	22.3 [22.1-22.5]	35.6 [35.4-35.8]	19.4 [18.9-19.9]	28.1 [28.0-28.3]	38.1 [37.1-39.0]	18.9 [18.6-19.1]	13.9 [13.7-14.1]	21.6 [21.1-22.2]	27.9 [26.4-26.9]	22.9 [22.8-23.1]	33.2 [33.0-33.4]	15.5 [15.4-15.6]	92.6 [91.8-93.4]	36.1 [36.0-36.2]	17.4 [17.3-17.5]	
Male/female ratio	1.0	1.4	0.9	0.9	1.0	0.7	0.8	0.9	0.7	1.1	0.9	0.8	0.8	0.9	0.7	1.3	0.7	
Prevalence ratio (time trend)	1.35 [1.35-1.36]	1.91 [1.83-2.00]	1.12 [1.12-1.13]	1.53 [1.51-1.54]	0.95 [0.93-0.98]	1.16 [1.15-1.17]	1.46 [1.42-1.50]	0.67 [0.66-0.68]	1.65 [1.62-1.67]	1.24 [1.21-1.27]	1.87 [1.85-1.89]	0.95 [0.94-0.95]	1.10 [1.10-1.11]	0.88 [0.88-0.89]	0.98 [0.97-0.99]	1.03 [1.02-1.03]	1.88 [1.86-1.89]	
p-value (time trend)	<.0001	<.0001	<.0001	<.0001	0.0002	<.0001	<.0001	<.0001	<.0001	<.0001	<.0001	<.0001	<.0001	<.0001	<.0001	<.0001	<.0001	
All ages (age standardised values)																		
Total	14.2	3.7	17.4	26.2	15.5	15.2	30.8	15.1	8.0	19.1	22.1	16.9	20.3	11.3	61.3	59.7	11.6	

Annotations: Numbers in brackets: 95% confidence intervals
Trend=relative increase/decrease during the 2005–2014 period, with the following exceptions: Colombia (2006–2014), France (2006–2014), Japan (2006–2014), Spain (2011–2014), Sweden (2006–2014), Taiwan (2005–2013), and publicly insured US population (2005–2010).

with antipsychotic prescription) in those populations where antipsychotic use was already relatively high.

Regarding the increased utilisation of atypical antipsychotics, the indications for which these drugs are prescribed have broadened both in the form of approved and of off-label use. Several new indications have been approved for atypical antipsychotics in recent years, e.g. bipolar depression (quetiapine), augmentation therapy in major depressive disorder (quetiapine, aripiprazole), and autism spectrum disorder (aripiprazole, risperidone) (Maher and Theodore, 2012); nonetheless off-label use of antipsychotics remains high. In a recent review, Carton et al. (2015) estimated that 40–75% of all antipsychotic prescriptions were off-label, with mood disorders, anxiety disorders, insomnia and agitation being the leading indications of such prescribing. In a study in UK primary care, a significant share of individuals prescribed antipsychotics had no record of a psychotic or bipolar disorder, i.e. the “classical” indications for antipsychotics (Marston et al., 2014). Similarly, only about 30% of prescriptions for antipsychotics in

Belgium were for psychotic disorders, suggesting a significant amount of off-label use (Morrens et al., 2015).

In contrast, a recent study on elderly patients in Taiwan suggested that around 80% of atypical antipsychotics users had a psychiatric disorder, while only about 20% of typical antipsychotics users had an underlying psychiatric condition (Kuo et al., 2016).

4.2. Antipsychotic use by country population

Some country-specific findings deserve mention: The highest overall prevalence of antipsychotic use among the 16 studied countries, across all ages, was found in Taiwan. A possible explanation for this high prevalence is the frequent use of antipsychotics in Taiwan not only for psychiatric disorders, but also for a wide range of somatic conditions, such as diseases of the digestive system, the respiratory system, the circulatory system and the nervous system (Chien et al., 2008). The overall antipsychotic use prevalence was also high in the publicly insured US population,

which is attributable to the generally higher psychiatric morbidity and lower socio-economic status of those with public insurance, i.e. Medicaid beneficiaries (Kasper, 1986).

Although the lowest overall antipsychotic use prevalence was found in Colombia, the use of antipsychotics in 0-19 year olds in Colombia increased over the studied period, which is probably due to an increase in the number of antipsychotic substances that were licensed for this age group in Colombia during the studied period.

