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Revealing the reporting disparity: VigiBase highlights underreporting of clozapine in other Western European countries compared to the UK

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ABSTRACT

Background: Pharmacovigilance studies indicate clozapine history is marked by adverse drug reactions (ADRs). *Objective:* In a 2021 article, the United Kingdom (UK) had >90 % of European clozapine-related fatal outcomes in VigiBase, the World Health Organization's pharmacovigilance database. Two possibly opposing hypotheses could explain this disparity: 1) fewer reported fatal outcomes in other Western European countries mainly reflect underreporting to VigiBase, and 2) the higher number of UK reports reflects higher real relative mortality. *Methods:* VigiBase reports from clozapine's introduction to December 31, 2022, were studied for ADRs and the top 10 causes of fatal outcomes. The UK was compared with 11 other top reporting Western countries (Germany, Denmark, France, Finland, Ireland, Italy, Netherlands, Norway, Spain, Sweden and Switzerland). Nine countries (except Ireland and Switzerland) were compared after controlling for population and clozapine prescriptions.

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Results: The UK accounted for 29 % of worldwide clozapine-related fatal outcomes, Germany 2 % and <1 % in each of the other countries. The nonspecific label "death" was the top cause in the world (46 %) and in the UK (33 %). "Pneumonia" was second in the world (8 %), the UK (12 %), Ireland (8 %) and Finland (14 %). Assuming that our corrections for population and clozapine use are correct, other countries underreported only 1–10 % of the UK clozapine fatal outcome number.

Conclusions: Different Western European countries consistently underreport to VigiBase compared to the UK, but have different reporting/publishing styles for clozapine-related ADRs/fatal outcomes. Three Scandinavian registries suggest lives are saved as clozapine use increases, but this cannot be studied in pharmacovigilance databases.

1. Introduction

This introduction begins with a discussion of the two divergent views of clozapine described in the literature: clozapine is a "toxic" drug, and clozapine is an excellent drug for treatment-resistant schizophrenia (TRS) and is underused due to barriers (Verdoux et al., 2018; Farooq et al., 2019), leading to uneven use across the world (Bachmann et al., 2017). Then the introduction presents a summary of clozapine history and fatal outcomes in 11 other Western European countries and the United Kingdom (UK), which is used as a comparison.

1.1. Clozapine as a "toxic" drug

The idea that clozapine is a "toxic" drug with potentially lethal adverse drug reactions (ADRs) has led to the descriptive term "clozaphobia" (Cetin, 2014). The "bad press" on clozapine started even before it was marketed. Some French authors did not like it (Simon, 2000; Deniker, 1990) while some German authors were the main defenders (Hippius, 1989; Crilly, 2007; de Leon et al., 2022a).

The history of the major clozapine-related ADRs are summarized in three Supplementary Boxes: S1 for agranulocytosis (Idänpään-Heikkilä et al., 1975; Kane et al., 1988; Anderman and Griffith, 1997; Simon, 2000; Crilly, 2007; Moore et al., 2007; Leung et al., 2022; de Leon et al., 2022b, 2023), S2 for myocarditis (Blum and Mauruschat, 1972; Vesterby et al., 1980; Gaertner et al., 1989; Helmchen, 1989; Naber et al., 1989; Committee on Safety of Medicines, 1993; Kilian et al., 1999; Devarajan et al., 2000; Coulter et al., 2001; La Grenade et al., 2001; Raaska et al., 2002; de Leon and Diaz, 2003; Haack et al., 2003; Egger et al., 2010; Clark et al., 2018; Ruan et al., 2018; Verdoux et al., 2019; de Filippis et al., 2020, 2021, 2022, 2024; De Las Cuevas et al., 2022a, 2022b, 2022c de Leon, 2022a; de Leon et al., 2020a, 2022c; Ertuğrul et al., 2022; Koenig et al., 2022; Shelton et al., 2022; Leung et al., 2023; Carswell et al., 2024; Kikuchi et al., 2024) and S3 for three other box warnings in the US package insert: 1) orthostatic hypotension, bradycardia and syncope; 2) seizure; and 3) increased mortality in elderly patients with dementia-related psychosis (Gaertner et al., 1989; Safferman et al., 1991; Pacia and Devinsky, 1994; U.S. Food and Drug Administration, 2005; Crilly, 2007; McCollum et al., 2018; Cicala et al., 2019; Papola et al., 2019; Schoretsanitis et al., 2019; de Leon et al., 2020b; de Leon et al., 2022c; Correll et al., 2022; De Las Cuevas et al., 2024).

1.2. Clozapine as the best drug for TRS

Supplementary Box S4 provides the support that clozapine is the best drug for TRS according to meta-analysis and systematic reviews (Siskind et al., 2016, 2017; Land et al., 2017; Huhn et al., 2019; Vermeulen et al., 2019; Masuda et al., 2019; Correll et al., 2022) and the Scandinavian national registries (Tiihonen et al., 2009; Gjerden et al., 2010; Kiviniemi et al., 2013; Ringbäck Weitoft et al., 2014; Wimberley et al., 2017; Rohde et al., 2018a; Taipale et al., 2018, 2020; van der Zalm et al., 2019, 2021) which are summarized in detail in Supplementary Table S1.

1.3. Clozapine in other Western European countries: contributions and pharmacovigilance

Supplementary Table S2 describes the historical and pharmacovigilance contributions of these 11 other European countries.

1.3.1. Contributions from Germany

Supplementary Table S2 describes German contributions to: 1) history (Blum and Mauruschat, 1972; Schmidt et al., 1983; Helmchen, 1989; Pfuhlmann et al., 2009), 2) therapeutic drug monitoring (TDM) (Baumann et al., 2004; Hiemke et al., 2011, 2018; Schoretsanitis et al., 2021a), 3) pharmacoepidemiology (Bender et al., 2004; Druschky et al., 2019; Sanader et al., 2019; Friedrich et al., 2020) and 4) fatal outcomes (Schmedt et al., 2016).

