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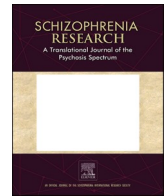
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Revealing the reporting disparity: VigiBase highlights underreporting of clozapine in other Western European countries compared to the UK

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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 “clozapinobia” (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; Ertugrul 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 Weitof 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) (Facciola 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 Delilieri, 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 Weitoff 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 (CdIC) 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	46 % 1 st (10,551)	33 % 1 st (2169)	33 % 1 st (121)	15 % 1 st (31)	12 % 3 rd (16)	56 % 1 st (33)	50 % 1 st (29)	13 % 2 nd (6)	77 % 1 st (33)	15 % (5) 1 st	31 % 1 st (9)		12 % 1 st (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	2 nd 8 % (1818)	2 nd 12 % (793)	2 nd 8 % (28)	8 th 5 % (11)	6 th <1 % (1)		6 th 5 % (3)	7 th 2 % (1)	2 nd 14 % (6)	9 th 3 % (1)	6 th 3 % (1)	4 th 4 % (1)	
Myocardial infarction	3 rd 5 % (1189)	6 rd 4 % (284)	5 th 6 % (21)	3 % (6)		6 th <1 % (3)		8 th 2 % (1)			3 rd 7 % (2)		
Cardiac arrest	4 th 4 % (919)	9 th 4 % (237)	3 rd 7 % (25)	5 th 9 % (19)	4 th 5 % (6)	7 th <1 % (3)	2 nd 9 % (5)	1 st 16 % (7)	5 th 2 % (1)	2 nd 15 % (5)	4 th 7 % (2)	3 rd 7 % (2)	6 th 4 % (1)
Completed suicide	5 th 3 % (716)		7 th 5 % (19)	6 th 7 % (14)	7 th <1 % (1)			9 th 2 % (1)		4 th 6 % (2)	10 th 3 % (1)	1 st 19 % (5)	2 nd 8 % (2)
Sudden death	6 th 3 % (633)	8 th 4 % (254)	4 th 6 % (22)	2 nd 14 % (30)	1 st 15 % (20)	2 nd 20 % (12)	3 rd 7 % (4)	3 rd 13 % (6)	6 th 2 % (1)	3 th 9 % (3)	2 nd 24 % (7)	2 nd 19 % (5)	3 rd 8 % (2)
Neutrophil count increased	7 th 3 % (618)	3 th 7 % (459)	8 th 4 % (16)										
White blood cell counts increased	8 th 2 % (574)	4 th 7 % (443)	6 th 6 % (20)	<1 % (1)									
Malignant lung neoplasm	9 th 2 % (538)		9 th 4 % (15)										
Pulmonary embolism	10 th 2 % (512)	10 th 3 % (222)	10 th 2 % (8)	10 th 4 % (9)	5 th 2 % (2)	3 rd 17 % (10)	7 th 3 % (2)	4 th 7 % (3)	7 th 2 % (1)	5 th 6 % (2)	5 th 7 % (2)	5 th 4 % (1)	7 th 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
Denmark	Yes CLO: 3 % ^a person-years	No	1st myocarditis case 9 studies from registry	10 %	1 Cardiac arrest 2 Death 3 Sudden death	Past relevant pharmacovigilance articles 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
Ireland	No	No	No	No data on CLO use	1 Death 2 Pneumonia 3 Cardiac arrest	Registry: ↓ mortality on CLO patients 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 S11; 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 ($0.097/0.0299 = 3.2$) 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 webpage. 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, Finnish 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 Viatrix. 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 Dexel 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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is drug-related is not the same in all cases. However, the opinions and conclusions of this study are not necessarily those of the various centers or of the WHO.

Appendix A. Supplementary data

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

References

- Allorge, D., Chevalier, D., Lo-Guidice, J.M., Cauffiez, C., Suard, F., Baumann, P., Eap, C. B., Broly, F., 2003. Identification of a novel splice-site mutation in the CYP1A2 gene. *Br. J. Clin. Pharmacol.* 56, 341–344. <https://doi.org/10.1046/j.1365-2125.2003.01858.x>.
- Anderman, B., Griffith, R.W., 1997. Clozapine-induced agranulocytosis: a situation report up to August 1976. *Eur. J. Clin. Pharmacol.* 11, 199–201. <https://doi.org/10.1007/BF00606410>.
- Arrojo-Romero, M., Codesido-Barcala, M.R., de Leon, J., 2022. A Covid-19 outbreak in a Spanish long-term psychiatric hospital led to infections in 6 clozapine-treated patients: elevations in their plasma clozapine levels. *Rev. Psiquiatr. Salud Ment. (Engl Ed.)* 15, 290–292. <https://doi.org/10.1016/j.rpsmen.2022.06.010>.
- Atkinson, J.M., Douglas-Hall, P., Fischetti, C., Sparshatt, A., Taylor, D.M., 2007. Outcome following clozapine discontinuation: a retrospective analysis. *J. Clin. Psychiatry* 68, 1027–1030. <https://doi.org/10.4088/jcp.v68n0708>.
- Bachmann, C.J., Aagaard, L., Bernardo, M., Brandt, L., Cartabia, M., Clavenna, A., Coma Fusté, A., Furu, K., Garuoliené, K., Hoffmann, F., Hollingworth, S., Huybrechts, K.F., Kalverdijk, L.J., Kawakami, K., Kieler, H., Kinoshita, T., López, S.C., Machado-Alba, J.E., Machado-Duque, M.E., Mahesri, M., Nishtala, P.S., Piovani, D., Reutfors, J., Saastamoinen, L.K., Sato, I., Schuiling-Veninga, C.C.M., Shyu, Y.C., Siskind, D., Skurtveit, S., Verdoux, H., Wang, L.J., Zara Yahni, C., Zoëga, H., Taylor, 2017. International trends in clozapine use: a study in 17 countries. *Acta Psychiatr. Scand.* 136, 37–51. <https://doi.org/10.1111/acps.12742V>.
- Baker, M., White, T., 2004. Life after clozapine. *Med. Sci. Law* 44, 217–221. <https://doi.org/10.1258/rsmmsl.44.3.217>.
- Baumann, P., Hiemke, C., Ulrich, S., Eckermann, G., Gaertner, I., Gerlach, M., Kuss, H.J., Laux, G., Müller-Oerlinghausen, B., Rao, M.L., Riederer, P., Zernig, G., 2004. Arbeitsge-meinschaft für neuropsychopharmakologie und pharmakopsychiatrie. The AGNP-TDM expert group consensus guidelines: therapeutic drug monitoring in psychiatry. *Pharmacopsychiatry* 37, 243–265. <https://doi.org/10.1055/s-2004-832687>.
- Bender, S., Eap, C.B., 1998. Very high cytochrome P4501A2 activity and nonresponse to clozapine. *Arch. Gen. Psychiatry* 55 (11), 1048–1050. <https://doi.org/10.1001/archpsyc.55.11.1048>.
- Bender, S., Grohmann, R., Engel, R.R., Degner, D., Dittmann-Balcar, A., Rütter, E., 2004. Severe adverse drug reactions in psychiatric inpatients treated with neuroleptics. *Pharmacopsychiatry* 37 (Suppl. 1), S46–S53. <https://doi.org/10.1055/s-2004-815510>.
- Bertilsson, L., Carrillo, J.A., Dahl, M.L., Llerena, A., Alm, C., Bondesson, U., Lindström, L., Rodríguez de la Rubia, I., Ramos, S., Benitez, J., 1994. Clozapine disposition covaries with CYP1A2 activity determined by a caffeine test. *Br. J. Clin. Pharmacol.* 38, 471–473. <https://doi.org/10.1111/j.1365-2125.1994.tb04385.x>.
- Bertoli, S., Casetta, C., Giordano, B., D'Agostino, A., 2023. A national pharmacovigilance study of haematological adverse drug reactions to clozapine vs other second-generation antipsychotics in Italy. *Schizophr. Res.* 257, 25–26. <https://doi.org/10.1016/j.schres.2023.05.009>.
- Blum, A., Mauruschat, W., 1972. Temperaturanstiege und Bluteiweißveränderungen unter der Therapie mit Neuroleptika-unter besonderer Berücksichtigung des neuartigen Dibenzodiazepin-Derivates Clozapin. *Pharmacopsychiatry* 5, 155–169. <https://doi.org/10.1055/s-0028-1094343>.
- Bogers, J.P.A.M., Schulte, P.F.J., Broekman, T.G., de Haan, L., 2023. Feasibility and effect of increasing clozapine plasma levels in long-stay patients with treatment-resistant schizophrenia. *J. Clin. Psychopharmacol.* 43, 97–105. <https://doi.org/10.1097/JCP.0000000000001657>.