Generally, the observed disparity in antipsychotic use between countries might represent different licensing and prescribing policies within individual countries. Other health system factors, e.g. density and accessibility of psychiatrists and other physicians, pricing and reimbursement practices (Kim et al., 2010), and availability of other antipsychotic substances (Koskinen et al., 2014; Quitian Reyes et al., 2016) most likely also play a part.

Our findings demonstrate well the relationship between national licensing policies and antipsychotic utilisation. Next to Colombia with its increase in the number of licensed antipsychotic substances, France is another good example: The absence of quetiapine in the French top 5 substances is likely due to the fact that quetiapine has only been licensed in France since June 2011, and is marketed almost exclusively for the indication of bipolar depression. Similarly, the increase in the use of atypical antipsychotics in New Zealand may also be attributed to changes in licensing policies, as Special Authority prescribing restrictions were removed for quetiapine in 2008, for risperidone in 2009, and for olanzapine in 2011 (Ndukwe et al., 2014).

4.3. Antipsychotic use by age and sex

Interestingly, with increasing age there was a change in the median male/female ratio in our study data, shifting from a male preponderance in children and adolescents to a female preponderance in older adults. This probably reflects the epidemiologic distribution of those psychiatric disorders and

symptoms for which treatment with antipsychotics is an option (Ford et al., 2003; Reynolds et al., 2015).

Antipsychotic use in children and adolescents increased in 14 of 16 studied countries. Behind this trend might be a considerable amount of off-label use prescribing, e.g. in adolescent boys with aggressive behaviour (Olsson et al., 2015b). In an international review on off-label use of antipsychotics in children, the prevalence of off-label use ranged from 36% to 93%, with attention-deficit/hyperactivity disorder, anxiety and mood disorders being the main indications (Carton et al., 2015). Given the very limited evidence for the effectiveness of antipsychotics in this age group for these indications (Alexander et al., 2011; Loy et al., 2012), this trend raises concerns, especially in the light of the lack of long-term studies in minors (Ben Amor, 2012; Pringsheim et al., 2011).

In older adults, the prevalence of antipsychotic use increased in less than half of the studied populations. Yet, in this age group, the absolute prevalence of antipsychotic use (with a maximum of about 15% in Taiwan) is of interest. According to Carton et al. (2015), the main indication for the prescription of antipsychotics in older adults is agitation, which is often a symptom of dementia (Schulze et al., 2013a; Taipale et al., 2014). As adverse reactions caused by antipsychotics are more frequent in older adults, the increasing antipsychotic use in this age group is a reason for severe concern, especially when these are utilised instead of non-pharmacological approaches (Schulze et al., 2013a). While there are clear recommendations against unrestricted antipsychotic prescription in this age group (2015) due to possible adverse effects (e.g. falls; Janus et al., 2017), to date these warnings appear not to have had much effect (Gallini et al., 2014; Schulze et al., 2013b). Nevertheless, some countries in our study showed a decrease in antipsychotic utilisation in older adults, which might be due to cautious use of antipsychotics or successful withdrawal (Declercq et al., 2013).

Given the nature of the underlying data, we are unable to conclusively assess the appropriateness of antipsychotic

