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International trends in clozapine use: a study in 17 countries

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Objective: There is some evidence that clozapine is significantly underutilised. Also, clozapine use is thought to vary by country, but so far no international study has assessed trends in clozapine prescribing. Therefore, this study aimed to assess clozapine use trends on an international scale, using standardised criteria for data analysis.
Method: A repeated cross-sectional design was applied to data extracts (2005–2014) from 17 countries worldwide.
Results: In 2014, overall clozapine use prevalence was greatest in Finland (189.2/100 000 persons) and in New Zealand (116.3/100 000), and lowest in the Japanese cohort (0.6/100 000), and in the privately insured US cohort (14.0/100 000). From 2005 to 2014, clozapine use increased in almost all studied countries (relative increase: 7.8–197.2%). In most countries, clozapine use was highest in 40–59-year-olds (range: 0.6/100 000 (Japan) to 344.8/100 000 (Finland)). In youths (10–19 years), clozapine use was highest in Finland (24.7/100 000) and in the publicly insured US cohort (15.5/100 000).
Conclusion: While clozapine use has increased in most studied countries over recent years, clozapine is still underutilised in many countries, with clozapine utilisation patterns differing significantly between countries. Future research should address the implementation of interventions designed to facilitate increased clozapine utilisation.

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Key words: clozapine; pharmacoepidemiology; psychotic disorders

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Significant outcomes

- Clozapine use varies markedly between countries in matters of general prevalence and patients' age. The underlying mechanisms are most likely complex, encompassing a set of factors at the individual level and the health system level.
- Clozapine underutilisation is an almost ubiquitous phenomenon, thus constituting a major public health challenge.
- To offer all patients with treatment-resistant schizophrenia adequate clozapine treatment, the broadly based development and implementation of interventions designed to increase clozapine utilisation should be pursued.

Limitations

- The majority of the studied countries were high-income countries, thus precluding the generalisability of our findings to low- and middle-income countries.
- Data on the indications for clozapine prescription were not available, so the proportion of clozapine prescription for treatment-resistant schizophrenia cannot be exactly determined.

Introduction

Clozapine is an antipsychotic that first came onto the market in Europe in the early 1970s as the world's first atypical antipsychotic (1). Following reports of clozapine-related deaths in Finland in 1975 (2), in most countries clozapine was withdrawn by the manufacturer. Clozapine was

re-introduced to most markets in the 1990s, with an approval mainly for treatment-resistant schizophrenia (TRS), and under strict haematological monitoring obligations (3).

Clozapine is currently the most effective antipsychotic substance in the therapy of TRS (4–6) and is listed on the *WHO Model List of Essential Medicines* (7). Besides its efficacy in TRS, clozapine carries also some significant adverse effects, including metabolic syndrome, diabetes mellitus, seizures and – most severe – agranulocytosis, myocarditis and bowel obstruction (8–11). While clozapine's main indication is TRS (3), in some countries it is also licensed for psychosis in Parkinson's disease, chorea in Huntington's disease, treatment-intolerant schizophrenia or recurrent suicidal behaviour in schizophrenia and schizoaffective disorder (4, 12). Most countries require at least weekly white blood cell and absolute neutrophil counts for the first weeks and months of clozapine treatment to detect agranulocytosis in a timely fashion (13).

Despite its efficacy in the treatment of TRS, there is some evidence that clozapine is underutilised in patients with this condition (14, 15), arguably making it 'one of the most underused evidence-based treatments available in psychiatry' (12). This is unfavourable, given the high personal and societal burden, and the excess mortality of schizophrenia (16), mortality that clozapine reduces (17).

There is a variety of potential reasons for this underutilisation of clozapine, including non-adherence to treatment guidelines, doctors' lack of experience in clozapine prescribing, patients' refusal of the necessary blood work, concerns regarding side-effects and differences in local practice patterns (18–24).

As both licensing and prescription regulations (Table 1) and attitudes towards clozapine vary considerably between countries (3, 25, 26), an international comparison of trends in clozapine use is useful to compare medication use patterns and establish the status quo of current practice.

Also, while in some countries clozapine use has increased in recent years (27, 28), other countries have reported a decrease in clozapine utilisation (29). Concluding, comprehensive and comparable data on clozapine utilisation on an international level are lacking.

Aims of the study

We therefore aimed to assess the prevalence of clozapine use and time trends in clozapine utilisation in youths, adults and older people in countries from Europe, Asia, North America, South America and Oceania, using standardised criteria for data analysis.

Material and methods

Data sources

To obtain data on clozapine use, we approached pharmacoepidemiological research groups and database providers from 32 countries. Of these, 15 countries either did not respond to our query or stated that they did not have access to the required data sets. The data from the remaining 17 countries formed the basis of this study. We used data from national or regional administrative databases from the following countries: Australia, Colombia, Denmark, Finland, France, Germany, Iceland, Italy, Japan, Lithuania, the Netherlands, New Zealand, Norway, Spain, Sweden, Taiwan and USA. The characteristics of the underlying databases are described in Table 2 and, in more detail, in Appendix S1.

Data analysis

We included individuals who were registered continuously in the respective database throughout at least one calendar year during the period 2005 (2006 for data from Colombia, Sweden and France, 2009 for data from Japan, 2011 for data from Spain) to 2014 (2010 for data from the publicly insured US cohort, 2013 for data from Australia and Taiwan, 2012 for data from Italy). Annual prevalence was defined as the proportion of individuals with one or more prescriptions or dispensings of clozapine (code N05AH02 within the Anatomical Therapeutic Chemical drug classification system employed by the WHO (30)).

For each of the data extracts, we determined the overall clozapine use prevalence per 100 000 persons per year. For the years 2005 and 2014, or (if data for these years were not available) for the first and last year of the period from which data from the respective country were available, we also investigated clozapine use prevalence stratified by sex and age group. Exact 95% confidence intervals (95% CI) using the Clopper–Pearson method were estimated. We also analysed trends (i.e. changes between the first and the last year of assessment) in overall clozapine use and calculated prevalence ratios (PR) with 95% CI and *P*-values using chi-squared tests. Additionally, the overall clozapine utilisation prevalence of each country was directly age-standardised to the WHO world standard population (31).