- Carswell, O., Wilton, L.R., Nicholls, K., Thomas, V., Clark, S.R., 2024. A 12-month audit of clozapine associated myocarditis in a South Australian local health network: the importance of screening and personalised titration. *Schizophr. Res.* 2023 <https://doi.org/10.1016/j.schres.2023.09.019> (Sep 16: S0920-9964(23)00329-8. Epub ahead of print).
- Castberg, I., Westin, A.A., Spigset, O., 2009. Does level of care, sex, age, or choice of drug influence adherence to treatment with antipsychotics? *J. Clin. Psychopharmacol.* 29, 415–420. <https://doi.org/10.1097/JCP.0b013e3181b2fced>.
- Cetin, M., 2014. Clozapinophobie; fear of prescribers of clozapine for treatment of schizophrenia. *Bull. Clin. Psychopharmacol.* 24, 295–301. <https://doi.org/10.5455/bcp.20141223052008>.
- Chaplin, S., 2006. The Yellow Card scheme - why are GPs under-reporting? *Prescriber* 17, 18–22. <https://doi.org/10.1002/psb.405>.
- Chen, W.-Y., Chen, P.-H., Pan, H.-C., Su, S.-S., Tsai, S.-Y., Chen, C.-C., Kuo, C.-J., 2024. Clozapine and its protective effect on all-cause, natural, and suicide mortality in patients with schizophrenia: a nationwide cohort study in Taiwan. *Schizophr. Res.* <https://doi.org/10.1016/j.schres.2023.07.014>. S0920-9964(23)00240-2. Advance online publication.

- Cho, J., Hayes, R.D., Jewell, A., Kadra, G., Shetty, H., MacCabe, J.H., Downs, J., 2019. Clozapine and all-cause mortality in treatment-resistant schizophrenia: a historical cohort study. *Acta Psychiatr. Scand.* 139, 237–247. <https://doi.org/10.1111/acps.12989>.
- Cicala, G., Barbieri, M.A., Spina, E., de Leon, J., 2019. A comprehensive review of swallowing difficulties and dysphagia associated with antipsychotics in adults. *Expert. Rev. Clin. Pharmacol.* 12, 219–234. <https://doi.org/10.1080/17512433.2019.1577134>.
- Clark, S.R., Warren, N.S., Kim, G., Jankowiak, D., Schubert, K.O., Kisely, S., Forrester, T., Baune, B.T., Siskind, D.J., 2018. Elevated clozapine levels associated with infection: a systematic review. *Schizophr. Res.* 192, 50–56. <https://doi.org/10.1016/j.schres.2017.03.045>.
- Committee on Safety of Medicines, 1993. Myocarditis with antipsychotics: recent cases with clozapine (Clozaril). In: *Current Problems in Pharmacovigilance*, 19, pp. 9–10.
- Correll, C.U., Solmi, M., Croatto, G., Schneider, L.K., Rohani-Montez, S.C., Fairley, L., Smith, N., Bitter, I., Gorwood, P., Taipale, H., Tiihonen, J., 2022. Mortality in people with schizophrenia: a systematic review and meta-analysis of relative risk and aggravating or attenuating factors. *World Psychiatry* 21, 248–271. <https://doi.org/10.1002/wps.20994>.
- Coulter, D.M., Bate, A., Meyboom, R.H., Lindquist, M., Edwards, I.R., 2001. Antipsychotic drugs and heart muscle disorder in international pharmacovigilance: data mining study. *BMJ* 322, 1207–1209. <https://doi.org/10.1136/bmj.322.7296.1207>.
- Crilly, J., 2007. The history of clozapine and its emergence in the US market: a review and analysis. *Hist. Psychiatry* 18, 39–60. <https://doi.org/10.1177/0957154X07070335>.
- de Filippis, R., Soldevilla-Matías, P., De Fazio, P., Guinart, D., Fuentes-Durá, I., Rubio, J.M., Kane, J.M., Schoretsanitis, G., 2020. Clozapine-related drug reaction with eosinophilia and systemic symptoms (DRESS) syndrome: a systematic review. *Expert. Rev. Clin. Pharmacol.* 13, 875–883. <https://doi.org/10.1080/17512433.2020>.
- de Filippis, R., Soldevilla-Matías, P., Guinart, D., De Fazio, P., Rubio, J.M., Kane, J.M., Schoretsanitis, G., 2021. Unravelling cases of clozapine-related Drug Reaction with Eosinophilia and Systemic Symptoms (DRESS) in patients reported otherwise: a systematic review. *J. Psychopharmacol.* 35, 1062–1073. <https://doi.org/10.1177/02698811211021587>.
- de Filippis, R., Kane, J.M., Kuzo, N., Spina, E., De Sarro, G., de Leon, J., De Fazio, P., Schoretsanitis, G., 2022. Screening the European pharmacovigilance database for reports of clozapine-related DRESS syndrome: 47 novel cases. *Eur. Neuropsychopharmacol.* 60, 25–37. <https://doi.org/10.1016/j.euroneuro.2022.04.009>.
- de Filippis, R., De las Cuevas, C., Sanz, E.J., Schoretsanitis, G., Correll, C.U., de Leon, J., 2024. Clozapine-associated pericarditis and pancreatitis in children and adolescents: a systematic literature review and pharmacovigilance study using VigiBase database. *Schizophr. Res.* <https://doi.org/10.1016/j.schres.2023.10.027>. S0920-9964(23)00387-0. Advance online publication.
- De las Cuevas, C., Baptista, T., Motuca, M., Villasante-Tezanos, G.A., Lazary, J., Pogány, L., De Leon, J., 2021. Poor adherence to oral psychiatric medication in adults with schizophrenia may be influenced by pharmacophobia, high internal health locus of control and treatment duration. *Neuropsychopharmacol. Hung.* 23, 388–404. <https://mppt.hu/magazin/pdf/vol23issue4/v23i4p388.pdf>.
- De las Cuevas, C., Sanz, E.J., Ruan, C.J., de Leon, J., 2022a. Clozapine-associated myocarditis in the World Health Organization's pharmacovigilance database: focus on reports from various countries. *Rev. Psiquiatr. Salud Ment. (Engl Ed)* 15, 238–250. <https://doi.org/10.1016/j.rpsmen.2021.07.005>.
- De las Cuevas, C., Sanz, E.J., Rohde, C., de Leon, J., 2022b. Association between myocarditis and antipsychotics other than clozapine: a systematic literature review and a pharmacovigilance study using VigiBase. *Expert. Rev. Clin. Pharmacol.* 15, 65–78. <https://doi.org/10.1080/17512433.2022.2032659>.
- De las Cuevas, C., Arjojo-Romero, M., Ruan, C.J., Schoretsanitis, G., Sanz, E.J., de Leon, J., 2022c. Clozapine-induced myocarditis in children and adolescents: a pharmacovigilance study using VigiBase and a systematic literature review. *Expert Opin. Drug Metab. Toxicol.* 18, 715–727. <https://doi.org/10.1080/17425255.2022.2160318>.
- De las Cuevas, C., Sanz, E.J., Villasante-Tezanos, A.G., de Leon, J., 2023. Respiratory aspiration during treatment with clozapine and other antipsychotics: a literature search and a pharmacovigilance study in vigiBase. *Expert Opin. Drug Metab. Toxicol.* 19, 57–74. <https://doi.org/10.1080/10.1080/17425255.2023.2192401>.
- De las Cuevas, C., Sanz, E.J., de Leon, J., 2024. Adverse drug reactions and their fatal outcomes in clozapine-treated patients in VigiBase: comparing the top four reporting countries (US, UK, Canada and Australia). *Schizophr. Res.* <https://doi.org/10.1016/j.schres.2023.05.004> (2023 Jun 8 :S0920-9964(23)00184-6).
- de Leon, J., 2022a. Reflections on the complex history of the concept of clozapine-induced inflammation during titration. *Psychiatr. Danub.* 34, 411–421. <https://doi.org/10.24869/psyd.2022.411>.
- de Leon, J., 2022b. According to the WHO clozapine pharmacovigilance database, the United Kingdom accounts for 968 fatal outcomes versus 892 in the rest of the world. *Br. J. Clin. Pharmacol.* 88, 5434–5435. <https://doi.org/10.1111/bcp.15522>.
- de Leon, J., 2023. Reflections on the lack of consideration of ethnic ancestry to stratify clozapine dosing. *Psychiatry Investig.* 20, 183–195. <https://doi.org/10.30773/pi.2022.0293>.