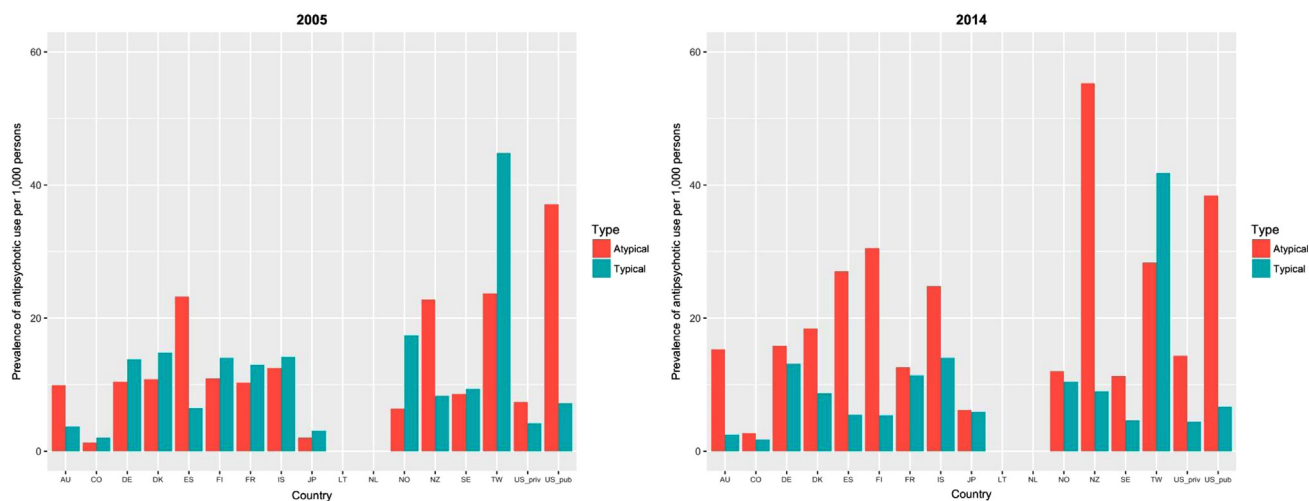


Figure 2 Prevalence of atypical and of typical antipsychotic use in populations from 14 countries in 2005 and 2014 (per 1000 persons), with the following exceptions: Australia (2006 vs. 2014), Colombia (2006 vs. 2014), France (2006 vs. 2014), Spain (2011 vs. 2014), Sweden (2006 vs. 2014), Taiwan (2005 vs. 2013) and the publicly insured US population (2005 vs. 2010).

Table 3 The top five utilised antipsychotic substances in populations from 14 countries (2005 vs. 2014), by age group (utilisation prevalence per 1000 persons).