Table 1. Clozapine licensing and prescription regulations in the studied countries (as of 10/2016)

			Indication					Prescribers		Mandatory medical monitoring	
Country	Licensed since (year)	Licensed from age (years)	Treatment-resistant schizophrenia	Psychosis in Parkinson's disease	Recurrent suicidal behaviour	Treatment-intolerant schizophrenia	Other	GPs	Specialist services	Haematological monitoring: Weekly for 18 weeks, then monthly	Other
Australia[1]	1993	No specific regulation	X			X		X	X	X	Troponin, CRP, ECG (weekly for first 4 weeks)[2]
Colombia	1994	16		X			Use as standard antipsychotic	X[3]	X[3]	Recommended, but not mandatory	
Denmark	1982	18	X	X		X			X	X	
Germany	1972	16	X	X		X		X	X	X	
Finland	1975/1990[4]	16	X	X		X			X[5]	X	
France	1991	16	X	X		X			X	X	
Iceland	1993	16	X	X		X		X	X	X[6]	
Italy	1995	16	X	X		X			X	X	
Japan	2009	20	X						X[7]	X[8]	Blood glucose level, mandatory hospitalisation for 18 weeks, mandatory availability of cooperating haematologist
Lithuania	1994	18	X	X		X			X	X	
Netherlands	1971/1988[9]	16	X	X				X	X	X[10]	
New Zealand	1993	16	X		X	X[11]		X[12]	X	X[6]	
Norway	1990	16	X	X		X		X	X	X[13]	
Spain	1975/1993[14]	16	X	X[15]		X			X	X[16]	
Sweden	1989	16	X	X		X[17]		X	X	X[18]	
Taiwan	1991	No specific regulation	X	X	X				X	X	
USA	1996	18	X		X	X[19]		X[20]	X[20]	X[21]	

[1]Unless otherwise noted, the regulations on clozapine prescription in this line relate to the Federal Government of Australia.

[2]Regulation by the State of Queensland.

[3]The prescribing physician has to use a special prescription form.

[4]First licensed 1975, since 1976 only compassionate use. Restricted license since 12/1990 for treatment-resistant schizophrenia.

[5]Clozapine may also be prescribed by physicians familiarised with treatment of psychiatric conditions with clozapine and follow-up of adverse effects.

[6]Monitoring must continue for 4 weeks after complete discontinuation of clozapine.

[7]Can only be prescribed in hospitals or pharmacies registered with Clozapine Prescription Monitoring Services (CPMS) and with patients' agreement about the CPMS restrictions.

[8]Weekly for 26 weeks with white blood count ≥4000 and absolute neutrophil count ≥2000, then once in 2 weeks.

[9]First licensed 1971, withdrawn 1975. Re-licensed since 01/1988.

[10]Haematological monitoring in the fourth week after discontinuation of clozapine.

[11]Intolerance of conventional antipsychotics.

[12]Changes to prescribing restrictions in 2013: all registered doctors employed by district health boards can prescribe clozapine, if under supervision of a psychiatrist.

[13]Monitoring must continue for at least 4 weeks after an eventual discontinuation, or until normal levels are restored.

[14]Clozapine was first licensed in 1975, but it was withdrawn in 1988, at marketing authorisation holder initiative. In 1993 after a new application, the drug was licensed under a new monitoring programme.

[15]If standard treatment has failed.

[16]Monthly monitoring must continue for life.

[17]Schizophrenia patients who have severe, untreatable neurological adverse reactions to other antipsychotic agents, including atypical antipsychotics.

[18]Monitoring must continue for 4 weeks after an eventual discontinuation.

[19]Schizophrenia patients with sensitivity to extrapyramidal side-effects and patients with tardive dyskinesia.

[20]Clinicians need to be registered in the Clozapine Risk Evaluation and Mitigation Strategy Program and need to demonstrate that they are competent to prescribe clozapine. Pharmacies also need to be certified if they dispense clozapine. To receive clozapine, a patient must be entered into this registry and undergo regular monitoring of absolute neutrophil count (ANC) that continues as long as a patient receives clozapine.

[21]Unlike other countries, in which a minimum ANC of ≥2000/μl is a prerequisite for clozapine, in USA the minimum ANC is ≥1500/μl (≥1000/μl for benign ethnic neutropenia). Haematological monitoring is weekly during the first 6 months of clozapine administration; every other week for the second 6 months; and every 4 weeks after 1 year for the duration of treatment.

Table 2. Database characteristics

Country	Database	Regional (R) or nationwide (N) data	Nationally representative data	Population under risk (in 2014 or most recent year available)			
				Total number	% of country population	Mean age in years (SD)	% females
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	54.6 (20.5)	54.4
Taiwan	National Health Insurance Research Database (NHIRD-TW) (presciptions from outpatient care claims, pharmacy claims, or hospital care claims)	N	Yes	23 m (cohort: 1 m random sample of population under risk)	100	42.2 (19.4)	51.0
Europe							
Denmark	Danish Registry of Medicinal Products Statistics (national database with all outpatient prescriptions/dispensings)	N	Yes (total population)	5.6 m	100	40.9 (15.3)	50.4
Finland	Finnish Prescription Registry (all reimbursed outpatient prescriptions/dispensings)	N	Yes (total population)	5.5 m	100	47.4 (23.1)	50.8
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	39.6 (23.8)	51.7
Germany	BARMER GEK public health insurance funds (all reimbursed outpatient prescriptions)	N	No	8.6 m	10.6	46.2 (23.2)	58.1
Iceland	Icelandic Medicines Registry (all outpatient prescription dispensings, since 2011 also including nursing homes)	N	Yes (total population)	0.3 m	100	N/A	49.9
Italy	Regional Administrative Database of Lombardy (all community prescriptions reimbursed by the national health service)	R	No	4.7 m	7.8	43.9 (23.3)	51.5
Lithuania	National Health Insurance Fund database (reimbursed outpatient prescriptions)	N	Yes (total population)	2.9 m	100	N/A	53.9
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	44.5 (22.6)	51.3
Norway	Norwegian Prescription Database (NorPD) (national database with all outpatient prescriptions/dispensings)	N	Yes (total population)	5.2 m	100	38.9 (23.1)	49.7
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	55.5 (32.4)	50.7
Sweden	Swedish Prescribed Drug Register (national database with all outpatient prescriptions/dispensings)	N	Yes (total population)	9.7 m	100	41.2 (23.8)	50.0
Oceania							
Australia	iPharmacy® database, Queensland state (all outpatient dispensings from pharmacies at public hospitals)	R	No	4.7 m	20.0	37.3 (22.8)	N/A
New Zealand	Pharms database, Ministry of Health (all outpatient community pharmacy dispensings)	N	Yes (total population)	4.5 m	100	N/A	51.0
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	54.4 (22.4)	51.8
USA (privately insured cohort)	UnitedHealth database (outpatient prescription dispensings)	N	No	9.9 m	3.1	45.4 (23.7)	51.3
USA (publicly insured cohort)	Medicaid Analytic eXtract (MAX) (outpatient prescription dispensings from the majority of US federal states)	N	Yes	33.4 m	10.5	17.8 (15.6)	56.4