- de Leon, J., Diaz, F.J., 2003. Serious respiratory infections can increase clozapine levels and contribute to side effects: a case report. *Prog. Neuro-Psychopharmacol. Biol. Psychiatry* 27, 1059–1063. [https://doi.org/10.1016/S0278-5846\(03\)00148-9](https://doi.org/10.1016/S0278-5846(03)00148-9).
- de Leon, J., Ruan, C.J., Schoretsanitis, G., De las Cuevas, C., 2020a. A rational use of clozapine based on adverse drug reactions, pharmacokinetics, and clinical pharmacopsychology. *Psychother. Psychosom.* 89, 200–214. <https://doi.org/10.1159/000507638>.
- de Leon, J., Sanz, E.J., De las Cuevas, C., 2020b. Data from the World Health Organization's pharmacovigilance database supports the prominent role of pneumonia in mortality associated with clozapine adverse drug reactions. *Schizophr. Bull.* 46, 1–3. <https://doi.org/10.1093/schbul/sbz093>.
- de Leon, J., Rajkumar, A.P., Kaithi, A.R., Schoretsanitis, G., Kane, J.M., Wang, C.Y., Tang, Y.L., Lin, S.K., Hong, K.S., Farooq, S., Ng, C.H., Ruan, C.J., Andrade, C., 2020c. Do Asian patients require only half of the clozapine dose prescribed for Caucasians? A critical overview. *Indian J. Psychol. Med.* 42, 4–10. https://doi.org/10.4103/LPSYM.LPSYM_379_19.
- de Leon, J., Schoretsanitis, G., Ruan, C.J., De las Cuevas, C., Kane, J.M., Correll, C.U., 2022a. An international clozapine titration guideline to increase its safety and move forward on the route started by German-speaking psychiatrists in the 1960s. *Eur. Arch. Psychiatry Clin. Neurosci.* 272, 537–540. <https://doi.org/10.1007/s00406-022-01407-7>.
- de Leon, J., De las Cuevas, C., Sanz, E.J., Ruan, C.J., Correll, C.U., 2022b. Clozapine and the risk of haematological malignancies. *Lancet Psychiatry* 9, 537–538. [https://doi.org/10.1016/S2215-0366\(22\)00154-7](https://doi.org/10.1016/S2215-0366(22)00154-7).
- de Leon, J., Schoretsanitis, G., Smith, R.L., Molden, E., Solismaa, A., Seppälä, N., Kopeček, M., Švancer, P., Olmos, I., Ricciardi, C., Iglesias-García, C., Iglesias-Alonso, A., Spina, E., Ruan, C.J., Wang, C.Y., Wang, G., Tang, Y.L., Lin, S.K., Lane, H. Y., Kim, Y.S., Kim, S.H., Rajkumar, A.P., González-Esquivel, D.F., Jung-Cook, H., Baptista, T., Rohde, C., Nielsen, J., Verdoux, H., Quiles, C., Sanz, E.J., De las Cuevas, C., Cohen, D., Schulte, P.F.J., Ertugrul, A., Yağcıoğlu, A.E.A., Chopra, N., McCollum, B., Shelton, C., Cotes, R.O., Kaithi, A.R., Kane, J.M., Farooq, S., Ng, C.H., Bilbily, J., Hiemke, C., López-Jaramillo, C., McGrane, I., Lana, F., Eap, C.B., Arrojo-Romero, M., Rădulescu, F.Ş., Seifritz, E., Every-Palmer, S., Bousman, C.A., Bewawi, E., Bhattacharya, R., Kelly, D.L., Otsuka, Y., Lazary, J., Torres, R., Yecora, A., Motuca, M., Chan, S.K.W., Zolezzi, M., Ouanes, S., Berardis, D., Grover, S., Procyshyn, R.M., Adebayo, R.A., Kirilochov, O.O., Soloviev, A., Fountoulakis, K.N., Wilkowska, A., Cubala, W.J., Ayub, M., Silva, A., Bonelli, R.M., Villagrán-Moreno, J.M., Crespo-Facorro, B., Temmingh, H., Declodt, E., Pedro, M. R., Takeuchi, H., Tsukahara, M., Gründer, G., Sagud, M., Celofiga, A., Ristic, D.I., Ortiz, B.B., Elkis, H., Pacheco Palha, A.J., Llerena, A., Fernandez-Egea, E., Siskind, D., Weizman, A., Masmoudi, R., Saffian, S.M., Leung, J.G., Buckley, P.F., Marder, S.R., Citrome, L., Freudenreich, O., Correll, C.U., Müller, D.J., 2022c. An international adult guideline for making clozapine titration safer by using six ancestry-based personalized dosing titrations, CRP, and clozapine levels. *Pharmacopsychiatry* 55, 73–86. <https://doi.org/10.1055/a-1625-6388>.
- de Leon, J., Arrojo-Romero, M., Verdoux, H., Ruan, C.-J., Schoretsanitis, G., Rohde, C., Cohen, D., Schulte, P.F.J., Kim, S.H., Cotes, R.O., Leung, J.G., Otsuka, Y., Kirilochov, O.O., Baptista, T., Grover, S., Every-Palmer, S., Clark, S., McGrane, I.R., Motuca, M., Olmos, I., Wilkowska, A., Sagud, M., Anil Yağcıoğlu, A.E., Ignjatovic Ristic, D., Lazary, J., Sanz, E.J., De las Cuevas, C., 2023. Escaping the long shadow of agranulocytosis. Reflections on a clozapine pharmacovigilance focused on the United Kingdom. *J. Clin. Psychopharmacol.* 43, 239–245. <https://doi.org/10.1097/JCP.0000000000001678>.
- Deniker, P., 1990. The neuroleptics: a historical survey. *Acta Psychiatr. Scand. Suppl.* 358, 83–87. <https://doi.org/10.1111/j.1600-0447.1990.tb05295.x>.
- Devarajan, S., Kutchner, S.P., Dursun, S.M., 2000. Clozapine and sudden death. *Lancet* 355, 841. [https://doi.org/10.1016/S0140-6736\(00\)00035-0](https://doi.org/10.1016/S0140-6736(00)00035-0).
- Diaz, F.J., Eap, C.B., Ansermot, N., Crettol, S., Spina, E., de Leon, J., 2014. Can valproic acid be an inducer of clozapine metabolism? *Pharmacopsychiatry* 47, 89–96. <https://doi.org/10.1055/s-0034-1371866>.
- Druschky, K., Bleich, S., Grohmann, R., Engel, R.R., Neyazi, A., Stübner, S., Toto, S., 2019. Seizure rates under treatment with antipsychotic drugs: data from the AMSP project. *World J. Biol. Psychiatry* 20, 732–741. <https://doi.org/10.1080/15622975.2018.1500030>.
- Egger, C., Muehlbacher, M., Grohmann, R., Stuppach, C., 2010. Clozapine intoxication in a patient with lamotrigine-induced rash. *Pharmacopsychiatry* 43, 35–36. <https://doi.org/10.1055/s-0029-1239542>.
- Ertugrul, A., Anil Yağcıoğlu, A.E., Ağaoglu, E., Karakaşlı, A.A., Ak, S., Yazıcı, M.K., de Leon, J., 2022. Valproate, obesity and other causes of clozapine poor metabolism in the context of rapid titration may explain clozapine-induced myocarditis: a re-analysis of a Turkish case series. *Rev. Psiquiatr. Salud Ment. (Engl Ed)* 15, 281–286. <https://doi.org/10.1016/j.rpsmen.2021.10.001>.
- Facciola, G., Avenoso, A., Spina, E., Perucca, E., 1998. Inducing effect of phenobarbital on clozapine metabolism in patients with chronic schizophrenia. *Ther. Drug Monit.* 20, 628–630. <https://doi.org/10.1097/00007691-199812000-00008>.
- Facciola, G., Avenoso, A., Scordo, M.G., Madia, A.G., Ventimiglia, A., Perucca, E., Spina, E., 1999. Metabolites in patients with schizophrenic or affective disorders. *Ther. Drug Monit.* 21, 341–345. <https://doi.org/10.1097/00007691-199906000-00017>.
- Farooq, S., Choudry, A., Cohen, D., Naeem, F., Ayub, M., 2019. Barriers to using clozapine in treatment-resistant schizophrenia: systematic review. *Br. J. Psych. Bull.* 43, 8–16. <https://doi.org/10.1192/bjb.2018.67>.