1.3.2. Contributions from Denmark

Supplementary Table S2 describes the Danish contributions to: 1) myocarditis (Vesterby et al., 1980; Juul Povlsen et al., 1985), 2) efficacy studies (Nielsen et al., 2012a, 2012b; Rohde et al., 2018b; Rohde et al., 2018c); 3) pharmacoepidemiology studies (Nielsen et al., 2009, 2010, 2012c; Nielsen and Meyer, 2012; Sneider et al., 2015; Polcwiartek et al., 2016; Rohde et al., 2018a, 2020; Villasante-Tezanos et al., 2020) and 4) fatal outcomes in the registry.

1.3.3. Contributions from Finland

Supplementary Table S2 describes the Finish contributions to 1) agranulocytosis (Idänpään-Heikkilä et al., 1975; Lahdelma and Appelberg, 2012), 2) clozapine intoxications during pneumonia (Raaska et al., 2002), 3) pharmacoepidemiology (Lieslehto et al., 2022; Solmi et al., 2022), and 4) fatal outcomes in the registry.

1.3.4. Contributions from France

Supplementary Table S2 describes the French contributions to 1) TDM (Allorge et al., 2003), 2) pharmacoepidemiology (Peyrière et al., 2009; Verdoux and Pambrun, 2014; Verdoux et al., 2016) and 3) lack of description of fatal outcomes in discontinuation studies (Hiltgen et al., 2006; Levoyer et al., 2004).

1.3.5. Contributions from Ireland

Supplementary Table S2 shows that the Irish contribution is limited to discontinuation studies with no data on fatal outcomes (MacGillivray et al., 2003; Rowntree et al., 2020).

1.3.6. Contributions from Italy

Supplementary Table S2 describes the Italian contributions to 1) TDM studies focused on drug-drug interactions (DDIs) (Facciolà et al., 1998, 1999; Spina et al., 1998, 2000, 2001, 2006; Zoccali et al., 2003; Migliardi et al., 2007; Santoro et al., 2010), and 2) pharmacovigilance (Lambertenghi Deliliers, 2000; Bertoli et al., 2023).

1.3.7. Contributions from the Netherlands

Supplementary Table S2 describes the Dutch contributions as: 1) their guideline (Netherlands clozapine collaboration group, 2013), 2) TDM studies (Mookhoek and Loonen, 2004; Geers et al., 2017; Bogers

et al., 2023) and 3) pharmacoepidemiology studies (van de Vijver et al., 2002; van der Zalm et al., 2020).

1.3.8. Contributions from Norway

Supplementary Table S2 describes the Norwegian contributions as studies 1) from its registry studies (Gjerden et al., 2010; Skrede et al., 2015), and 2) on TDM (Castberg et al., 2009; Smith et al., 2021).

1.3.9. Contributions from Spain

Supplementary Table S2 describes the Spanish contributions through studies using: 1) TDM (Arrojo-Romero et al., 2022) and 2) pharmacovigilance (Pons et al., 2012; Lertxundi et al., 2015).

1.3.10. Contributions from Sweden

Supplementary Table S2 describes the Swedish contributions in 1) metabolism (Bertilsson et al., 1994), 2) TDM (Jerling et al., 1994), 3) pharmacovigilance (Hägg et al., 1998, 2000), and 4) fatal outcomes in its registry (Ringbäck Weitoft et al., 2014; Taipale et al., 2018).

1.3.11. Contributions from Switzerland

Clozapine was first approved in 1972 in Switzerland (and Austria). Supplementary Table S2 describes the Swiss contributions in 1) TDM (Bender and Eap, 1998; Zullino et al., 2002; Diaz et al., 2014), and 2) fatal outcomes (Pfeifer et al., 2020).

1.4. UK contributions and concerning data on clozapine pharmacovigilance

Supplementary Table S3 demonstrate that that UK discontinuation studies are best among Western European countries without registry (Baker and White, 2004; Taylor et al., 2009; Mustafa et al., 2015; Legge et al., 2016; Atkinson et al., 2007; Gee et al., 2018).

Supplementary Box S5 describes the data on mortality in clozapine-treated patients from 4 large cohort studies (Windfuhr et al., 2011; Hayes et al., 2015; Cho et al., 2019; Rose et al., 2020) and data on respiratory deaths from discontinuation studies. Then it describes the UK as a pioneering country in several aspects of clozapine pharmacovigilance including: 1) myocarditis (Committee on Safety of Medicines, 1993), 2) benign ethnic neutropenia (Rajagopal, 2005), and 3) pneumonia (Taylor et al., 2009) and infections in general (Mace et al., 2022).

Based only on physician reports to VigiBase, Montastruc et al. (2021) proposed clozapine as the fourth most frequently reported drug associated with fatal ADRs worldwide and the most lethal in Europeans and non-geriatric adults. The careful review of the UK data led to three shocking findings for the UK pharmacovigilance system (Supplementary Box S5): 1) a high annual fatal outcome count in UK clozapine-treated patients (Handley et al., 2022; UK Medicines and Healthcare Products Regulatory Agency, 2023), 2) UK reporting that accounted for more than half the fatal outcomes worldwide (De Las Cuevas et al., 2024), and 3) UK reporting that accounted for >90 % of European fatal outcomes (de Leon, 2022b).

Two possibly opposing hypotheses could explain the apparent discrepancy in reports of fatal outcomes in clozapine-treated patients in the UK versus other Western European countries: 1) fewer reported fatal outcomes in other Western European countries mainly reflects under-reporting by their drug agencies to VigiBase, and 2) the higher number of UK reports reflects higher real relative mortality. Obviously, both hypotheses may be partially correct and somehow complement each other, but the key question is whether reality aligns closer to hypothesis 1 or to hypothesis 2. These two hypotheses are explored in this VigiBase search comparing the UK with 11 other Western European countries.