Age group/ Rank	Australia		Colombia		Denmark		Finland		France		Germany		Iceland		Japan																	
	2006 Prev.	2014 Prev.	2006 Prev.	2014 Prev.	2005 Prev.	2014 Prev.	2005 Prev.	2014 Prev.	2006 Prev.	2014 Prev.	2005 Prev.	2014 Prev.	2005 Prev.	2014 Prev.	2006 Prev.	2014 Prev.																
0-19 years																																
1	RIS	0.6	RIS	2.2	HAL	0.1	RIS	1.0	RIS	1.0	QUE	1.5	RIS	1.3	QUE	4.1	RIS	1.1	RIS	2.1	RIS	0.7	RIS	1.7	RIS	5.3	RIS	6.6	RIS	1.2	RIS	1.1
2	OLZ	0.4	QUE	1.0	LEV	0.04	QUE	0.1	CHL	0.7	RIS	1.0	QUE	0.8	RIS	3.5	CYA	0.8	CYA	1.3	PIP	0.4	PIP	0.6	QUE	2.6	ARI	3.0	SUL	0.9	ARI	0.8
3	QUE	0.2	OLZ	0.4	RIS	0.03	CLZ	0.1	OLZ	0.3	CHL	1.0	OLZ	0.3	OLZ	0.5	SUL	0.2	ARI	0.5	PRO	0.4	QUE	0.6	LEV	1.0	QUE	2.6	OLZ	0.4	SUL	0.4
4	PEC	0.1	ARI	0.2	PIP	0.01	OLZ	0.1	QUE	0.3	ARI	0.9	LEV	0.1	LEV	0.1	TIA	0.2	LOX	0.2	TIA	0.3	ARI	0.3	OLZ	0.3	LEV	1.2	HAL	0.3	OLZ	0.2
5	ARI	0.1	PEC	0.1	CLZ	0.01	ARI	0.04	LEV	0.2	OLZ	0.2	PER	0.02	CLZ	0.1	OLZ	0.2	OLZ	0.1	OLZ	0.1	CHL	0.2	ARI	0.3	OLZ	0.3	LEV	0.2	QUE	0.1
20-64 years																																
1	OLZ	5.5	QUE	7.8	CLZ	0.8	LEV	1.1	CHL	5.0	QUE	11.8	QUE	4.9	QUE	20.8	CYA	7.4	CYA	6.9	FLP	3.0	QUE	6.4	LEV	8.2	QUE	19.6	SUL	5.3	SUL	4.4
2	RIS	3.1	OLZ	5.3	HAL	0.7	QUE	0.8	OLZ	4.0	CHL	4.9	RIS	4.9	OLZ	6.2	RIS	4.1	RIS	4.5	OLZ	2.3	RIS	2.9	QUE	7.3	LEV	8.0	RIS	3.4	RIS	2.3
3	QUE	2.4	RIS	2.7	LEV	0.5	CLZ	0.7	LEV	3.6	OLZ	3.6	OLZ	4.8	RIS	4.8	OLZ	3.7	ARI	3.5	RIS	2.0	OLZ	2.4	OLZ	3.5	OLZ	4.0	OLZ	1.6	ARI	2.4
4	CPR	1.1	ARI	1.5	OLZ	0.1	RIS	0.5	RIS	3.0	RIS	3.1	LEV	3.4	CLZ	2.9	HAL	2.6	OLZ	3.2	SUL	1.9	PIP	2.0	RIS	3.3	RIS	3.1	HAL	1.4	OLZ	1.9
5	AMI	1.0	PAL	1.1	RIS	0.03	OLZ	0.4	FLU	2.2	ARI	2.4	PER	2.7	LEV	2.4	AMI	2.2	LOX	2.1	QUE	1.5	ARI	1.7	CPR	2.9	CHL	3.0	LEV	1.4	QUE	1.3
65+ years																																
1	RIS	10.6	RIS	13.3	HAL	9.8	QUE	7.8	RIS	8.3	QUE	9.9	RIS	13.0	QUE	24.8	RIS	9.4	RIS	10.3	MEL	14.9	MEL	14.4	LEV	13.3	QUE	24.2	SUL	3.7	SUL	4.7
2	OLZ	9.4	OLZ	8.1	CLZ	6.9	LEV	6.2	LEV	6.9	RIS	5.9	QUE	9.5	RIS	21.0	TIA	7.9	CYA	6.7	RIS	8.8	RIS	11.5	RIS	6.6	LEV	16.8	RIS	1.7	QUE	2.0
3	HAL	6.4	QUE	7.4	LEV	2.2	CLZ	3.9	OLZ	6.4	OLZ	4.6	PER	4.1	OLZ	6.7	HAL	7.4	TIA	5.1	SUL	7.4	QUE	9.9	PCP	4.6	RIS	11.5	QUE	0.8	RIS	2.0
4	QUE	2.4	HAL	4.8	OLZ	0.3	OLZ	1.6	FLU	5.8	HAL	4.3	OLZ	3.9	LEV	2.7	CYA	6.7	HAL	4.6	FLP	6.3	PIP	7.4	CHL	4.1	OLZ	6.5	HAL	0.6	OLZ	0.8
5	PEC	2.3	CPR	0.9	RIS	0.1	RIS	1.3	CHL	4.9	CHL	3.7	LEV	3.8	CLZ	1.0	SUL	5.7	OLZ	2.8	PIP	5.2	SUL	4.1	OLZ	3.7	HAL	5.3	OLZ	0.4	PCP	0.7
All ages																																
1	OLZ	4.7	QUE	6.0	HAL	0.9	LEV	1.0	CHL	4.0	QUE	9.0	RIS	5.3	QUE	17.9	CYA	5.7	CYA	5.5	MEL	3.8	QUE	6.3	LEV	6.6	QUE	15.5	SUL	4.0	SUL	3.8
2	RIS	3.4	OLZ	4.5	CLZ	0.9	QUE	0.9	OLZ	3.5	CHL	3.7	QUE	4.7	RIS	7.8	RIS	4.2	RIS	4.9	RIS	3.2	RIS	4.9	QUE	5.5	LEV	7.3	RIS	2.5	RIS	2.0
3	QUE	1.9	RIS	4.1	LEV	0.5	RIS	0.7	RIS	3.3	RIS	3.1	OLZ	3.6	OLZ	5.0	HAL	2.7	OLZ	2.4	FLP	3.1	MEL	4.6	RIS	4.3	RIS	5.2	OLZ	1.0	QUE	1.5
4	HAL	1.3	ARI	1.1	OLZ	0.05	CLZ	0.7	LEV	3.3	OLZ	3.0	LEV	2.7	LEV	2.0	OLZ	2.5	ARI	2.3	SUL	2.7	PIP	3.2	OLZ	2.6	OLZ	3.3	HAL	0.9	ARI	1.5
5	CPR	0.9	HAL	1.0	RIS	0.03	OLZ	0.4	FLU	2.2	LEV	1.2	PER	2.3	CLZ	1.9	TIA	2.5	HAL	2.0	OLZ	1.9	OLZ	2.0	CHL	1.9	CHL	2.3	LEV	0.8	OLZ	1.2