- Friedrich, M.E., Winkler, D., Konstantinidis, A., Huf, W., Engel, R., Toto, S., Grohmann, R., Kasper, S., 2020. Cardiovascular adverse reactions during antipsychotic treatment: results of AMSP, a drug surveillance program between 1993 and 2013. *Int. J. Neuropsychopharmacol.* 23, 67–75. <https://doi.org/10.1093/ijnp/pty046>.
- Gaertner, H.J., Fischer, E., Hoss, J., 1989. Side effects of clozapine. *Psychopharmacology* 99 (Suppl.), S97–100. <https://doi.org/10.1007/BF00442570>.

- Gee, S.H., Shergill, S.S., Taylor, D.M., 2018. Long-term follow-up of clozapine prescribing. *J. Psychopharmacol.* 32, 552–558. <https://doi.org/10.1177/0269881118760666>.
- Geers, L.M., Cohen, D., Wehkamp, L.M., van Hateren, K., Koster, R.A., Fedorenko, O.Y., Semke, A.V., Bokhan, N., Ivanova, S.A., Kosterink, J.G.W., Loonen, A.J.M., Touw, D. J., 2017. Dried blood spot analysis for therapeutic drug monitoring of clozapine. *J. Clin. Psychiatry* 78, e1211–e1218. <https://doi.org/10.4088/JCP.16m11164>.
- Gjerden, P., Slørdal, L., Bramness, J.G., 2010. Prescription persistence and safety of antipsychotic medication: a national registry-based 3-year follow-up. *Eur. J. Clin. Pharmacol.* 66, 911–917. <https://doi.org/10.1007/s00228-010-0839-9>.
- Glorigrijević, N., Vasović, T., Lević, S., Miljević, Č., Nedić, O., Nikolić, M., 2020. Atypical antipsychotic clozapine binds fibrinogen and affects fibrin formation. *Int. J. Biol. Macromol.* 154, 142–149. <https://doi.org/10.1016/j.ijbiomac.2020.03.119>.
- Grover, S., Naskar, C., 2024. Patient and caregivers perspective about clozapine: a systematic review. *Schizophr. Res.* <https://doi.org/10.1016/j.schres.2023.06.005> (2023 Jun 27:S0920-9964(23)00223-2).
- Haack, M.J., Bak, M.L., Beurskens, R., Maes, M., Stolk, L.M., Delespaul, P.A., 2003. Toxic rise of clozapine plasma concentrations in relation to inflammation. *Eur. Neuropsychopharmacol.* 13, 381–385. [https://doi.org/10.1016/s0924-977x\(03\)00042-7](https://doi.org/10.1016/s0924-977x(03)00042-7).
- Hägg, S., Joelsson, L., Mjörndal, T., Spigset, O., Oja, G., Dahlqvist, R., 1998. Prevalence of diabetes and impaired glucose tolerance in patients treated with clozapine compared with patients treated with conventional depot neuroleptic medications. *J. Clin. Psychiatry* 59, 294–299. <https://doi.org/10.4088/jcp.v59n0604>.
- Hägg, S., Spigset, O., Söderström, T.G., 2000. Association of venous thromboembolism and clozapine. *Lancet* 355, 1155–1156. [https://doi.org/10.1016/S0140-6736\(00\)02066-3](https://doi.org/10.1016/S0140-6736(00)02066-3).
- Handley, S.A., Every-Palmer, S., Ismail, A., Flanagan, R.J., 2022. Clozapine-induced gastrointestinal hypomotility: presenting features and outcomes, UK pharmacovigilance reports, 1992–2017. *Br. J. Psychiatry* 220, 355–363. <https://doi.org/10.1192/bjp.2022.24>.
- Hayes, R.D., Downs, J., Chang, C.K., Jackson, R.G., Shetty, H., Broadbent, M., Hotopf, M., Stewart, R., 2015. The effect of clozapine on premature mortality: an assessment of clinical monitoring and other potential confounders. *Schizophr. Bull.* 41, 644–655. <https://doi.org/10.1093/schbul/sbu120>.
- Hazell, L., Shakir, S.A., 2006. Under-reporting of adverse drug reactions: a systematic review. *Drug Saf.* 29, 385–396. <https://doi.org/10.2165/00002018-200629050-00003>.
- Helmchen, H., 1989. Clinical experience with clozapine in Germany. *Psychopharmacology* 99 (Suppl), S80–S83. <https://doi.org/10.1007/BF00442566>.
- Hewer, W., Rössler, W., Fätkenheuer, B., Löffler, W., 1995. Mortality among patients in psychiatric hospitals in Germany. *Acta Psychiatr. Scand.* 91, 174–179. <https://doi.org/10.1111/j.1600-0447.1995.tb09762.x>.
- Hiemke, C., Baumann, P., Bergemann, N., Conca, A., Dietmaier, O., Egberts, K., Fric, M., Gerlach, M., Greiner, C., Gründer, G., Haen, E., Havemann-Reinecke, U., Jaquenoud, B., Kirshherr, H., Laux, G., Lutz, U.C., Messer, T., Müller, M.J., Pfuhlmann, B., Rambeck, B., Riederer, P., Schoppek, B., Stingl, J., Uhr, M., Ulrich, S., Waschgler, R., Zernig, G., 2011. AGNP consensus guidelines for therapeutic drug monitoring in psychiatry: update 2011. *Pharmacopsychiatry* 44, 195–235. <https://doi.org/10.1055/s-0031-1286287>.
- Hiemke, C., Bergemann, N., Clement, H.W., Conca, A., Deckert, J., Domschke, K., Eckermann, G., Egberts, K., Gerlach, M., Greiner, C., Gründer, G., Haen, E., Havemann-Reinecke, U., Hefner, G., Helmer, R., Janssen, G., Jaquenoud, E., Laux, G., Messer, T., Mössner, R., Müller, M.J., Paulzen, M., Pfuhlmann, B., Riederer, P., Saria, A., Schoppek, B., Schoretsanitis, G., Schwarz, M., Gracia, M.S., Stegmann, B., Steimer, W., Stingl, J.C., Uhr, M., Ulrich, S., Unterecker, S., Waschgler, R., Zernig, G., Zurek, G., Baumann, P., 2018. Consensus guidelines for therapeutic drug monitoring in neuropsychopharmacology: update 2017. *Pharmacopsychiatry* 51 (1–02), 9–62. <https://doi.org/10.1055/s-0043-116492>.
- Hiltgen, S., Mantelet, S., Pinabel, F., Enjaume, F., 2006. Etude rétrospective sur l'utilisation de la clozapine en Ile-de-France [Retrospective study of clozapine use in Ile-de-France]. *Encephale* 32 (5 Pt 1), 688–696 (French). [https://doi.org/10.1016/s0013-7006\(06\)76220-0](https://doi.org/10.1016/s0013-7006(06)76220-0).
- Hippis, H., 1989. The history of clozapine. *Psychopharmacology* 99 (Suppl), S3–S5. <https://doi.org/10.1007/BF00442551>.
- HLS Therapeutics, Inc, 2023. CLOZARIL-Clozapine Tablet. HLS Therapeutics (USA), Inc, Rosemont, PA. Revised in May 2023. <https://dailymed.nlm.nih.gov/dailymed/drugInfo.cfm?setid=90876802-0e3a-44c9-9ff7-1754dfbe736a>. (Accessed 30 June 2023).
- Huhn, M., Nikolakopoulou, A., Schneider-Thoma, J., Krause, M., Samara, M., Peter, N., Arndt, T., Bäckers, L., Rothe, P., Cipriani, A., Davis, J., Salanti, G., Leucht, S., 2019. Comparative efficacy and tolerability of 32 oral antipsychotics for the acute treatment of adults with multi-episode schizophrenia: a systematic review and network meta-analysis. *Lancet* 394, 939–951. [https://doi.org/10.1016/S0140-6736\(19\)31135-3](https://doi.org/10.1016/S0140-6736(19)31135-3).
- Idänpään-Heikkilä, J., Alhava, E., Olkinuora, M., Palva, I., 1975. Letter: clozapine and agranulocytosis. *Lancet* 2, 611. [https://doi.org/10.1016/s0140-6736\(75\)90206-8](https://doi.org/10.1016/s0140-6736(75)90206-8).
- Inman, W.H.W., 1976. Assessment drug safety problems. In: Gent, M., Shigematsu, I. (Eds.), *Epidemiological Issues in Reported Drug Induced Illnesses*. McMaster University Library Press, Honolulu, Ontario, pp. 17–24.