2. Methods

2.1. VigiBase search

VigiBase is the World Health Organization (WHO) global pharmacovigilance database of reported potential ADRs of medicinal products. This study utilized VigiBase for an observational, retrospective analysis conducted on January 15, 2023. Supplementary Box S6 (Bachmann et al., 2017; Whiskey et al., 2021; de Leon, 2022b) provides further details.

2.2. Literature search

The first (CdlC) and the last (JdL) authors made several attempts using PubMed searches to develop Supplementary Table S2 for the 11 other countries and Supplementary Box S5 for the UK. The final version was developed after 12 different PubMed searches, one for each country. Supplementary Box S7 provides further details.

3. Results

3.1. Comparing the top 10 fatal outcomes from clozapine-related ADRs

Table 1 describes the top reporting countries in Western Europe as the UK with 29 % of fatal outcomes worldwide followed by Germany with 2 %, and the other 10 Western European countries reporting <1 % each. Non-specific "death" was the top worldwide ADR associated with fatal outcome in VigiBase at 46 %; in the UK it was associated with 33 % of fatal outcomes. In the other 11 countries, "death" was the first in fatal outcomes in 8 countries, ranging from 12 % to 77 %. "Pneumonia" was the second most frequent ADR at 8 % of fatal outcomes globally; in the UK it was also second at 12 %. In the other Western European countries, pneumonia was second in fatal outcomes in Ireland with 8 % (28/362) and in Finland with 14 % (6/43). In the other seven countries pneumonia ranked between 4th and 9th; in the two other countries it did not reach the top 10. "Myocardial infarct" was the third most frequent ADR at 5 % of fatal outcomes worldwide and was 6th in the UK at 4 %. In only 4 of the 11 Western European countries did myocardial infarct reach the top 10 in fatal outcomes.

Several categories of infections are associated with fatal outcomes and they can overlap. In the UK there were 1876 reports of ADRs associated with fatal outcomes in the context of infections but 1157 patients provided these 1876 reports (one can have >1 ADR report). These values mean that at least 24 % (1577/6576) of UK fatal outcomes in clozapine-treated patients were during infections. The percentage of fatal outcomes during infections was <10 % in 7 of the 11 Western European countries. Finland had 26 % (11/43), Ireland had 18 % (65/362), Germany 13 % (27/212) and the Netherlands 12 % (7/58) of fatal outcomes during infections. Pulmonary embolism was the 10th top cause in the world and ranged between 3rd and 10th in Western European countries.

3.2. Comparing the UK and other Western European countries after adjustments

The limited cross-sectional information on clozapine prescriptions from published articles allows the comparison of 9 other countries with the UK (Supplementary Table S3). Based on these estimations, three countries use clozapine more than the UK: Finland (2.7 times that of the UK), the Netherlands (1.5 times) and Germany (1.4 times). In six countries clozapine was less frequently prescribed than in UK: Sweden (0.9 times), Denmark (0.8 times), Norway and Spain (around 0.7 times), France and Italy (around 0.6 times). Assuming that these population and clozapine use estimations are correct, the 11 continental countries have considerably fewer fatal outcomes than the UK with corrected ratios ≤0.10, which means that they report ≤10 % of the UK fatal outcomes.

Table 1
Top ten most-reported clozapine-related ADRs worldwide and global fatal outcomes: the UK vs. 11 other Western European countries.

	Global		UK		IRE		GER		FRA		SWE		NET		DEN		FIN		SWI		NOR		ITA		SPA	
No. of fatal outcomes	22,956		6567		362		212		132		59		58		45		43		33		29		26		25	
% of fatal outcomes	100 %		29 %		2 %		1 %		<1 %		<1 %		<1 %		<1 %		<1 %		<1 %		<1 %		<1 %		<1 %	
Death	1st	46 % (10,551)	1st	33 % (2169)	1st	33 % (121)	1st	15 % (31)	3rd	12 % (16)	1st	56 % (33)	1st	50 % (29)	2nd	13 % (6)	1st	77 % (33)	1st	15 % (5	1st	31 % (9)			1st	12 % (3)
With no other ADRs		30 % (6808)		22 % (1420)		21 % (77)		6 % (13)		8 % (10)		5 % (3)		12 % (7)		11 % (5)		2 % (1)		9 % (3)		3 % (1)				4 % (1)
Pneumonia	2nd	8 % (1818)	2nd	12 % (793)	2nd	8 % (28)	8th	5 % (11)	6th	<1 % (1)			6th	5 % (3)	7th	2 % (1)	2nd	14 % (6)	9th	3 % (1)	6th	3 % (1)	4th	4 % (1)		
Myocardial infarction	3rd	5 % (1189)	6rd	4 % (284)	5th	6 % (21)		3 % (6)			6th	<1 % (3)			8th	2 % (1)					3rd	7 % (2)				
Cardiac arrest	4th	4 % (919)	9th	4 % (237)	3rd	7 % (25)	5th	9 % (19)	4th	5 % (6)	7th	<1 % (3)	2nd	9 % (5)	1st	16 % (7)	5th	2 % (1)	2nd	15 % (5)	4th	7 % (2)	3rd	7 % (2)	6th	4 % (1)
Completed suicide	5th	3 % (716)			7th	5 % (19)	6th	7 % (14)	7th	<1 % (1)					9th	2 % (1)			4th	6 % (2)	10th	3 % (1)	1st	19 % (5)	2nd	8 % (2)
Sudden death	6th	3 % (633)	8th	4 % (254)	4th	6 % (22)	2nd	14 % (30)	1st	15 % (20)	2nd	20 % (12)	3rd	7 % (4)	3rd	13 % (6)	6th	2 % (1)	3th	9 % (3)	2nd	24 % (7)	2nd	19 % (5)	3rd	8 % (2)
Neutrophil count increased	7th	3 % (618)	3th	7 % (459)	8th	4 % (16)																				
White blood cell counts increased	8th	2 % (574)	4th	7 % (443)	6th	6 % (20)		<1 % (1)																		
Malignant lung neoplasm	9th	2 % (538)			9th	4 % (15)																				
Pulmonary embolism	10th	2 % (512)	10th	3 % (222)	10th	2 % (8)	10th	4 % (9)	5th	2 % (2)	3rd	17 % (10)	7th	3 % (2)	4th	7 % (3)	7th	2 % (1)	5th	6 % (2)	5th	7 % (2)	5th	4 % (1)	7th	4 % (1)
Associated with infections[a]		4745		1876		102		29		8		3		9		3		11		3		1		2		2
1 ADR associated with infection[b]		3764 16 %		1577 24 %		65 18 %		27 13 %		8 6 %		3 5 %		7 12 %		2 4 %		11 26 %		3 9 %		1 3 %		2 8 %		2 8 %