New Zealand		Norway		Spain		Sweden		Taiwan		USA (publicly insured)		USA (privately insured)															
2005 Prev.	2014 Prev.	2005 Prev.	2014 Prev.	2011 Prev.	2014 Prev.	2006 Prev.	2014 Prev.	2005 Prev.	2013 Prev.	2005 Prev.	2010 Prev.	2005 Prev.	2014 Prev.														
RIS	2.7	QUE	6.5	RIS	0.7	RIS	1.0	RIS	3.9	RIS	3.8	RIS	0.9	RIS	1.1	PCP	21.3	PCP	20.4	RIS	10.4	RIS	10.1	RIS	3.0	RIS	2.9
QUE	1.4	RIS	4.0	OLZ	0.3	QUE	1.0	ARI	0.9	ARI	1.8	OLZ	0.3	ARI	0.7	SUL	4.1	SUL	4.1	QUE	6.0	ARI	6.8	QUE	1.9	ARI	2.9
OLZ	0.7	OLZ	2.0	QUE	0.3	ARI	0.4	QUE	0.7	QUE	0.8	LEV	0.1	QUE	0.5	CPR	0.9	ARI	1.7	ARI	5.0	QUE	4.8	ARI	1.9	QUE	1.7
CLZ	0.4	ARI	0.6	LEV	0.2	CHL	0.3	OLZ	0.5	OLZ	0.6	DIX	0.1	OLZ	0.5	RIS	0.9	RIS	1.5	OLZ	1.9	ZIP	1.2	OLZ	0.6	OLZ	0.5
HAL	0.1	CLZ	0.4	CHL	0.2	LEV	0.1	LEV	0.3	PAL	0.4	ARI	0.1	LEV	0.1	HAL	0.8	FLU	0.6	ZIP	1.4	OLZ	1.1	PCP	0.6	ZIP	0.4
RIS	7.5	QUE	32.0	LEV	6.4	QUE	9.1	QUE	5.3	QUE	6.6	OLZ	3.5	QUE	4.8	PCP	40.6	PCP	33.4	QUE	33.1	QUE	30.4	PCP	4.3	QUE	5.9
QUE	7.3	OLZ	13.9	OLZ	4.2	OLZ	4.2	OLZ	5.0	OLZ	5.0	RIS	2.6	OLZ	4.5	SUL	20.7	SUL	15.9	RIS	27.9	ARI	19.7	QUE	3.3	ARI	4.3
OLZ	6.2	RIS	9.9	CHL	3.8	LEV	3.7	SUL	4.8	SUL	5.0	LEV	2.3	RIS	2.3	HAL	3.4	FLU	5.7	OLZ	21.8	RIS	19.0	RIS	1.6	PCP	2.9
CLZ	3.8	CLZ	5.7	PCP	2.8	CHL	1.6	RIS	4.3	RIS	3.8	DIX	2.1	ARI	2.3	RIS	3.0	QUE	5.7	ARI	13.8	OLZ	11.4	OLZ	1.6	RIS	2.7
CPR	1.8	ARI	2.8	CPR	1.9	RIS	1.5	ARI	1.9	ARI	2.5	ZUP	1.3	LEV	1.8	FLU	2.4	RIS	3.3	PCP	9.3	PCP	7.9	ARI	1.1	OLZ	1.8
RIS	32.8	QUE	44.0	PCP	14.4	LEV	7.0	RIS	21.9	QUE	28.7	RIS	17.0	RIS	9.9	PCP	63.9	PCP	42.2	RIS	27.0	QUE	6.6	PCP	8.2	QUE	9.4
HAL	16.7	RIS	28.7	LEV	11.6	PCP	5.6	QUE	18.4	RIS	20.7	HAL	7.1	HAL	4.7	SUL	38.0	QUE	25.6	OLZ	22.9	RIS	4.6	QUE	5.3	PCP	5.4
QUE	15.7	HAL	24.1	CHL	4.5	QUE	5.5	SUL	17.3	SUL	16.3	DIX	4.3	OLZ	4.3	QUE	10.9	SUL	24.0	QUE	21.1	OLZ	10.2	RIS	4.4	RIS	5.1
LEV	4.9	OLZ	12.2	HAL	3.7	OLZ	4.2	HAL	14.4	HAL	11.0	LEV	4.2	QUE	3.2	RIS	8.6	RIS	7.3	PCP	10.6	ARI	7.2	OLZ	3.7	OLZ	3.0
OLZ	4.6	LEV	6.8	OLZ	3.2	CHL	4.0	OLZ	5.1	OLZ	4.5	OLZ	3.2	LEV	2.1	HAL	7.7	FLU	7.0	HAL	9.2	PCP	6.5	HAL	1.3	ARI	2.0
RIS	9.2	QUE	26.8	LEV	5.6	QUE	6.5	RIS	7.2	QUE	9.3	RIS	4.7	OLZ	3.6	PCP	37.9	PCP	32.8	RIS	15.2	QUE	13.3	PCP	3.6	QUE	6.1
QUE	6.6	RIS	11.0	PCP	3.9	LEV	3.7	QUE	6.5	RIS	6.8	OLZ	2.7	QUE	3.5	SUL	18.1	SUL	15.4	QUE	13.4	RIS	13.1	QUE	3.0	ARI	3.4
OLZ	4.4	OLZ	10.4	OLZ	3.1	OLZ	3.3	SUL	5.9	SUL	6.0	LEV	2.1	RIS	3.5	HAL	3.1	QUE	8.1	OLZ	7.4	ARI	11.1	RIS	2.2	RIS	3.4
HAL	3.1	HAL	4.8	CHL	3.0	CHL	2.9	OLZ	4.1	OLZ	4.0	DIX	2.0	ARI	1.6	RIS	3.0	FLU	5.1	ARI	7.4	OLZ	4.5	OLZ	1.5	PCP	3.1
CLZ	2.5	CLZ	3.6	RIS	1.7	PCP	1.8	HAL	3.3	HAL	2.6	HAL	1.9	LEV	1.5	QUE	2.5	RIS	3.7	ZIP	3.3	ZIP	3.3	ARI	1.3	OLZ	1.9