- Jerling, M., Lindström, L., Bondesson, U., Bertilsson, L., 1994. Fluvoxamine inhibition and carbamazepine induction of the metabolism of clozapine: evidence from a therapeutic drug monitoring series. *Ther. Drug Monit.* 16, 368–374. <https://doi.org/10.1097/00007691-199408000-00006>.
- Juul Povlsen, U., Noring, U., Fog, R., Gerlach, J., 1985. Tolerability and therapeutic effect of clozapine. A retrospective investigation of 216 patients treated with clozapine for up to 12 years. *Acta Psychiatr. Scand.* 71, 176–185. <https://doi.org/10.1111/j.1600-0447.1985.tb01268.x>.
- Kane, J., Honigfeld, G., Singer, J., Meltzer, H., 1988. Clozapine for the treatment-resistant schizophrenic: a double-blind comparison with chlorpromazine. *Arch. Gen. Psychiatry* 45, 789–796. <https://doi.org/10.1001/archpsyc.1988.01800330013001>.
- Kang, N., Kim, S.H., Kim, J., Kim, S., Jang, J., Yoon, H., Lee, J., Kim, M., Kim, Y.S., Kwon, J.S., 2024a. Association between initial pattern of clozapine titration, concentration-to-dose ratio, and incidence of fever in patients with schizophrenia spectrum disorders in a Korean tertiary hospital. *Schizophr. Res.* <https://doi.org/10.1016/j.schres.2023.08.001> (2023 Aug 24:S0920-9964(23)00259-1. Epub ahead of print).
- Kang, N., Kim, S.H., Kim, J., Kim, S., Jang, J., Yoon, H., Lee, J., Kim, M., Kim, Y.S., Kwon, J.S., 2024b. Association between initial clozapine titration and pneumonia risk among patients with schizophrenia in a Korean tertiary hospital. *Schizophr. Res.* <https://doi.org/10.1016/j.schres.2023.09.029>.
- Kelly, D.L., McMahon, R.P., Liu, F., Love, R.C., Wehring, H.J., Shim, J.C., Warren, K.R., Conley, R.R., 2010. Cardiovascular disease mortality in patients with chronic schizophrenia treated with clozapine: a retrospective cohort study. *J. Clin. Psychiatry* 71, 304–311. <https://doi.org/10.4088/JCP.08m04718yel>.
- Kikuchi, Y., Komatsu, H., Otsuka, Y., Ito, F., Kanahara, N., Tanifujii, H., Tomita, H., 2024. Slower clozapine titration than the official Japanese protocol led to fewer inflammatory adverse effects: a retrospective chart review of seven hospitals. *Schizophr. Res.* <https://doi.org/10.1016/j.schres.2023.06.003> (S0920-9964(23)00220-7. Advance online publication).
- Kilian, J.G., Kerr, K., Lawrence, C., Celermajer, D.S., 1999. Myocarditis and cardiomyopathy associated with clozapine. *Lancet* 354, 1841–1845. [https://doi.org/10.1016/s0140-6736\(99\)10385-4](https://doi.org/10.1016/s0140-6736(99)10385-4).
- Kirillochev, O., Chumakov, E., Kuzo, N., Schoretsanitis, G., 2024. A scoping review of literature on clozapine from former Soviet Union states published in Russian language. *Schizophr. Res.* <https://doi.org/10.1016/j.schres.2023.09.020> (S0920-9964(23)00331-6. Advance online publication).
- Kiviniemi, M., Suvisaari, J., Koivumaa-Honkanen, H., Häkkinen, U., Isohanni, M., Hakko, H., 2013. Antipsychotics and mortality in first-onset schizophrenia: prospective Finnish register study with 5-year follow-up. *Schizophr. Res.* 150, 274–280. <https://doi.org/10.1016/j.schres.2013.07.043>.
- Koenig, M., McCollum, B., Spivey, J.K., Coleman, J.K., Shelton, C., Cotes, R.O., Goldsmith, D.R., De Leon, J., 2022. Four cases of myocarditis in US hospitals possibly associated with clozapine poor metabolism and a comparison with prior published cases. *Neuropsychopharmacol. Hung.* 24, 29–41. <https://mppt.hu/magazin/pdf/vol24issue1/v24i1p29.pdf>.
- La Grenade, L., Graham, D., Trontell, A., 2001. Myocarditis and cardiomyopathy associated with clozapine use in the United States. *N. Engl. J. Med.* 345, 224–225. <https://doi.org/10.1056/NEJM200107193450317>.
- Lahdelma, L., Appelberg, B., 2012. Clozapine-induced agranulocytosis in Finland, 1982–2007: long-term monitoring of patients is still warranted. *J. Clin. Psychiatry* 73, 837–842. <https://doi.org/10.4088/JCP.11m07244>.
- Lambertenghi Dellilieri, G., 2000. Blood dyscrasias in clozapine-treated patients in Italy. *Haematologica* 85, 233–237.
- Land, R., Siskind, D., McArdle, P., Kisely, S., Winckel, K., Hollingworth, S.A., 2017. The impact of clozapine on hospital use: a systematic review and meta-analysis. *Acta Psychiatr. Scand.* 135, 296–309. <https://doi.org/10.1111/acps.12700>.
- Legge, S.E., Hamshere, M., Hayes, R.D., Downs, J., O'Donovan, M.C., Owen, M.J., Walters, J.T.R., MacCabe, J.H., 2016. Reasons for discontinuing clozapine: a cohort study of patients commencing treatment. *Schizophr. Res.* 174, 113–119. <https://doi.org/10.1016/j.schres.2016.05.002>.
- Lertxundi, U., Ruiz, A.I., Aspiazú, M.A., Domingo-Echaburu, S., García, M., Aguirre, C., García-Moncó, J.C., 2015. Adverse reactions to antipsychotics in Parkinson disease: an analysis of the Spanish pharmacovigilance database. *Clin. Neuropharmacol.* 38, 69–84. <https://doi.org/10.1097/WNF.0000000000000080>.
- Leung, J.G., de Leon, J., Frye, M.A., Singh, B., Cotes, R.O., McElroy, S.L., 2022. The modernization of clozapine: a recapitulation of the past in the United States and the view forward. *J. Clin. Psychopharmacol.* 42, 565–580. <https://doi.org/10.1097/JCP.0000000000001606>.
- Leung, J.G., Zhang, L., Markota, M., Ellingrod, V.L., Gerber, D.J., Bishop, J.R., 2023. A systematic review of clozapine-associated inflammation and related monitoring. *Pharmacotherapy*. <https://doi.org/10.1002/phar.2887> (Advance online publication).
- Levoyer, D., Martinet, J.P., Badiche, A., Millet, B., 2004. Dix ans d'expérience clinique de la clozapine portant sur 170 patients [Ten years of clinical experience with clozapine about 170 patients]. *Encephale* 30, 285–295. [https://doi.org/10.1016/s0013-7006\(04\)95441-3](https://doi.org/10.1016/s0013-7006(04)95441-3) (French).
- Lieslehto, J., Tiitonen, J., Lähteenvu, M., Tanskanen, A., Taipale, H., 2022. Primary nonadherence to antipsychotic treatment among persons with schizophrenia. *Schizophr. Bull.* 48, 655–663. <https://doi.org/10.1093/schbul/sbac014>.
- Lopez-Gonzalez, E., Herdeiro, M.T., Figueiras, A., 2009. Determinants of under-reporting of adverse drug reactions: a systematic review. *Drug Saf.* 32, 19–31. <https://doi.org/10.2165/00002018-200932010-00002>.
- Mace, S., Dzahini, O., Cornelius, V., Langerman, H., Oloyede, E., Taylor, D., 2022. Incident infection during the first year of treatment - a comparison of clozapine and paliperidone palmitate long-acting injection. *J. Psychopharmacol.* 36, 232–237. <https://doi.org/10.1177/02698811211058973>.
- MacGillivray, S., Cooper, S.J., English, B., Millar, H., Williams, B., 2003. Predictors of discontinuation on clozapine: a population study. *Ir. J. Psychol. Med.* 20, 115–118. <https://doi.org/10.1017/S0790966700007904>.

- Malý, R., Masopust, J., Hošák, L., Konupčíková, K., 2008. Assessment of risk of venous thromboembolism and its possible prevention in psychiatric patients. *Psychiatry Clin. Neurosci.* 62, 3–8. <https://doi.org/10.1111/j.1440-1819.2007.01773.x>.
- Manoufi, S.A., Boussaid, M., Brahim, O., Ouanes, S., Mahjoub, Y., Zarrouk, L., Mesrati, M.A., Aissaoui, A., 2022. Fatal pulmonary embolism in patients on antipsychotics: case series, systematic review and meta-analysis. *Asian J. Psychiatr.* 73, 103105 <https://doi.org/10.1016/j.ajp.2022.103105>.