ADR: adverse drug reaction; CLO: clozapine; GER: Germany; FRA: France; DEN: Denmark; FIN: Finland; IRE: Ireland (Republic of Ireland not including Northern Ireland which is included in the UK reporting); ITA: Italy; NET: Netherlands; NOR: Norway; SPA: Spain; SWE: Sweden; SWI: Switzerland; UK: United Kingdom.

[a] We added all ADRs potentially associated with infections including "pneumonia", "neutrophil count increased", "white blood cell counts increased", "sepsis", "neutrophilia", "chronic obstructive pulmonary disease", "lower respiratory tract infection" and "aspiration pneumonia". The problem with this addition is that a patient may have more than 1 ADR reported (e.g., a patient can have "pneumonia" and "lower respiratory tract infection").

[b] This category corresponds to individual fatal outcomes which have at least one of the ADRs listed in footnote b. There may be a small underreport because these categories include the top 25 most frequent ADRs reported. For example, fatal outcomes associated with Covid-19 are not listed here.

In the UK almost 11 % of clozapine-related ADRs are associated with fatal outcomes; in the 11 other countries the range is almost 2 % in Spain to 10 % in Denmark. This was in an index of seriousness of clozapine-related ADRs reported; there were 3 continental countries around 10 % (Sweden, Denmark and Norway) that compared with the UK, which had ratios close to 1 (of ≥0.90 or 90 %), indicating that the seriousness of their clozapine-related ADRs was almost as high as in UK.

The UK appears to be the world's leader in reporting fatal outcomes in clozapine-treated patients during infection (De las Cuevas et al., 2024). Other Western European countries had very low ratios of percentage of infections within fatal outcomes in clozapine-treated patients when compared with the UK, <0.50, except for the Netherlands with 0.5, Ireland with 0.75 and Finland with 1.08.

Assuming that population estimations are correct, 3 of the 11 continental countries report more ADRs of all drugs than the UK: Sweden, the Netherlands and Denmark (ratios >1 when compared with the UK), two slightly fewer than the UK: Ireland and Norway (around 0.9) and the remaining considerably fewer than the UK. In the UK clozapine accounts for around 3.5 % of all drug-related ADRs and two continental countries had similar percentages: Ireland (4.1 %) and Finland (2.1 %). In the remaining 9 countries, clozapine accounted for many fewer than 1 % of ADRs from all drugs.

4. Discussion

4.1. Underreporting

Spontaneous reporting systems as VigiBase face a well-known limitation, underreporting of ADRs. Supplementary Box S8 describes the major relevant issues for underreporting (Inman, 1976; Hazell and Shakir, 2006; Lopez-Gonzalez et al., 2009; Varallo et al., 2014; Sandberg et al., 2020).

4.1.1. Underreporting in Germany

Table 1 indicates that there were only 212 German reports to VigiBase with fatal outcomes. Compared with the UK, very few pneumonia and myocardial infarct cases are reported to VigiBase from Germany. Based on our estimations (Supplementary Table S4) that Germany has a larger population than the UK and higher use, there is huge underreporting of fatal outcomes; 212 were observed and 11,103 fatal outcomes were expected, based on UK data. The correction for current population may not represent well the longitudinal population exposed to clozapine reporting to VigiBase since East Germany was added only in 1990. However, clozapine has been marketed in the UK only since 1990, while clozapine has been used in West Germany for many more years, since 1974.

There are fewer reports of ADRs from Germany (1,497,775) than from the UK (1,804,997), implying German underreporting of all drugs in general (Supplementary Table S4). German groups have extensively published on the better recognized clozapine-related ADRs (Supplementary Table S2) but this information has not been reported to VigiBase. Moreover, although many reports of pneumonia and myocardial infarct in clozapine-treated patients are sent from the UK and other English-speaking countries (De las Cuevas et al., 2024), it appears that German reports in these areas are not sent to VigiBase. An old German study from 1995 in psychiatric hospitals indicated that myocardial infarct and pneumonia were the major causes of death in patients taking antipsychotics including clozapine (Hewer et al., 1995). It is likely that these two categories, myocardial infarcts and pneumonia, continued to be very frequent causes of death in clozapine in German patients but they were not reported to VigiBase. There is great need to improve the reporting on clozapine pharmacovigilance sent to VigiBase from Germany.

4.1.2. Underreporting in Denmark

Table 1 indicates that VigiBase received only 45 fatal outcomes from Danish clozapine outcomes with "cardiac arrest" as the top cause of fatal outcomes and "death" as second. Based on our estimations (Supplementary Table S4), there is huge underreporting of fatal outcomes; instead of 45, from the UK data 469 fatal outcomes would be expected. Supplementary Table S4 also suggests that Denmark reports more all drug-related ADRs than the UK (ratio = 1.2), but underreports clozapine-related ADRs in general, since in Denmark clozapine ADR reports account for 0.2 % of all drugs vs 3.5 % in the UK. In spite of pioneering reports on myocarditis and the recent lack of fatal outcomes found in the Danish registry, there is great need to improve the clozapine pharmacovigilance reports sent from Denmark to VigiBase.