We performed all statistical analyses with SAS for Windows version 9.4 (SAS Institute Inc, Cary, NC, USA).

Ethical approval

Iceland. In September 2016, this study was approved by the National Bioethics Committee in Iceland, reference number VSN-16-117.

Japan. This study was approved by the ethical committee of Kyoto University Graduate School of Medicine on 30 August 2015 (reference number R0780).

New Zealand. The research was approved by the 'Human Ethics Committee (Health) Departmental Conditional Approval of Projects using Health Information', University of Otago (reference number HD16/034).

Sweden. The study was approved by the regional ethical review board in Stockholm.

Taiwan. The study was approved by the Institutional Review Board (IRB) of the Chang Gung Memorial Hospital (reference number: 103-0637B).

USA. The research was approved by 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.

Results

Overall clozapine use and differences between countries

In 2014, overall clozapine use was greatest in Finland (189.2/100 000 persons) and in the New Zealand cohort (116.3/100 000), and lowest in the Japan cohort (0.6/100 000), and in the privately insured US cohort (14.0/100 000), resulting in an up to 315-fold difference in clozapine use prevalence between countries (Table 3).

Employing age standardisation slightly reduced the span of overall clozapine use rates, ranging from 0.9/100 000 in the Japan cohort to 173.2/100 000 in Finland. Also, age standardisation led to an altered ranking in terms of clozapine utilisation, with the publicly insured US cohort replacing New Zealand on the second rank (Table 3).

Figure 1 shows the time trends in overall clozapine use in all studied countries.

Trends in clozapine use

During the studied period, there was a significant increase in the annual prevalence of clozapine use in most populations, with the PR (=most recent/earliest year of the studied period) in these countries ranging from 1.08 (Sweden) to 2.98 (privately insured US population) (Table 3). A significant decrease in clozapine use was found only in Colombia and in the publicly insured US cohort. The largest *absolute* increase in clozapine use happened in Finland (+49.0/100 000) and in the Netherlands cohort (+40.2/100 000).

Age and gender differences in clozapine use

Clozapine use by age and gender in 2014 is presented in Fig. 2.

With the exception of Colombia, Japan, France, the Netherlands and Iceland, overall clozapine use was highest in the 40–59 years age group, ranging from 25.5/100 000 (USA, privately insured) to 344.8/100 000 (Finland). In Colombia, France, Germany, the Netherlands and Iceland, there were marked clozapine use peaks in elderly people (80+ years), ranging from 99.7/100 000 to 922.4/100 000.

In youths (10–19 years), clozapine use was highest in Finland (24.7/100 000) and in the publicly insured US cohort (15.5/100 000).

Overall, there was a male preponderance in clozapine use in all countries. The highest clozapine use prevalence in men was found in men aged 80 years and older in the Colombia cohort (1200.7/100 000) and in Iceland (556.0/100 000), and in 40–59-year-old men in Finland (394.5/100 000) and in the publicly insured US cohort (400.0/100 000). In women, clozapine use prevalence was highest in 40–59-year-olds in Finland (294.5/100 000) and in the 80+ years age group in the Colombian population (761.9/100 000), and in Iceland (402.2/100 000).

Across the studied countries, the male/female ratio ranged from 1.3 to 4.2 in 2014, with the median male/female clozapine use ratio being 1.5.

Discussion

The main results of this study are as follows: while clozapine use prevalence increased in almost all populations during the studied period, we found significant differences between countries in the total prevalence of clozapine use. In most populations, clozapine use peaked at age 40–59 years, and there was a male preponderance.

Overall clozapine use and differences between countries

Given the fact that the worldwide prevalence of schizophrenia is about 0.5–0.7% (32, 33) and that about one-third of these patients shows treatment resistance (34, 35), an optimal treatment with clozapine of all these cases should result in a clozapine use prevalence of roughly 0.2% (200/100 000) of the adult population. While this is a theoretical figure (e.g. some TRS patients may not be eligible for clozapine for medical reasons), it nevertheless constitutes a comprehensive benchmark for the data found in our study.

Against this background, and despite the increased clozapine use in most countries, the fact that only few of the studied populations (Finland, Iceland, New Zealand, publicly insured US cohort), and only in selected age groups, reach the aforementioned prevalence of clozapine use is notable. Also, remarkable are the significant differences (up to more than 300-fold) of clozapine use between countries.

Interestingly, the data from both US cohorts are not among those with the highest clozapine use prevalence. This is in line with earlier reports (36), but stands in contrast to the majority of pharmacoepidemiological studies, in which usually US prescription rates are higher than other countries' (e.g. 37, 38). While we excluded patients with both Medicaid and Medicare eligibility (i.e., dual eligibles) from the cohort, some prescription medication use might nevertheless be missing from 2006 onwards with the introduction of Medicare Part D. If so, this could have affected the time trends for the publicly insured population.

The low use of clozapine in the privately insured US cohort can be explained by the fact that in the US private insurance is typically employer-based, so this population will not contain many patients with TRS. In contrast, the publicly insured population is enriched with mentally ill insurees, which explains the higher clozapine use.