- Masuda, T., Misawa, F., Takase, M., Kane, J.M., Correll, C.U., 2019. Association with hospitalization and all-cause discontinuation among patients with schizophrenia on clozapine vs other oral second-generation antipsychotics: a systematic review and meta-analysis of cohort studies. *JAMA Psychiatry* 76, 1052–1062. <https://doi.org/10.1001/jamapsychiatry.2019.1702>.
- McCullum, B., Barclay, J., de Leon, J., 2018. Unexpected falls during clozapine treatment explained by myoclonus. *Prim. Care Companion CNS Disord.* 20, 17102151 <https://doi.org/10.4088/PCC.17102151>.
- McLernon, D.J., Bond, C.M., Hannaford, P.C., Watson, M.C., Lee, A.J., Hazell, L., Avery, A., 2010. Yellow Card Collaboration. Adverse drug reaction reporting in the UK: a retrospective observational comparison of yellow card reports submitted by patients and healthcare professionals. *Drug Saf.* 33, 775–788. <https://doi.org/10.2165/11536510-000000000-00000>.
- Migliardi, G., D'Arrigo, C., Santoro, V., Bruno, A., Cortese, L., Campolo, D., Cacciola, M., Spina, E., 2007. Effect of topiramate on plasma concentrations of clozapine, olanzapine, risperidone, and quetiapine in patients with psychotic disorders. *Clin. Neuropharmacol.* 30, 107–113. <https://doi.org/10.1097/01.wnf.0000240955.49315.65>.
- Miklozek, C.L., Crumppacker, C.S., Royal, H.D., Come, P.C., Sullivan, J.L., Abelmann, W. H., 1988. Myocarditis presenting as acute myocardial infarction. *Am. Heart J.* 115, 768–776. [https://doi.org/10.1016/0002-8703\(88\)90877-0](https://doi.org/10.1016/0002-8703(88)90877-0).
- Montastruc, J.L., Lafaurie, M., de Canecaude, C., Durrieu, G., Sommet, A., Montastruc, F., Bagheri, H., 2021. Fatal adverse drug reactions: a worldwide perspective in the World Health Organization pharmacovigilance database. *Br. J. Clin. Pharmacol.* 87, 4334–4340. <https://doi.org/10.1111/bcp.14851>.
- Mookhoek, E.J., Loonen, A.J., 2004. Retrospective evaluation of the effect of omeprazole on clozapine metabolism. *Pharm. World Sci.* 26, 180–182. <https://doi.org/10.1023/b.phar.0000026808.97403.05>.
- Moore, T.J., Cohen, M.R., Furberg, C.D., 2007. Serious adverse drug events reported to the Food and Drug Administration, 1998–2005. *Arch. Intern. Med.* 167, 1752–1759. <https://doi.org/10.1001/archinte.167.16.1752>.
- Mustafa, F.A., Burke, J.G., Abukmeil, S.S., Scanlon, J.J., Cox, M., 2015. “Schizophrenia past clozapine”: reasons for clozapine discontinuation, mortality, and alternative antipsychotic prescribing. *Pharmacopsychiatry* 48, 11–14. <https://doi.org/10.1055/s-0034-1394397>.
- Naber, D., Leppig, M., Grohmann, R., Hippus, H., 1989. Efficacy and adverse effects of clozapine in the treatment of schizophrenia and tardive dyskinesia—a retrospective study of 387 patients. *Psychopharmacology* 99 (Suppl.), S73–S76. <https://doi.org/10.1007/BF00442564>.
- Netherlands Clozapine Collaboration Group, 2013. Guideline for the use of clozapine. <http://www.clozapinepluswerkroep.nl/wp-content/uploads/2013/07/Guideline-for-the-use-of-Clozapine-2013.pdf>. (Accessed 23 February 2020).
- Nielsen, J., Meyer, J.M., 2012. Risk factors for ileus in patients with schizophrenia. *Schizophr. Bull.* 38, 592–598. <https://doi.org/10.1093/schbul/sbq137>.
- Nielsen, J., Foldager, L., Meyer, J.M., 2009. Increased use of antibiotics in patients treated with clozapine. *Eur. Neuropsychopharmacol.* 19, 483–486. <https://doi.org/10.1016/j.euroneuro.2009.03.002>.
- Nielsen, J., Skadhede, S., Correll, C.U., 2010. Antipsychotics associated with the development of type 2 diabetes in antipsychotic-naïve schizophrenia patients. *Neuropsychopharmacology* 35, 1997–2004. <https://doi.org/10.1038/npp.2010.78>.
- Nielsen, J., Nielsen, R.E., Correll, C.U., 2012a. Predictors of clozapine response in patients with treatment-refractory schizophrenia: results from a Danish register study. *J. Clin. Psychopharmacol.* 32, 678–683. <https://doi.org/10.1097/JCP.0b013e318267b3cd>.
- Nielsen, J., Kane, J.M., Correll, C.U., 2012b. Real-world effectiveness of clozapine in patients with bipolar disorder: results from a 2-year mirror-image study. *Bipolar Disord.* 14, 863–869. <https://doi.org/10.1111/bdi.12018>.
- Nielsen, J., Røge, R., Schjerning, O., Sørensen, H.J., Taylor, D., 2012c. Geographical and temporal variations in clozapine prescription for schizophrenia. *Eur. Neuropsychopharmacol.* 22, 818–824. <https://doi.org/10.1016/j.euroneuro.2012.03.003>.
- Pacia, S.V., Devinsky, O., 1994. Clozapine-related seizures: experience with 5,629 patients. *Neurology* 44, 2247–2249. <https://doi.org/10.1212/wnl.44.12.2247>.
- Papola, D., Ostuzzi, G., Gastaldon, C., Morgano, G.P., Dragioti, E., Carvalho, A.F., Fusar-Poli, P., Correll, C.U., Solmi, M., Barbui, C., 2019. Antipsychotic use and risk of life-threatening medical events: umbrella review of observational studies. *Acta Psychiatr. Scand.* 140, 227–243. <https://doi.org/10.1111/acps.13066>.
- Peyrière, H., Roux, C., Ferard, C., Deleau, N., Kreft-Jais, C., Hillaire-Butys, D., Boulenger, J.P., Blayac, J.P., French Network of the Pharmacovigilance Centers, 2009. Antipsychotics-induced ischaemic colitis and gastrointestinal necrosis: a review of the French pharmacovigilance database. *Pharmacoevidemol. Drug Saf.* 18, 948–955. <https://doi.org/10.1002/pds.1801>.
- Pfeifer, P., Greusing, S., Kupferschmidt, H., Bartsch, C., Reisch, T., 2020. A comprehensive analysis of attempted and fatal suicide cases involving frequently used psychotropic medications. *Gen. Hosp. Psychiatry* 63, 16–20. <https://doi.org/10.1016/j.genhosppsych.2019.07.011>.
- Pfuhlmann, B., Hiemke, C., Unterecker, S., Burger, R., Schmidtke, A., Riederer, P., Deckert, J., Jabs, B., 2009. Toxic clozapine serum levels during inflammatory reactions. *J. Clin. Psychopharmacol.* 29, 392–394. <https://doi.org/10.1097/JCP.0b013e3181acd20b>.
- Polcwiartek, C., Vang, T., Bruhn, C.H., Hashemi, N., Rosenzweig, M., Nielsen, J., 2016. Diabetic ketoacidosis in patients exposed to antipsychotics: a systematic literature review and analysis of Danish adverse drug event reports. *Psychopharmacology* 233, 3663–3672. <https://doi.org/10.1007/s00213-016-4411-x>.
- Pons, A., Undurraga, J., Batalla, A., Bernardo, M., 2012. Clozapina y agranulocitosis en España: ¿tenemos una población más segura? Seguimiento hematológico a 5 años de una cohorte de pacientes tratados con clozapina [Clozapine and agranulocytosis in Spain: do we have a safer population? A 5-year hematologic follow-up]. *Rev. Psiquiatr. Salud Ment.* 5, 37–42. <https://doi.org/10.1016/j.rpsm.2011.11.003>.
- Ponsford, M., Castle, D., Tahir, T., Robinson, R., Wade, W., Steven, R., Bramhall, K., Moody, M., Carne, E., Ford, C., Farewell, D., Williams, P., El-Shanawany, T., Jolles, S., 2018. Clozapine is associated with secondary antibody deficiency. *Br. J. Psychiatry* 214, 1–7. <https://doi.org/10.1192/bjp.2018.152>.