4.1.3. Underreporting in Finland

VigiBase received only 43 fatal outcomes from Finland (Table 1), but the major top causes of fatal outcomes were similar to the UK. Based on our estimations (Supplementary Table S4), there is huge underreporting of fatal outcomes, instead of 43 from the UK data 1415 fatal outcomes would be expected. Supplementary Table S4 also suggests not only underreporting of clozapine-related fatal outcomes, but of all drug-related ADRs since, after correcting for population size, Finland reported a little more than half the UK number of clozapine-related fatal outcomes (ratio = 0.58). In spite of pioneering reports on agranulocytosis and clozapine intoxication during pneumonia, there is great need to improve the clozapine pharmacovigilance reports sent from Finland to VigiBase.

4.1.4. Underreporting in France

Table 1 indicates that French reports are relatively non-specific with "sudden death" as the top ADR associated with fatal outcomes. Based on our estimations (Supplementary Table S4) that France has a population similar to the UK (ratio = 0.96) and lower use (ratio = 0.62), there is huge underreporting of fatal outcomes; 132 fatal outcomes were observed, but 3921 were expected based on UK data. It is possible that fatal outcomes associated with infections may also be underreported, being 5 % in France vs. 24 % in the UK. Table 2 also suggests France not only underreports clozapine-related fatal outcomes but underreports clozapine-related ADRs in general, since in France clozapine ADR reports account for 0.2 % of all drugs vs. 3.5 % in the UK. Based on the limited published information (Supplementary Table S2) and on our results summarized in Supplementary Table S4, there is great need to improve French pharmacovigilance and clozapine reports sent to VigiBase.

4.1.5. Underreporting in Ireland

Supplementary Table S4 indicates that we could not estimate clozapine use in Ireland; therefore, clozapine comparisons with the UK and other Western European countries are not possible. Table 1 indicates that the top 10 clozapine-related ADRs are very similar in Ireland to those of the UK, including that pneumonia accounts for 8 % of fatal outcomes in Ireland (vs. 12 % in the UK) and that all infections account for 18 % (vs. 24 % in the UK). In summary, due to lack of published information on clozapine use it is difficult to estimate the underreporting of clozapine-related ADRs and fatal outcomes in Ireland but it appears that may be similar or slightly higher than the underreporting of clozapine-related fatal outcomes in the UK.

4.1.6. Underreporting in Italy

Table 1 indicates that VigiBase received only 26 fatal outcomes from Italy with "completed suicide" and "sudden death" sharing the top cause of fatal outcomes. Based on our estimations (Supplementary Table S4), there is an underreporting of fatal outcomes; instead of 26, 3532 fatal outcomes would be expected based on the UK data. Supplementary Table S4 also suggests that for all drug-related ADRs the number of reports is approximately half that of the UK (ratio of 0.52); thus, clozapine-related ADRs account for much <0.1 % versus 3.5 % in the UK. In spite of pioneering TDM studies on DDIs (Supplementary Table S2) there is

Table 2
Comparison of pharmacovigilance of CLO ADRs and CLO fatal outcomes: the UK vs. 11 other Western European countries.

Country	Published Information			VigiBase		
	National registries	Other large cohorts	Pharmacovigilance	ADRs: UK comparison	Top relevant categories	Conclusion
United Kingdom	No	3 cohorts ↓ mortality on CLO	1st drug agency to focus on myocarditis and BEN 1st pneumonia study	100 %	1 Death 2 Pneumonia 3 ↑ neutrophils	Top reporter of pneumonia and infections (24 % of fatal outcomes in CLO patients). Compared with US: MI underreport
Germany	No	No	4 ADR studies	2 %	1 Death 2 Sudden death	High use of CLO Major underreport compared with UK Past relevant pharmacovigilance articles
Denmark	Yes CLO: 3 %[a] person-years	No	1st myocarditis case 9 studies from registry	10 %	1 Cardiac arrest 2 Death 3 Sudden death	Major underreport compared with UK Registry: ↓ mortality on CLO ↑ mortality CLO 1st year No deaths by myocarditis 0.3 % deaths by pneumonia during titrations
France	No	No	1 ADR study	3 %	1 Death 2 Pneumonia 3 Cardiac arrest	Major underreport compared with UK
Finland	Yes CLO: 10 %[b] person-years	No	1st agranulocytosis cohort 3 other studies from registry	3 %	1 Death 2 Pneumonia	Very high use of CLO Major underreport compared with UK Infections explain 26 % of reported fatal outcomes in CLO patients Registry: ↓ mortality on CLO patients
Ireland	No	No	No	No data on CLO use	1 Death 2 Pneumonia 3 Cardiac arrest	Major underreport compared with UK Infections explain 18 % of fatal outcomes in CLO patients
Italy	No	No	2 ADR studies	<1 %	1 Completed suicide 2 Sudden death 3 Cardiac arrest	Major underreport compared with UK
The Netherlands	No	No	2 ADR studies	2 %	1 Death 2 Cardiac arrest 3 Sudden death	High use of CLO Major underreport compared with UK
Norway	No study on fatal outcomes	No	1 study from registry	8 %	1 Death 2 Sudden death 3 MI	Major underreport compared with UK Registry: no change in mortality in CLO patients (study had other focus).
Spain	No	No	1 ADR study	<1 %	1 Death 2 Completed suicide 3 Sudden death	Major underreport compared with UK
Sweden	Yes CLO: <1 %[c] person-years	No	2 ADR studies	7 %	1 Death 2 Sudden death	Major underreport compared with UK Registry: ↓ mortality on CLO patients with TRS
Switzerland	No	No	No	No data on CLO use	1 Death 2 Cardiac arrest 3 Sudden death	Major underreport compared with UK

ADR: adverse drug reaction; BEN: benign ethnic neutropenia; CLO: clozapine; MI: myocardial infarct; UK: United Kingdom; US: United States.