The below-average clozapine use in France and Italy is probably caused by a less prominent role of biological psychiatry and psychopharmacotherapy in these countries, resulting from a mixture of factors, including the countries' historical involvement in the antipsychiatry and deinstitutionalisation movements (39, 40), and – at least in France – a still strong influence of psychoanalytic concepts (41).

The extremely low clozapine use in Japan can be best explained by the very strict national regulations for clozapine initiation, which include hospitalisation for 18 weeks, weekly haematological tests for the first 26 weeks and several other logistically demanding precautions (e.g. 24/7 availability of a haematologist, cooperating diabetologist, prebooked haematological bed (in case of neutropenia), stocking of antibiotics in the psychiatric hospital). Also, clozapine has only been available in Japan market since 2009, so psychiatrists' experience is still limited (42). Another cause might be the method employed in this study: as only out-patient clozapine prescriptions were analysed, patients who receive clozapine treatment in psychiatric hospitals (in Asia, long-term institutionalisation of psychiatric patients is still much more frequent than in Western countries (43)) were not counted, which may have led to some underestimation of clozapine use. Preference of polypharmacy (44) and higher rates of clinical remission in schizophrenia in East Asia (45) may also play a role.

Remarkably, Finland, the country which reported the first cases of clozapine-related agranulocytosis, displayed much higher clozapine use rates than the other studied countries. The reasons for this finding are not completely clear. However, the landmark studies of Tiihonen et al. (17, 46) may have constituted an important influencing factor for clozapine prescribing in Finland. Based on data from national Finnish registers, Tiihonen et al. demonstrated in an 11-year follow-up study of patients with schizophrenia that clozapine treatment was associated with substantially lower mortality than other antipsychotics (17). In another cohort study, he found an association with clozapine and low-treatment discontinuation rates in patients with schizophrenia and schizoaffective disorder (46).

Generally, intercountry differences in clozapine prescription can be influenced by several factors, including health system resources (e.g. density of psychiatrists, organisational and financial means for haematological monitoring (47, 48)), clozapine pricing (in 2014: 0.04–0.52 USD per 100 mg tablet (49)) and reimbursement practices (50), availability and pricing of other antipsychotic substances (51, 52) and clozapine prescription and licensing regulations (3).

The effect of the aforementioned factors on clozapine use is probably the result of a combination of factors. This complex causality is illustrated by the case of Colombia, which is the only one of the studied countries where clozapine is a standard antipsychotic that can be prescribed for all patients with schizophrenia (i.e. not only for TRS), and where haematological monitoring in patients receiving clozapine is not mandatory. But, interestingly, despite this liberty in clozapine prescribing, the prevalence of clozapine use in Colombia is just about average.

Another explanation for the intercountry differences found in this study is the diversity of the underlying populations in terms of age and gender.

Table 3. Prevalence of clozapine use (per 100 000 persons) in 2014 (or the most recent year available), by country, age group and sex

Age group	Australia (2013)	Colombia	Denmark	Finland	France	Germany	Iceland	Italy (2012)	Japan
10–19									
Total	N/A	9.8 [7.1–13.2]	3.6 [2.3–5.3]	24.7 [20.9–29.0]	9.3 [3.4–20.3]	3.7 [2.5–5.3]	0 [0–8.5]	2.2 [1.0–4.1]	0 [0–1.8]
Male	N/A	13.6 [9.1–19.5]	2.5 [1.2–4.8]	19.3 [14.7–24.9]	12.1 [3.3–30.9]	3.7 [2.1–6.2]	0 [0–16.6]	2.8 [1.0–6.0]	0 [0–3.5]
Female	N/A	6.0 [3.2–10.3]	4.8 [2.7–7.7]	30.4 [24.4–37.4]	6.4 [0.8–23.2]	3.7 [2.0–6.1]	0 [0–17.2]	1.5 [0.3–4.4]	0 [0–3.7]
20–39									
Total	N/A	37.3 [33.7–41.3]	63.2 [59.1–67.5]	239.0 [231.0–247.3]	45.8 [35.3–58.5]	90.2 [86.0–94.5]	67.2 [51.6–86.2]	51.0 [46.9–55.4]	2.4 [1.3–4.1]
Male	N/A	56.8 [50.3–63.8]	74.2 [68.0–80.9]	295.1 [282.6–308.0]	66.5 [48.7–88.7]	132.3 [124.9–139.9]	95.7 [69.8–128.1]	74.5 [67.6–81.9]	4.5 [2.1–8.2]
Female	N/A	19.0 [15.4–23.1]	51.9 [46.6–57.6]	180.0 [170.0–190.4]	25.6 [15.1–40.4]	52.9 [48.6–57.5]	37.6 [21.9–60.2]	27.0 [22.8–31.6]	1.0 [0.2–2.8]
40–59									
Total	N/A	83.2 [76.2–90.6]	107.3 [102.3–112.6]	344.8 [335.2–354.6]	56.7 [45.1–70.3]	146.9 [142.2–151.7]	132.1 [108.7–159.1]	68.5 [64.3–73.0]	0.6 [0.2–1.5]
Male	N/A	102.1 [91.0–114.2]	131.6 [123.7–139.9]	394.5 [380.1–409.3]	68.4 [50.4–90.6]	175.5 [167.3–184.0]	174.0 [136.4–218.8]	84.0 [77.4–91.0]	0.9 [0.2–2.7]
Female	N/A	66.2 [57.8–75.6]	82.8 [76.5–89.5]	294.5 [282.0–307.4]	45.7 [31.6–63.8]	128.6 [122.9–134.4]	90.3 [63.9–123.9]	53.0 [47.8–58.7]	0.3 [0–1.5]
60–79									
Total	N/A	182.2 [163.9–202.0]	58.4 [54.0–63.0]	160.5 [153.4–167.9]	55.3 [41.3–72.5]	101.2 [97.1–105.5]	202.6 [164.5–246.9]	31.5 [28.2–35.2]	0.1 [0–0.5]
Male	N/A	230.9 [200.7–264.3]	68.8 [62.1–76.2]	169.2 [158.6–180.3]	71.2 [48.4–101.1]	100.3 [93.6–107.4]	208.6 [154.9–274.9]	36.7 [31.4–42.7]	0.2 [0–1.2]
Female	N/A	141.2 [119.7–165.5]	48.7 [43.2–54.7]	152.8 [143.3–162.8]	41.5 [25.7–63.5]	101.7 [96.5–107.2]	196.7 [145.1–260.8]	27.1 [22.9–31.9]	0 [0–0.7]
80+									
Total	N/A	922.4 [812.0–1043.4]	24.7 [18.8–31.9]	34.6 [28.0–42.2]	99.7 [67.3–142.4]	84.7 [77.1–92.8]	465.4 [350.8–605.4]	32.4 [26.3–39.4]	0 [0–1.1]
Male	N/A	1200.7 [995.6–1435.1]	25.3 [15.8–38.2]	19.2 [11.4–30.3]	146.2 [81.8–241.0]	86.6 [73.2–101.8]	556.0 [366.7–807.9]	27.9 [18.6–40.3]	0 [0–2.8]
Female	N/A	761.9 [637.4–903.5]	24.4 [17.1–33.7]	42.4 [33.5–52.9]	75.7 [42.4–124.8]	83.7 [74.7–93.6]	402.2 [267.4–580.8]	34.6 [27.0–43.6]	0 [0–1.7]
All ages (crude values)									
Total	61.9 [59.7–64.3]	57.3 [54.5–60.2]	58.3 [56.3–60.4]	189.2 [185.6–192.9]	43.1 [37.8–49.0]	94.9 [92.9–97.0]	100.1 [89.5–111.6]	41.8 [40.0–43.7]	0.6 [0.3–0.9]
Male	N/A	71.7 [67.2–76.5]	69.9 [66.8–73.1]	220.5 [215.0–226.2]	54.9 [46.3–64.7]	108.8 [105.4–112.3]	119.4 [103.2–137.4]	53.6 [50.7–56.7]	1.0 [0.5–1.6]
Female	N/A	43.9 [40.5–47.5]	46.9 [44.4–49.5]	158.9 [154.3–163.7]	32.1 [25.8–39.4]	85.0 [82.4–87.6]	80.7 [67.5–95.7]	30.7 [28.6–33.0]	0.2 [0.1–0.6]
M/F	N/A	1.6	1.5	1.4	1.7	1.3	1.5	1.7	4.2
All ages (age-standardised values)									
Total	N/A	65.8	50.7	173.2	35.3	73.2	78.3	33.9	0.9
Prevalence trends									
Prevalence ratio	1.28 [1.21–1.36]	0.74 [0.69–0.80]	0.98 [0.94–1.03]	1.35 [1.31–1.39]	2.08 [1.65–2.62]	1.12 [1.08–1.15]	1.83 [1.51–2.20]	1.12 [1.05–1.20]	N/A
P-value	<0.0001	<0.0001	0.51	<0.0001	<0.0001	<0.0001	<0.0001	0.0004	0.0003