- Poudyal, R., Lohani, S., 2019. Clozapine associated pulmonary embolism: systematic review. *J. Commun. Hosp. Intern. Med. Perspect.* 9, 300–304. <https://doi.org/10.1080/20009666.2019.1627848>.
- Raaska, K., Raitasuo, V., Arstila, M., Neuvonen, P.J., 2002. Bacterial pneumonia can increase serum concentration of clozapine. *Eur. J. Clin. Pharmacol.* 58, 321–322. <https://doi.org/10.1007/s00228-002-0486-x>.
- Rajagopal, S., 2005. Clozapine, agranulocytosis, and benign ethnic neutropenia. *Postgrad. Med. J.* 81, 545–546. <https://doi.org/10.1136/pgmj.2004.031161>.
- Reeves, S., Bertrand, J., Obee, S.J., Hunter, S., Howard, R., Flanagan, R.J., 2023. A population pharmacokinetic model to guide clozapine dose selection, based on age, sex, ethnicity, body weight and smoking status. *Br. J. Clin. Pharmacol.* <https://doi.org/10.1111/bcp.15691> (Advance online publication).
- Ringbäck Weitöft, G., Berglund, M., Lindström, E.A., Nilsson, M., Salmi, P., Rosén, M., 2014. Mortality, attempted suicide, re-hospitalisation and prescription refill for clozapine and other antipsychotics in Sweden—a register-based study. *Pharmacoevidemol. Drug Saf.* 23, 290–298. <https://doi.org/10.1002/pds.3567>.
- Rohde, C., Polcwiartek, C., Kragholm, K., Ebdrup, B.H., Siskind, D., Nielsen, J., 2018a. Adverse cardiac events in out-patients initiating clozapine treatment: a nationwide register-based study. *Acta Psychiatr. Scand.* 137, 47–53. <https://doi.org/10.1111/acps.12827>.
- Rohde, C., Polcwiartek, C., Correll, C.U., Nielsen, J., 2018b. Real-world effectiveness of clozapine for borderline personality disorder: results from a 2-year mirror-image study. *J. Personal. Disord.* 32, 823–837. <https://doi.org/10.1521/pedi.2017.31.328>.
- Rohde, C., Hilker, R., Siskind, D., Nielsen, J., 2018c. Real-world effectiveness of clozapine for intellectual disability: results from a mirror-image and a reverse-mirror-image study. *J. Psychopharmacol.* 32, 1197–1203. <https://doi.org/10.1177/0269881118783322>.
- Rohde, C., Siskind, D., de Leon, J., Nielsen, J., 2020. Antipsychotic medication exposure, clozapine, and pneumonia: results from a self-controlled study. *Acta Psychiatr. Scand.* 142, 78–86. <https://doi.org/10.1111/acps.13142>.
- Rose, E., Chen, S., Turroni, C., Jenkins, C., Cardinal, R.N., Fernandez-Egea, E., 2020. Causes of death in clozapine-treated patients in a catchment area: a 10-year retrospective case-control study. *Eur. Neuropsychopharmacol.* 36, 160–166. <https://doi.org/10.1016/j.euroneuro.2020.05.011>.
- Rotella, F., Cassioli, E., Calderani, E., Lazzaretto, L., Ragghianti, B., Ricca, V., Mannucci, E., 2020. Long-term metabolic and cardiovascular effects of antipsychotic drugs: A meta-analysis of randomized controlled trials. *Eur. Neuropsychopharmacol.* 32, 56–65. <https://doi.org/10.1016/j.euroneuro.2019.12.118>.
- Rowntree, R., Murray, S., Fanning, F., Keating, D., Szigeti, A., Doyle, R., McWilliams, S., Clarke, M., 2020. Clozapine use - has practice changed? *J. Psychopharmacol.* 34, 567–573. <https://doi.org/10.1177/0269881120913152>.
- Ruan, C.J., Zhang, X.L., Guo, W., Li, W.B., Zhuang, H.Y., Li, Y.Q., Wang, C.Y., Tang, Y.L., Zhou, F.C., de Leon, J., 2018. Two cases of high serum clozapine concentrations occurring during inflammation in Chinese patients. *Int. J. Psychiatry Med.* 53, 292–305. <https://doi.org/10.1177/0091217417497999>.
- Ruan, C.J., Zang, Y.N., Cheng, Y.H., Wang, C.Y., de Leon, J., 2020. Around 3% of 1,300 levels were elevated during infections in a retrospective review of 131 Beijing Hospital in-patients with more than 24,000 days of clozapine treatment. *Psychother. Psychosom.* 89, 255–257. <https://doi.org/10.1159/000506355>.
- Ruan, C.J., Olmos, I., Ricciardi, C., Schoretsanis, G., Vincent, P.D., Anil Yağcıoğlu, A.E., Eap, C.B., Molden, E., Baptista, T., Clark, S.R., Fernandez-Egea, E., Kim, S.H., Lane, H.-Y., Leung, J., Maroñas, Amigo, O., Motuca, M., Every-Palmer, S., Procyshyn, R.M., Rohde, C.G., Suhas, S., Schulte, P.F.J., Spina, E., Takeuchi, H., Verdoux, H., Correll, C.U., Molden, E., De las Cuevas, C., de Leon, J., 2024. Exploring low clozapine C/D ratios, inverted clozapine-norclozapine ratios and undetectable concentrations as measures of non-adherence in clozapine-treated patients: A literature review and a case series of 15 patients from 3 studies. *Schizophr. Res.* <https://doi.org/10.1016/j.schres.2023.07.002>. S0920-9964(23)00228-1. Advance online publication.
- Safferan, A., Lieberman, J.A., Kane, J.M., Szymanski, S., Kinon, B., 1991. Update on the clinical efficacy and side effects of clozapine. *Schizophr. Bull.* 17, 247–261. <https://doi.org/10.1093/schbul/17.2.247>.
- Sagud, M., Breznovcakova, D., Celofiga, A., Ignjatovic Ristic, D., Injac Stevovic, L., Kopecek, M., Katrin Kurvits, K., Kuzo, N., Lazary, J., Mazaliauskienė, R., Novotni, A., Pikirenia, U., Rădulescu, F.S., Taube, M., Tomori, S., Wilkowska, A., De las Cuevas, C., Sanz, E.J., de Leon, J., 2024. An expert review of clozapine in Eastern European countries: use, regulations and pharmacovigilance. *Schizophr. Res.* <https://doi.org/10.1016/j.schres.2023.09.002>. S0920-9964(23)00312-2. Advance online publication.
- Sanader, B., Grohmann, R., Grötsch, P., Schumann, T., Toto, S., Fernando, P., Stübner, S., 2019. Clozapine-induced DRESS syndrome: a case series from the AMSP multicenter

- drug safety surveillance project. *Pharmacopsychiatry* 52, 156–159. <https://doi.org/10.1055/a-0586-8983>.
- Sandberg, A., Salminen, V., Heinonen, S., Sivén, M., 2020. Under-reporting of adverse drug reactions in Finland and healthcare professionals' perspectives on how to improve reporting. *Healthcare (Basel)*. 10, 1015. <https://doi.org/10.3390/healthcare10061015>.
- Santoro, V., D'Arrigo, C., Spina, E., Micò, U., Muscatello, M.R., Zoccali, R., 2010. Effect of adjunctive duloxetine on the plasma concentrations of clozapine, olanzapine, and risperidone in patients with psychotic disorders. *J. Clin. Psychopharmacol.* 30, 634–636. <https://doi.org/10.1097/JCP.0b013e3181ee2afe>.
- Schmedt, N., Kollhorst, B., Enders, D., Jobski, K., Krappweis, J., Garbe, E., Schink, T., 2016. Comparative risk of death in older adults treated with antipsychotics: a population-based cohort study. *Eur. Neuropsychopharmacol.* 26, 1390–1400. <https://doi.org/10.1016/j.euroneuro.2016.07.006>.
- Schmidinger, S., Hofer, A., 2014. Pulmonary embolism and aspiration pneumonia after reexposure to clozapine: pulmonary adverse effects of clozapine. *J. Clin. Psychopharmacol.* 34, 385–387. <https://doi.org/10.1097/JCP.0000000000000124>.
- Schmidt, L.G., Niemeyer, R., Müller-Oerlinghausen, B., 1983. Drug prescribing pattern of a psychiatric university hospital in Germany. *Pharmacopsychiatry* 16, 35–42. <https://doi.org/10.1055/s-2007-1017445>.