[a] van der Zalm et al. (2020) described 22,110 patients with a first diagnosis of non-affective psychosis with 195,461 person-years. Clozapine accounted for 3.0 % of all person-years (5845/195,461 = 0.0299).

[b] Tiihonen et al. (2009) described 66,881 patients with schizophrenia and 328,130 person-years. Clozapine accounted for approximately 10 % of all person-years (32,000/328,130 = 0.097).

[c] Taipale et al. (2018) described 29,823 with schizophrenia and 171,244 person-years. Clozapine accounted for <1 % of all person-years (14,460/171,244 = 0.0085).

great need to improve Italian pharmacovigilance and clozapine reports to VigiBase.

4.1.7. Underreporting in the Netherlands

Table 1 indicates that Dutch reports are relatively non-specific with "death" as the top ADR and "cardiac arrest" as second. Based on our estimations (Supplementary Table S4), the Netherlands hugely underreports fatal outcomes; 58 were observed and 2539 were expected based on the UK data. Supplementary Table S4 also suggests that the Netherlands not only underreports clozapine-related fatal outcomes but underreports clozapine-related ADRs in general, since in the Netherlands clozapine ADR reports account for 0.1 % of all drugs vs. 3.5 % in the UK. In spite of the great contribution of the Dutch clozapine guideline bringing attention to clozapine-related ADRs, there is great need to improve Dutch pharmacovigilance and clozapine reports to VigiBase.

4.1.8. Underreporting in Norway

Table 1 indicates that VigiBase received only 29 fatal outcomes from Norway with death as the first cause and sudden death as the second. Based on our estimations (Supplementary Table S4), there is underreporting of fatal outcomes, instead of 29, 375 fatal outcomes would be expected based on the UK data. Supplementary Table S4 also suggests all their drug-related ADRs are similar in Norway to the UK (ratio = 0.95); thus, clozapine-related ADRs account for much less, 0.2 % versus 3.5 % in the UK. In spite of data in the national registry on antipsychotic use and pioneering use of TDM for nonadherence (Supplementary Table S2) there is great need to improve clozapine reports from Norway to VigiBase.

4.1.9. Underreporting in Spain

Table 1 indicates that VigiBase received only 25 fatal outcomes from Spain with "death" as the top cause of fatal outcomes. Based on our estimations (Supplementary Table S4), there is underreporting of fatal outcomes; instead of 25, 3208 fatal outcomes would be expected based on the UK data. Supplementary Table S4 also suggests that for all drug-related ADRs the number of reports is approximately half that of the UK (ratio of 0.44); thus, clozapine-related ADRs account for much less, 0.3 % versus 3.5 % in the UK. Based on the limited published information (Supplementary Table S2) and on Supplementary Table S4, there is great need to improve Spanish pharmacovigilance and clozapine reports to VigiBase.

4.1.10. Underreporting in Sweden

Table 1 indicates that VigiBase received only 59 clozapine-related fatal outcomes from Sweden with death as the first cause and sudden death as the second. Pulmonary embolism is third, which is not surprising since the Swedes were pioneers in associating clozapine with venous thromboembolism (Hägg et al., 2000). Based on our estimations (Supplementary Table S4), there is huge underreporting of fatal outcomes in Sweden; instead of 59, based on extrapolation from the UK data 855 fatal outcomes would be expected. Supplementary Table S4 also suggests that all drug-related ADRs are more often reported than in the UK (Swedish ratio = 1.24); thus, clozapine-related ADRs account for 0.2 % versus 3.5 % in the UK. In spite of pioneering published reports on aspiration, diabetes mellitus and venous thromboembolism (Supplementary Table S2) there is great need to improve clozapine reports from Sweden to VigiBase.

4.1.11. Underreporting in Switzerland

Supplementary Table S4 indicates that we could not estimate clozapine use in Switzerland; therefore, clozapine comparisons with the UK and other Western European countries are not possible. Table 1 indicates that the top clozapine-related ADRs with similar numbers were death and cardiac arrest. Supplementary Table S4 also suggests regarding all drug-related ADRs that Switzerland underreports, when compared with the UK (ratio of 0.7); thus, clozapine-related ADRs account for much less, 0.5 % versus 3.5 % in the UK. In summary, due to lack of published information on clozapine use it is difficult to estimate the underreporting of clozapine-related ADRs and fatal outcomes in Switzerland but there is lack of attention to specific fatal outcomes in clozapine-treated patients. Based on the published information (Supplementary Table S2) and on Supplementary Table S4, there is great need to improve Swiss pharmacovigilance and clozapine reports to VigiBase.

4.1.12. Underreporting in the UK

Compared with the other 11 countries, the UK overreports but we are convinced that there is some level of underreporting and not all clozapine-related ADRs and their associated fatal outcomes are reported to the UK pharmacovigilance agency. This agency is called the Medicines and Healthcare products Regulatory Agency (MHRA) and submits its data to VigiBase. The MHRA provides a webpage with updated general summaries of clozapine reports including fatal outcomes. The limited data provided by the MHRA webpage does not provide any data on relevant confounding variables such as psychiatric diagnosis, and co-medications included in individual reports (Yellow Cards) are incomplete or absent. The MHRA webpage prioritizes only one reported ADR associated with each fatal outcome. Thus, Supplementary Table S5 includes 16 non-overlapping terms, but on average UK patients have 3.2 ADRs in VigiBase (De las Cuevas et al., 2024). This fact contributes to minor underreporting when comparing UK MHRA data (UK Medicines and Healthcare Products Regulatory Agency, 2023) to the UK data on VigiBase.

As the UK has no national registry like the Scandinavians, we do not know how many of the fatal outcomes in clozapine-treated patients have not been reported to the UK MHRA. There is no way to estimate the underreporting of fatal outcomes of clozapine-treated patients who do not have a Yellow Card submitted to the UK MHRA, but there is general agreement that there is significant underreporting of all drug-related ADRs in the UK (Chaplin, 2006; McLernon et al., 2010).