Annotations: Numbers in brackets: 95% confidence intervals. Trend=relative increase/decrease during the 2005–2014 period, with the following exceptions: Australia (2005–2013), Colombia (2006–2014), France (2006–2014), Italy (2005–2012), Japan (2009–2014), Spain (2011–2014), Sweden (2006–2014), Taiwan (2005–2013) and publicly insured US cohort (2005–2010).
M/F, male/female ratio.

The proportion of females ranged from 49.7% in Norway to 56.4% in the publicly insured US cohort. As our reference population did not allow gender standardisation, this incomplete standardisation might have caused a bias towards lower clozapine use rates in populations with higher proportions of females.

The effect of age distribution within the studied populations is best visible in the publicly insured US population, which contains a large proportion of youths. Without age standardisation, this cohort was on rank 7 in terms of overall clozapine use, but advanced to the second rank after employing age standardisation.

Also, cultural influences, for example cultural attitudes towards psychopharmacotherapy (38) and different historical experiences of clozapine in different countries (1, 53), may also be relevant determinants of clozapine use.

Finally, influencing factors on the prescriber and patient level must also be drawn into account, for example patient age and influence of caregivers (54), patients' aversion of haematological monitoring or side-effects (e.g. sedation, weight gain) (21, 55), prescribers' experience with clozapine, prescribers' attitude towards clozapine (e.g. perception of clozapine as a dangerous medication (56)) and resulting delays in clozapine initiation (20, 22).

Trends in clozapine use

The increase in clozapine use over time in most countries can probably be explained with growing experience with this drug and perhaps also in the context of a general increase of antipsychotic prescription in most Western countries. Increased rates of clozapine treatment may also be the result of longer treatment duration, increased life expectancy or above-average compliance in this patient group (54, 57). It remains to be seen whether pharmacogenetic testing, once established in clinical routine, will influence clozapine utilisation trends in the future (58).

Age and gender differences in clozapine use

Concerning age, in most countries the clozapine use prevalence peaked in middle age, which is about 10 years later than the known average age of