Abbreviations: AMI=amisulpride, ARI=aripiprazole, CHL=chlorprothixene, CLZ=clozapine, CPR=chlorpromazine, CYA=cyamemazine, DIX=dixyrazine, FLP=fluspirilene, FLU=flupentixol, HAL=haloperidol, LEV=levomepromazine, LOX=loxapine, MEL=melperone, OLZ=olanzapine, PAL=paliperidone, PCP=prochlorperazine, PEC=pericyazine, PER=perphenazine, PIP=pipamperone, PRO=promazine, QUE=quetiapine, RIS=risperidone, SUL=sulpiride, TIA=tiapride, ZIP=ziprasidone, ZUP= zuclopentixol, prev.=Prevalence.
 Annotation: Antipsychotic substances that were among the top 5 in ≥ three countries were coloured in shades of blue (typical antipsychotics) and shades of yellow-red (atypical antipsychotics), respectively.

prescribing, e.g. whether an increasing use indicates potential overtreatment or a compensation of former undertreatment (Taylor, 2013). Nevertheless, based on prevalence figures of psychiatric disorders which usually require treatment with antipsychotics, e.g. schizophrenia (0.5-0.7% (McGrath et al., 2008; Simeone et al., 2015) and bipolar disorder (ca. 1.0-1.6% (Clemente et al., 2015)), a lower threshold for antipsychotic use prevalence of about 10-15 per 1000 persons can be estimated. In this study, overall antipsychotic use prevalence was above that threshold in the majority of populations.

4.4. Antipsychotic drug use by type

While in 2005 the prevalence of typical antipsychotics use was higher than that of atypical antipsychotics in 10 of 14 countries, in 2014 this was only the case in one country. This tendency of increased atypical antipsychotic utilisation is in line with what has been reported in the literature, demonstrating an increasing share of atypical antipsychotics prescribed both in primary care and by psychiatrists and neurologists, and by younger physicians in general (Marston et al., 2014; Morrens et al., 2015). Yet, while the newer atypical antipsychotics are often perceived (and marketed) as more effective, this may not always be the case (Leucht et al., 2013, 2009). The fact that between all studied populations the five top ranked antipsychotics contained 26 distinct antipsychotic substances (Table 3) demonstrates the diversity of therapeutic approaches, guidelines and health system frameworks in an international context. Regarding the above-mentioned growth in atypical antipsychotic use, several antipsychotic substances have specifically contributed to this trend. This is particularly the case with quetiapine, which has become the most-prescribed antipsychotic in several countries in recent years (Table 3) (Carton et al., 2015; Donohue et al., 2014; Duncan et al., 2016; Morrens et al., 2015).