One of the major differences between UK and other Western European countries is that the UK has a formal registry of clozapine patient and the other countries do not. This fact surely contributes to differences between the UK and these other countries; on the other hand, the registries of clozapine-treated patients may work differently in different countries (Supplementary Box S9, De Las Cuevas et al., 2022a, 2024).

4.2. Does the higher number of UK fatal outcomes really reflect higher relative mortality?

The prior section has emphasized the underreporting of other countries to VigiBase when compared with the UK, particularly during infections. Currently we cannot explore the hypothesis that the UK may have higher real mortality in clozapine-treated patients. When other Western European countries reach the same level of thorough reporting to VigiBase as the UK, we will be able to explore that hypothesis. The UK had an important number of deaths in clozapine-treated patients associated with pneumonia and other infections and this appears to us to be explained by very good reporting and not be due to a real increase in fatal outcomes in infections, but that latter hypothesis needs to be considered, too. Future studies need to provide better information from other Western European countries on fatal outcomes in clozapine-treated patients during infections. Studies from the Danish and Finish registries need to explore the contribution of infections to the fatal outcomes of clozapine-treated patients in their countries. Moreover, there is a need for better understanding of the different reporting styles in different countries (Supplementary Box S10; Wakao et al., 2019). Assuming that our correction for population size and clozapine use is accurate, the UK is the leader in reporting both clozapine-related ADRs and clozapine-related fatal outcomes. Regarding fatal outcomes, a concerning level of underreporting is present in the other Western countries which rank from <1 % to 10 % of the UK's fatal outcomes. In summary,

different Western European countries have different pharmacovigilance reporting styles of clozapine-related ADRs, which may or may not include important published contributions, but they appear to consistently underreport to VigiBase when compared with the UK (Table 2).

4.3. Clozapine-related ADRs associated with fatal outcomes

The relationship between clozapine and fatal outcomes varies according to the ADRs from strong for pneumonia and infections (Supplementary Box 11; de Leon and Diaz, 2003; Clark et al., 2018; Ponsford et al., 2018; Cicala et al., 2019; Ruan et al., 2020; UK Medicines and Healthcare Products Regulatory Agency, 2020; Schoretsanitis et al., 2021b; Villasante-Tezanos et al., 2020; Arrojo-Romero et al., 2022; Veerman et al., 2022; De Las Cuevas et al., 2023; HLS Therapeutics, Inc., 2023; Kang et al., 2024a, 2024b), to possible for pulmonary embolism (Supplementary Box S12; Malý et al., 2008; Schmidinger and Hofer, 2014; Poudyal and Lohani, 2019; Gligorijević et al., 2020; Manoubi et al., 2022) and to unlikely for myocardial infarct (Supplementary Box S13; Miklozek et al., 1988; Kelly et al., 2010; Stolz et al., 2019; Rotella et al., 2020; Papola et al., 2019; Yang et al., 2021).

4.4. Comment on the greater number of patients of Asian ancestry in the UK

The most important difference between the UK and 11 other countries was related to the fatal outcomes associated with infections. The UK reports to VigiBase indicated that 24 % of fatal outcomes in clozapine-treated patients may be associated with pneumonia and other infections. Only Ireland, with 18 %, and Finland, with 26 %, appear to pay attention to infections as a cause of clozapine-related fatal outcomes. The other 9 Western European countries appear to ignore infections as a cause of fatal outcomes in clozapine-treated patients.

One possible reason for the UK's pioneering role in demonstrating the association between clozapine and infections is the recommendation of the UK's pharmacovigilance agency in 2020 that clozapine levels be monitored during infections, compared with the recent vague recommendation from the FDA in May 2023 (Supplementary Box S11). On the other hand, it is possible that the greater number of reports of fatal outcomes of UK clozapine-treated patients during infection may be real and partly explained by some specific factor in the UK. One possible factor may be the high number of patients of Asian ancestry receiving clozapine in the UK. Patients of Asian ancestry need lower clozapine doses (de Leon et al., 2020c; Reeves et al., 2023) and the UK clozapine guidelines and review articles do not reflect that fact (de Leon, 2023). Future studies of fatal outcomes in UK clozapine-treated patients need to pay attention to the ancestry of the patients and explore whether or not individuals of Asian ancestry are overrepresented in UK clozapine-treated patients dying from infection (de Leon, 2023). One can propose that current UK clozapine doses are too high for patients of Asian ancestry. Clozapine doses that are too high, especially during titration, increases the risk of aspiration pneumonia, pneumonia and other infections. In addition, the higher plasma concentration may lead to increased risk of fatal outcomes because, on average, even before an infection occurs Asian patients have plasma concentration concentrations that are too high, and these already elevated clozapine concentrations are then further increased by the cytokines released during infection that inhibit clozapine metabolism.

4.5. Limitations

Supplementary Box S8 describes the limitation of the VigiBase pharmacovigilance data. This study did not include data from Russia since there were no clozapine reports to VigiBase despite clozapine's wide use in Russia (Kirilochev et al., 2024) or from other Eastern European countries which contributed an extremely low number of reports (Sagud et al., 2024). Similarly, other smaller Western European countries had such limited numbers that we did not include them in Table 1.

Supplementary Table S4 is limited by used of a cross-sectional estimation of the current population and of clozapine use based in published articles (Bachmann et al., 2017; Whiskey et al., 2021) instead of the accumulated population and use since clozapine was introduced in each country which are not available. Based in estimations we used, Finland has 3.2 times more use of clozapine than Denmark (189.2/58.3 = 3.2) and 3.1 times more than Sweden (189.2/61.0 = 3.1). Based in the cohorts of the Scandinavian registries (Supplementary Table S1), Finland has 3.2 times more clozapine use than Denmark (0.097/0.0299) but 11.4 times more use than Sweden (0.097/0.0085 = 11.4).