Lithuania	Netherlands	New Zealand	Norway	Spain	Sweden	Taiwan (2013)	USA (publicly insured) (2010)	USA (privately insured)
3.1 [1.5–5.7]	1.5 [0–8.6]	10.8 [8.4–13.8]	1.6 [0.8–2.9]	8.3 [6.3–10.6]	2.3 [1.5–3.4]	3.2 [0.9–8.2]	15.5 [14.7–16.3]	3.0 [2.0–4.3]
3.6 [1.3–7.9]	0 [0–11.3]	14.1 [10.2–18.9]	1.9 [0.7–4.0]	8.5 [5.8–12.0]	2.9 [1.7–4.8]	4.6 [1.0–13.5]	18.1 [16.9–19.3]	4.0 [2.5–6.1]
2.6 [0.7–6.6]	3.1 [0.1–17.3]	7.4 [4.6–11.2]	1.3 [0.4–3.3]	8.0 [5.3–11.5]	1.6 [0.7–3.1]	1.7 [0–9.4]	13.0 [11.9–14.0]	2.0 [1.0–3.7]
73.8 [67.8–80.1]	103.3 [87.7–120.9]	180.2 [172.6–188.1]	58.5 [54.5–62.7]	72.4 [68.7–76.1]	49.2 [46.5–52.0]	86.5 [76.5–97.5]	134.0 [131.2–136.8]	12.5 [11.0–14.0]
98.9 [89.3–109.3]	162.4 [134.2–194.7]	276.9 [263.5–290.8]	80.5 [74.0–87.4]	103.7 [97.6–110.0]	63.1 [58.9–67.6]	107.5 [91.5–125.4]	368.7 [359.3–378.2]	15.3 [13.1–17.7]
48.0 [41.3–55.5]	49.6 [35.3–67.8]	87.0 [79.6–94.8]	35.3 [30.9–40.1]	39.9 [36.1–43.9]	34.5 [31.3–37.9]	67.1 [55.0–81.0]	60.3 [58.2–62.5]	9.5 [7.8–11.6]
104.4 [97.7–111.5]	146.8 [128.6–166.9]	203.9 [196.0–212.1]	95.2 [90.1–100.4]	83.9 [80.1–87.8]	114.9 [110.8–119.2]	141.2 [128.4–154.9]	276.3 [271.0–281.7]	25.5 [23.6–27.5]
123.8 [113.2–135.2]	192.2 [162.9–225.3]	284.1 [270.6–298.0]	113.2 [105.6–121.3]	104.7 [98.8–110.9]	138.3 [131.9–144.9]	174.5 [154.4–196.5]	400.0 [389.6–410.6]	29.0 [26.2–32.0]
87.3 [78.9–96.4]	101.8 [80.8–126.5]	129.7 [121.0–138.9]	76.1 [69.7–83.0]	62.6 [58.0–67.5]	90.9 [85.7–96.4]	108.8 [93.3–126.1]	201.7 [195.9–207.5]	21.9 [19.5–24.6]
52.0 [46.2–58.3]	110.6 [91.5–132.4]	74.3 [68.2–80.8]	44.2 [40.0–48.7]	21.4 [19.0–24.1]	81.7 [77.7–85.7]	60.8 [48.9–74.7]	184.9 [176.2–193.9]	14.6 [13.1–16.1]
55.5 [46.1–66.4]	111.5 [84.7–144.1]	76.2 [67.4–85.9]	47.0 [40.8–53.8]	20.5 [17.1–24.4]	94.4 [88.4–100.8]	44.2 [30.0–62.7]	182.9 [169.0–197.6]	14.7 [12.6–17.1]
49.8 [42.7–57.7]	109.7 [83.7–141.2]	72.4 [64.1–81.5]	41.5 [35.9–47.8]	22.2 [18.9–26.0]	69.4 [64.3–74.7]	75.7 [57.6–97.7]	186.1 [175.1–197.6]	14.4 [12.5–16.6]
7.5 [3.8–13.5]	282.2 [219.6–357.0]	22.4 [15.7–31.1]	11.2 [7.3–16.4]	6.3 [4.2–9.2]	31.6 [26.9–37.0]	47.3 [27.6–75.7]	5.2 [1.4–13.3]	4.7 [3.2–6.6]
10.3 [2.8–26.3]	302.8 [197.9–443.4]	15.4 [7.4–28.3]	13.9 [7.2–24.2]	5.3 [2.3–10.4]	36.8 [28.7–46.5]	45.5 [19.6–89.6]	7.8 [0.9–28.2]	3.8 [1.8–6.9]
6.5 [2.6–13.4]	271.1 [196.2–364.9]	27.2 [17.8–39.9]	9.6 [5.2–16.1]	6.9 [4.2–10.8]	28.5 [22.8–35.1]	49.0 [22.4–93.0]	3.9 [0.5–14.0]	5.2 [3.3–7.9]
60.3 [57.5–63.2]	103.1 [94.9–111.9]	116.3 [113.2–119.5]	50.1 [48.1–52.0]	49.1 [47.5–50.7]	61.0 [59.4–62.5]	87.5 [81.7–93.7]	66.7 [65.8–67.6]	14.0 [13.3–14.8]
74.6 [70.0–79.3]	129.6 [116.4–143.8]	162.1 [156.8–167.5]	62.2 [59.2–65.4]	65.0 [62.5–67.7]	73.6 [71.2–76.1]	102.6 [93.6–112.2]	88.7 [87.2–90.2]	15.8 [14.7–17.0]
48.1 [44.8–51.7]	78.0 [68.1–88.9]	72.3 [68.9–75.9]	37.7 [35.4–40.2]	33.6 [31.8–35.5]	48.3 [46.4–50.3]	73.0 [65.6–81.1]	49.7 [48.7–50.7]	12.3 [11.3–13.3]
1.5	1.7	2.2	1.6	1.9	1.5	1.4	1.8	1.3
53.0	82.9	112.7	44.4	44.0	50.4	64.2	122.8	11.6
1.41 [1.31–1.51]	1.64 [1.44–1.87]	1.29 [1.23–1.34]	1.26 [1.18–1.33]	1.16 [1.11–1.22]	1.08 [1.04–1.12]	1.22 [1.10–1.34]	0.87 [0.85–0.89]	2.98 [2.66–3.33]
<0.0001	<0.0001	<0.0001	<0.0001	<0.0001	<0.0001	0.0001	<0.0001	<0.0001

onset in adult-onset schizophrenia (59), and which might indicate a delay in the initiation of clozapine treatment, which is not an uncommon finding in clinical practice (review: (60)). In the majority of countries, clozapine use in men peaked several years earlier than in women (Fig. 2), which is in line with the epidemiology of schizophrenia (59).

In the data sets from Colombia, France, Germany, the Netherlands and Iceland, there was a significant age peak in elderly people, which is probably due to the use of clozapine for the treatment of psychosis in Parkinson's disease and also for treatment of several types of dementia (61). At least for France, there is evidence for a significant portion of clozapine prescriptions in elderly patients being due to the treatment of psychotic symptoms in Parkinson's disease (62). Nevertheless, current guidelines encourage a careful and limited use of clozapine in elderly patients and in patients with dementia because of its strong anticholinergic properties (63).