In children and adolescents, risperidone is clearly the favourite antipsychotic (Carton et al., 2015; Foster et al., 2016). This may be due to its frequent low-dose use for the treatment of aggressiveness and impulsivity, e.g. in conduct disorder or attention deficit/hyperactivity disorder (Bachmann et al., 2014), despite the limited evidence for effectiveness in such indications and the lack of long-term data (Loy et al., 2012).

4.5. Strengths and limitations

This study is the first to describe the prevalence of antipsychotic use on an international scale over a period of ten years. The majority of databases employed in this study are nationally representative, thus strengthening the validity of our findings.

The study has several limitations. First, the study data did not contain information on important clinical characteristics, e.g. underlying diagnosis, symptom severity, dosage, and comorbidity, as these were not available for all of the participating countries. This hampers inferences regarding the appropriateness of and reasons behind the observed

patterns of antipsychotic use across populations. Second, the prescription or dispensing of medication as depicted in this study is not equivalent to actual consumption, and a patient only required one prescription to be counted as a prevalent user. Third, many of the databases used in this study only contained information on drugs prescribed or dispensed to outpatients, but not for institutionalised people (e.g. in nursing homes). This is likely to have caused an underestimation of the prevalence of antipsychotic use, especially in older adults.

Moreover, some inherent differences in the coverage or completeness of underlying databases should be kept in mind when interpreting variations in antipsychotic use across country populations. Firstly, data from the Netherlands and from Spain were extracted from regional databases, thus being liable to geographical bias. Moreover, for the year 2005, data for patients aged 80 years or older in the privately insured US population were not available due to confidentiality rules. Finally, while we excluded patients with both Medicaid and Medicare eligibility (i.e., dual eligibles) from the US publicly insured cohort, some prescription medication use is likely to be missing from 2006 onwards with the introduction of Medicare Part D. This could partially explain the marked decreases in prevalence of use seen between 2005 and 2007 in the adult and older adult publicly insured population.

Concluding, this study contributes to a realistic picture of recent international trends in antipsychotic utilisation, and its results underline the value of pharmacoepidemiologic monitoring of antipsychotic utilisation. While generally there was a trend towards higher antipsychotic use, and towards increased use of atypical antipsychotics, there were also populations that countered this trend. Both prevalence of antipsychotic use and favoured antipsychotics varied markedly between populations, with the high antipsychotic utilisation in older adults in some populations deserving further investigation.

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The funding sources had no further role in study design; in the collection, analysis and interpretation of data; in the writing of the report; and in the decision to submit the paper for publication.

Contributors

Óskar Hálfánarson and Christian Bachmann conceptualized and designed the study, drafted the initial manuscript, and approved the final manuscript as submitted.

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All authors mentioned above agree to be accountable for all aspects of the work.

Conflict of interest

Christian J. Bachmann is author (unpaid) of a study on antipsychotic prescriptions based on BARMER GEK data, and has authored (paid) a book chapter for BARMER GEK health insurance funds.

Miquel Bernardo has been a consultant for, received grant/research support and honoraria from, and been on the speakers/advisory board of ABBiotics, Adamed, Almirall, Amgen, Boehringer, Eli Lilly, Ferrer, Forum Pharmaceuticals, Gedeon, Hersill, Janssen-Cilag, Lundbeck, Otsuka, Pfizer, Roche, Servier and has obtained research funding from the Ministry of Education, Culture and Sport, the Spanish Ministry of Economy and Competiveness, the Spanish Ministry of Science and Innovation, Centro de Investigaci  n Biom  dica en Red de Salud Mental (CIBERSAM), by the Government of Catalonia, Secretaria d'Universitats i Recerca del Departament d'Economia i Coneixement (2014SGR441), Foundation European Group for Research In Schizophrenia (EGRIS), and the 7th Framework Program of the European Union.

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Luuk J. Kalverdi  k has authored (unpaid) a study on antipsychotic prescriptions based on IADB.nl data, is author and former chair (unpaid) of the medication committee of the Dutch Knowledge Centre for Child and Adolescent Psychiatry, and has acted as an advisor (unpaid) to the European Medicines Authority (EMA).

Lena Brandt, Helle Kieler, and Johan Reutfors are employed at the Centre for Pharmacoepidemiology, Karolinska Institutet, which receives grants from several entities (pharmaceutical companies, regulatory authorities and contract research organizations) for performance of drug safety and drug utilization studies. These entities had no role in the data collection and analysis and were not involved in the interpretation of results, writing, revision, and approval of the manuscript.

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