Our comparison on discrepancy between the UK and other Western European countries used VigiBase data that is received from various national pharmacovigilance agencies. As the UK pharmacovigilance agency provides a comprehensive summary of clozapine ADRs on their webpage (Supplementary Table S4), we are pretty sure that the data analyzed by us is very similar to what is reported on the UK MHRA web page. The other national drug agency does not provide a summary of clozapine ADRs so we cannot compare the data they have sent to VigiBase with any other source.

Supplementary Box S14 (Tiihonen et al., 2009; Bachmann et al., 2017; Taipale et al., 2020; Takeuchi et al., 2020; Verdoux and Quiles, 2020; De Las Cuevas et al., 2021; van der Zalm et al., 2021; de Leon et al., 2022c; Lieslehto et al., 2022; de Leon, 2023; Chen et al., 2024; Grover and Naskar, 2024; Ruan et al., 2024; Verdoux et al., 2024a, 2024b) elaborates on the possibility that clozapine saves lives. If this is true, the major problem with any pharmacovigilance study is that it does not estimate the lives saved by clozapine but only allows the estimation of fatal outcomes in clozapine-treated patients.

5. Conclusions

Assuming that our corrections for country-related population size and clozapine use are approximately correct, other Western European countries have majorly underreported of clozapine-related fatal outcomes to VigiBase when compared with UK. These 11 countries reported only between <1 % to 10 % of UK fatal outcomes indicating that published report for clozapine use had to be massively wrong for explaining these underreports. The UK excelled in reports on infections as 24 % of fatal outcomes in UK clozapine-treated patients were associated with pneumonia and other infections. Only Ireland, with 18 %, and Finland, with 26 %, paid significant attention to infections as a cause of clozapine-related fatal outcomes. The other 9 Western European countries appear to mostly ignore infections as a potential cause of fatal outcomes in their reporting of clozapine-treated patients to VigiBase. The UK's pioneering role on the association between clozapine and infections is further demonstrated by the UK pharmacovigilance agency recommending in 2020 that clozapine levels be monitored during infections.

Various Western European countries consistently underreport to VigiBase when compared with the UK, but may have different reporting and publishing styles for clozapine-related ADRs and fatal outcomes. Their contributions include bringing attention to new ADRs, such as clozapine-induced inflammation (Germany), agranulocytosis (Finland) and myocarditis (Denmark); more importantly, the Scandinavian registries indicate that clozapine-treated patients may have a lower mortality rate than those taking other oral antipsychotic or no antipsychotics (Table 2).

Future studies need to provide better information from Western European countries other than the UK on clozapine-related fatal outcomes. Studies from the Danish, Finish and Swedish registries need to explore the contribution of infections and other clozapine-related ADRs to the fatal outcomes of the clozapine-treated patients in their countries. Pharmacovigilance studies only describe fatal outcomes in clozapine-treated patients but cannot estimate or correct for the lives saved by

increased clozapine use. Pneumonia and other infections may be associated with TRS with some possible additional contributions from clozapine. Our study can also promote saving lives by encouraging better management of infections, including pneumonia, in clozapine-treated patients.

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CRediT authorship contribution statement

Carlos De las Cuevas: Conceptualization, Data curation, Formal analysis, Investigation, Methodology, Project administration, Supervision, Writing – original draft, Writing – review & editing. **Emilio J. Sanz:** Methodology, Resources, Writing – review & editing. **Jason A. Gross:** Writing – review & editing. **Christoph U. Correll:** Writing – review & editing. **Hélène Verdoux:** Writing – review & editing. **John Lally:** Writing – review & editing. **Renato de Filippis:** Writing – review & editing. **Peter F.J. Schulte:** Writing – review & editing. **Espen Molden:** Writing – review & editing. **Manuel Arrojo-Romero:** Writing – review & editing. **Adrian D. Bostrom:** Writing – review & editing. **Georgios Schoretsanitis:** Writing – review & editing. **Emilio Fernandez-Egea:** Writing – review & editing. **Jose de Leon:** Conceptualization, Formal analysis, Investigation, Methodology, Writing – original draft, Writing – review & editing.

Declaration of competing interest

In the last 3 years, JAG reports he is Vice President Scientific Affairs of HLS Therapeutics, Toronto, Canada which is the manufacturer of CLOZARIL in the USA and Canada; CUC has been a consultant and/or advisor to or has received honoraria from: AbbVie, Acadia, Alkermes, Allergan, Angelini, Aristo, Boehringer-Ingelheim, Cardio Diagnostics, Cerevel, CNX Therapeutics, Compass Pathways, Darnitsa, Denovo, Gedeon Richter, Hikma, Holmusk, IntraCellular Therapies, Janssen/J&J, Karuna, LB Pharma, Lundbeck, MedAvante-ProPhase, MedInCell, Merck, Mindpax, Mitsubishi Tanabe Pharma, Mylan, Neurocrine, Newron, Noven, Novo Nordisk, Otsuka, Pharmabrain, PPD Biotech, Recordati, Relmada, Reviva, Rovi, Seqirus, SK Life Science, Sunovion, Sun Pharma, Supernus, Takeda, Teva, and Viatris. He provided expert testimony for Janssen and Otsuka. He served on a Data Safety Monitoring Board for Compass Pathways, Denovo, Lundbeck, Relmada, Reviva, Rovi, Supernus, and Teva. He has received grant support from Janssen and Takeda. He received royalties from UpToDate and is also a stock option holder of Cardio Diagnostics, Mindpax, LB Pharma and Quantic; RdF has received speaker fees from Janssen Pharmaceutica and travel support from Janssen Pharmaceutica and ROVI; GS has received speaker/consultation fees from Dexcel Pharma, HLS Therapeutics and Thermo Fisher. In the last 3 years, the remaining authors report no conflicts of interest.

Data availability

VigiBase does not allow the distribution of their file.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.schres.2023.11.010.

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