In this study, clozapine utilisation in youths (i.e. 10- to 19-year-olds) ranged from 0 to 24.7/100 000. With early-onset schizophrenia (EOS) being less frequent (≤40/100 000 (64)) than schizophrenia in adults, and acute treatment response rates in EOS ranging from 34% to 50% (4), a conservative approximation of optimal clozapine treatment in this age group yields clozapine use rates of about 10 to 20/100 000, which are met by a number of countries in this study. Possible reasons for low rates of clozapine in youths include psychiatrists' lack of experience with clozapine in this age group (20), delayed initiation of clozapine (65), misdiagnosed EOS diagnoses (64) and the fact that in most countries clozapine is prescribed off-label in patients under 16 or 18 years of age (Table 1).

Regarding sex distribution, the male/female ratio in clozapine use found in this study (median: 1.5) is almost equivalent to the male/female ratio of 1.4 in adults with schizophrenia (32). This finding might indicate a narrow or even non-existing gender gap in clozapine treatment of TRS.

Regarding EOS, the prevalence of this disorder does not differ markedly between males and females (66), which is reflected in our results by smaller gender ratios and even a female preponderance in youths in some countries.

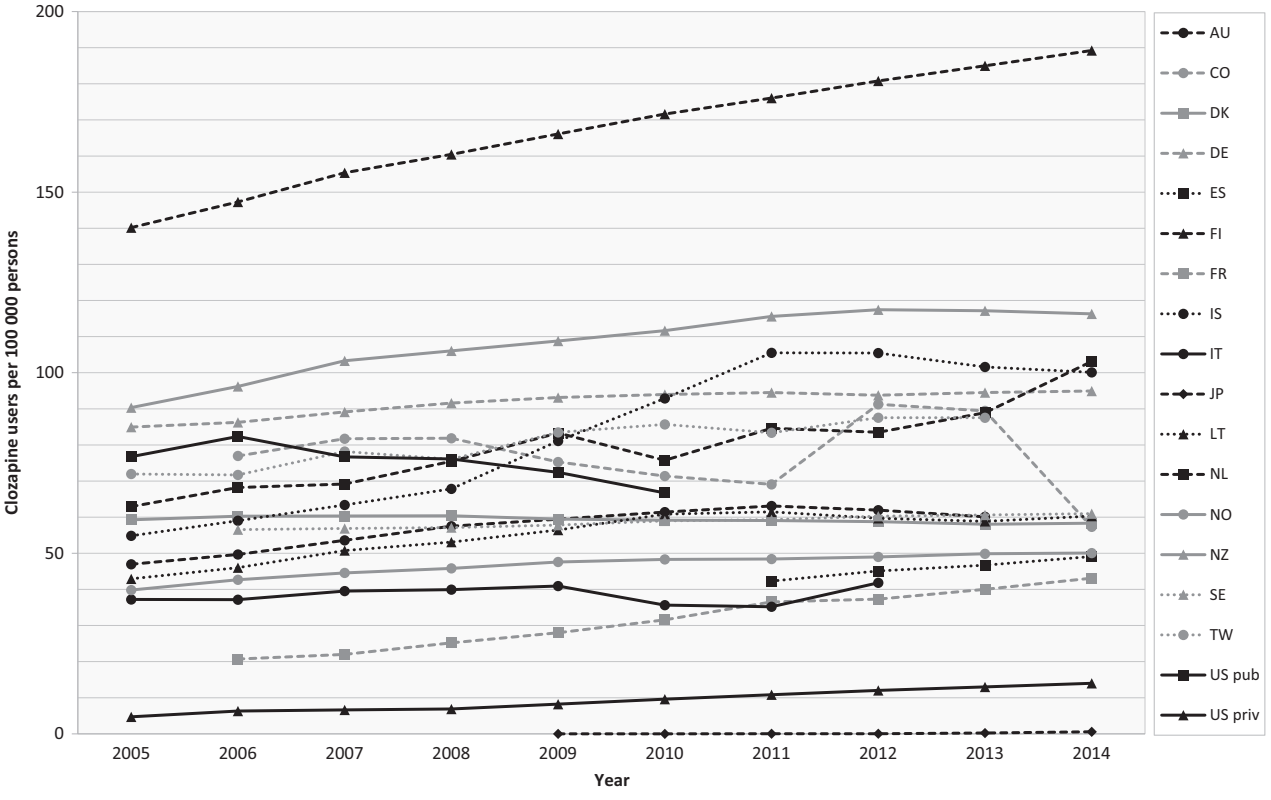

Fig. 1. Overall prevalence of clozapine use (per 100 000 persons) in cohorts from 17 countries, 2005–2014.

Beyond the above-mentioned possible reasons for variations in clozapine use by country, time, sex or age, the question remains, how to increase clozapine prescribing rates to a satisfactory level? A significant lead towards an answer is provided by recent research: over the last years, several interventions designed to increase clozapine use in patients with TRS have been successfully evaluated (67–70). While these interventions employ very different approaches, for example specialist-led outpatient clinics for patients with suspected TRS (67), a combination of clinical guidelines with practical clozapine titration schemes, a clozapine information brochure for patients and finger-prick tests for haematological monitoring (70), a state-wide implementation of a clozapine management system centred around nurse-led clinics, including standardised clozapine documentation and GP education packages (69), and state-wide action plans, feedback and internet-based educational programmes (68), all of them have succeeded in increasing the rates of TRS patients receiving clozapine. Nevertheless, these interventions have not yet been established on a broad level.

Therefore, it would seem appropriate and timely to evaluate the clinical and cost-effectiveness of the above-mentioned interventions within a national or international context (adapted to the respective local health services structures), followed, if successful, by a broad-based implementation in real-world clinical practice.

Strengths and limitations

This study is the first that compares clozapine use on an international scale over a period of 10 years, which constitutes a major strength. Also, more than half of the underlying databases were fully representative of the respective countries' population, thus reducing potential bias.

This study used secondary data from health funds and prescription databases as data sources. To maintain a uniform methodology, we had to determine a core data set, which lacked information on important clinical characteristics, for example indication, comorbidity, co-medication, actual clozapine dosage, treatment duration and adherence, as these were not available for all of the participating nations. This constitutes a limitation of this study. Also, the dispensings and prescriptions of clozapine counted in this study are not equivalent to the actual consumption. In most studied countries, the analysed data include only prescriptions for ambulatory patients, but not

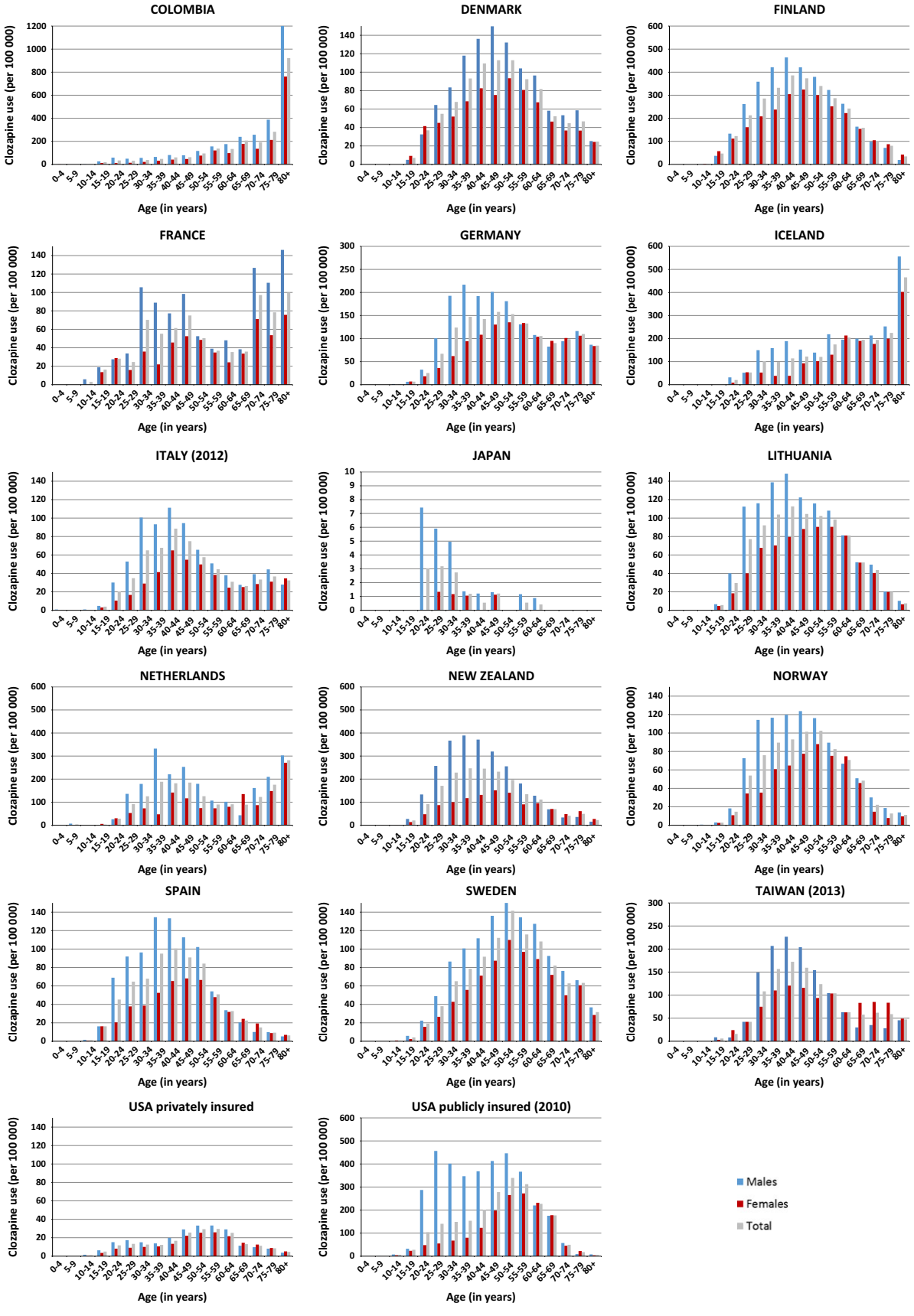

Fig. 2. Clozapine use (per 100 000 persons) in 16 countries, by sex and age, in 2014 (or the most recent year available). Annotations: The scale of the *y*-axis may differ between countries. For Australia, there was no sex- or age-specific data available. [Colour figure can be viewed at wileyonlinelibrary.com]

prescriptions for institutionalised people (e.g. in nursing homes), which may lead to underestimation of drug utilisation.

The databases employed include population cohorts, which are roughly representative of the general populations. However, some countries' data stem from regional databases (Australia, Italy, Spain, the Netherlands), and it is known that clozapine use may vary between different geographical regions (19, 36). Also, we were only able to obtain data from 17 countries worldwide, which were (with the exception of Colombia) high-income countries. This bias is due to the employed methodology, as pharmacoepidemiological databases are generally a byproduct of highly developed public health systems and therefore exist less frequently in low- and middle-income countries.

As mentioned in the discussion section, our reference population (31) did not allow gender standardisation. This might have led to an underestimation of clozapine use in most countries. However, the WHO world standard population is widely used and builds on fairly recent data.

As mentioned above, the benchmark for optimum clozapine use employed in this study (200/100 000 adults) is a theoretical figure, and it might vary between countries because of some variance in schizophrenia prevalence. Also, a part of clozapine prescriptions in elderly patients is written for other indications than TRS, for example psychosis in Parkinson's disease, so in this age group, the extent of clozapine use for the indication TRS cannot be exactly determined. Nevertheless, because of the limited indications for clozapine, and the higher age of onset for Parkinson's disease and dementia, the majority of clozapine prescriptions in non-elderly persons can be attributed to TRS.

Further relevant methodological limitations include limited availability of data (only from 2011 on) in the Spanish cohort, the lack of information on age and gender in the Australia cohort, the lack of data for patients aged 80 years or older for the year 2005 in the privately insured US cohort and some possible imprecision in the earlier years of the New Zealand data due to lower national health index capture.

In conclusion, despite some increase in clozapine use over recent years, the results of this study point to an underutilisation of clozapine in many countries. Moreover, this study found significant differences in clozapine use between countries. To facilitate adequate clozapine utilisation in patients with TRS, interventions for increasing clozapine use should be implemented in real-world mental health settings on a broad basis.

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Supporting Information

Additional Supporting Information may be found in the online version of this article:
Appendix S1. Database characteristics.