- Schoretsanitis, G., Kane, J.M., Ruan, C.J., Spina, E., Hiemke, C., de Leon, J., 2019. A comprehensive review of the clinical utility of and a combined analysis of the clozapine/norclozapine ratio in therapeutic drug monitoring for adult patients. *Expert. Rev. Clin. Pharmacol.* 12, 603–621. <https://doi.org/10.1080/17512433.2019.1617695>.
- Schoretsanitis, G., Kuzin, M., Kane, J.M., Hiemke, C., Paulzen, M., Haen, E., 2021a. Elevated clozapine concentrations in clozapine-treated patients with hypersalivation. *Clin. Pharmacokinet.* 60, 329–335. <https://doi.org/10.1007/s40262-020-00944-5>.
- Schoretsanitis, G., Ruan, C.J., Rohde, C., Verdoux, H., De Las Cuevas, C., Spina, E., de Leon, J., 2021b. An update on the complex relationship between clozapine and pneumonia. *Expert. Rev. Clin. Pharmacol.* 14, 145–149. <https://doi.org/10.1080/17512433.2021.1877135>.
- Shelton, C., Ruan, C.J., Ertugrul, A., Cotes, R.O., De Leon, J., 2022. Should we routinely add CRP to clozapine titrations? - learning from three cases. *Neuropsychopharmacol. Hung.* 24, 153–161 <https://mppt.hu/magazin/pdf/vol24issue4/v24i4p153.pdf>.
- Simon, P., 2000. Chapter 25. In: Healy, D. (Ed.), *The Psychopharmacologists III: Interviews by David Healy*. Oxford University Press, London/New York, pp. 523–537.
- Siskind, D., McCartney, L., Goldschlager, R., Kisely, S., 2016. Clozapine v. first- and second-generation antipsychotics in treatment-refractory schizophrenia: systematic review and meta-analysis. *Br. J. Psychiatry* 209, 385–392. <https://doi.org/10.1192/bjp.bp.115.177261>.
- Siskind, D., Siskind, V., Kisely, S., 2017. Clozapine response rates among people with treatment-resistant schizophrenia: data from a systematic review and meta-analysis. *Can. J. Psychiatr.* 62, 772–777. <https://doi.org/10.1177/0706743717718167>.
- Skrede, S., Tveit, I.F., Tanum, L., Steen, V.M., Bramness, J.G., 2015. Incident users of antipsychotic agents and future use of cholesterol-lowering drugs: an observational, pharmacoepidemiologic study. *J. Clin. Psychiatry* 76, e111–e116. <https://doi.org/10.4088/JCP.14m08996>.
- Smith, R.L., Tveit, M., Kylesø, L., Jukic, M.M., Ingelman-Sundberg, M., Andreassen, O. A., Molden, E., 2021. Rates of complete nonadherence among atypical antipsychotic drugs: a study using blood samples from 13,217 outpatients with psychotic disorders. *Schizophr. Res.* 228, 590–596. <https://doi.org/10.1016/j.schres.2020.11.025>.
- Sneider, B., Pristed, S.G., Correll, C.U., Nielsen, J., 2015. Frequency and correlates of antipsychotic polypharmacy among patients with schizophrenia in Denmark: a nation-wide pharmacoepidemiological study. *Eur. Neuropsychopharmacol.* 25, 1669–1676. <https://doi.org/10.1016/j.euroneuro.2015.04.027>.
- Solmi, M., Tiihonen, J., Lähteenvuo, M., Tanskanen, A., Correll, C.U., Taipale, H., 2022. Antipsychotics use is associated with greater adherence to cardiometabolic medications in patients with schizophrenia: results from a nationwide, within-subject design study. *Schizophr. Bull.* 48, 166–175. <https://doi.org/10.1093/schbul/sbab087>.
- Spina, E., Avenoso, A., Facciola, G., Fabrizio, M., Monteleone, P., Maj, M., Perucca, E., Caputi, A.P., 1998. Effect of fluoxetine on the plasma concentrations of clozapine and its major metabolites in patients with schizophrenia. *Int. Clin. Psychopharmacol.* 13, 141–145. <https://doi.org/10.1097/00004850-199805000-00009>.
- Spina, E., Avenoso, A., Salemi, M., Facciola, G., Scordo, M.G., Ancione, M., Madia, A., 2000. Plasma concentrations of clozapine and its major metabolites during combined treatment with paroxetine or sertraline. *Pharmacopsychiatry* 33, 213–217. <https://doi.org/10.1055/s-2000-8361>.
- Spina, E., Avenoso, A., Scordo, M.G., Ancione, M., Madia, A., Levita, A., 2001. No effect of reboxetine on plasma concentrations of clozapine, risperidone, and their active metabolites. *Ther. Drug Monit.* 23, 675–678. <https://doi.org/10.1097/00007691-200112000-00014>.
- Spina, E., D'Arrigo, C., Migliardi, G., Santoro, V., Muscatello, M.R., Micò, U., D'Amico, G., Perucca, E., 2006. Effect of adjunctive lamotrigine treatment on the plasma concentrations of clozapine, risperidone and olanzapine in patients with schizophrenia or bipolar disorder. *Ther. Drug Monit.* 28, 599–602. <https://doi.org/10.1097/01.ftd.0000246763.59506.b0>.
- Stolz, P.A., Wehring, H.J., Liu, F., Love, R.C., Ellis, M., DiPaula, B.A., Kelly, D.L., 2019. Effects of cigarette smoking and clozapine treatment on 20-year all-cause & cardiovascular mortality in schizophrenia. *Psychiatry* Q. 90, 351–359. <https://doi.org/10.1007/s1126-018-9621-4>.
- Taipale, H., Mittendorfer-Rutz, E., Alexanderson, K., Majak, M., Mehtälä, J., Hoti, F., Jedenius, E., Enksson, D., Leval, A., Sermon, J., Tanskanen, A., Tiihonen, J., 2018. Antipsychotics and mortality in a nationwide cohort of 29,823 patients with schizophrenia. *Schizophr. Res.* 197, 274–280. <https://doi.org/10.1016/j.schres.2017.12.010>.
- Taipale, H., Tanskanen, A., Mehtälä, J., Vattulainen, P., Correll, C.U., Tiihonen, J., 2020. 20-year follow-up study of physical morbidity and mortality in relationship to antipsychotic treatment in a nationwide cohort of 62,250 patients with schizophrenia (FIN20). *World Psychiatry* 19, 61–68. <https://doi.org/10.1002/wps.20699>.
- Takeuchi, H., Borlido, C., Sanches, M., Teo, C., Harber, L., Agid, O., Remington, G., 2020. Adherence to clozapine vs. other antipsychotics in schizophrenia. *Acta Psychiatr. Scand.* 142, 87–95. <https://doi.org/10.1111/acps.13208>.
- Taylor, D.M., Douglas-Hall, P., Olofinjana, B., Whiskey, E., Thomas, A., 2009. Reasons for discontinuing clozapine: matched, case-control comparison with risperidone long-acting injection. *Br. J. Psychiatry* 194, 165–167. <https://doi.org/10.1192/bjp.bp.108.051979>.
- Tiihonen, J., Lönnqvist, J., Wahlbeck, K., Klaukka, T., Niskanen, L., Tanskanen, A., Haukka, J., 2009. 11-year follow-up of mortality in patients with schizophrenia: a population-based cohort study (FIN11 study). *Lancet* 374, 620–627. [https://doi.org/10.1016/S0140-6736\(09\)60742-X](https://doi.org/10.1016/S0140-6736(09)60742-X).
- U.S. Food and Drug Administration, 2005. Public health advisory: deaths with antipsychotics in elderly patients with behavioral disturbances on April 11, 2005. Currently available at. <https://psychrights.org/drugs/FDAantipsychotics4elderlywarning.htm>. (Accessed 26 May 2023).
- UK Medicines and Healthcare Products Regulatory Agency, 2020. Clozapine and other antipsychotics: monitoring blood concentrations for toxicity. <https://www.gov.uk/drug-safety-update/clozapine-and-other-antipsychotics-monitoring-blood-concentrations-for-toxicity>. (Accessed 21 January 2023) (Published 26 August 2020).
- UK Medicines and Healthcare Products Regulatory Agency, 2023. Data available until December 31, 2022. https://info.mhra.gov.uk/drug-analysis-profiles/dap.html?drug=/UK_EXTERNAL/NONCOMBINED/UK_NON_000299949199.zip&agen cy=MHRA. (Accessed 21 January 2023).
- van de Vijver, D.A., Roos, R.A., Jansen, P.A., Porsius, A.J., de Boer, A., 2002. Antipsychotics and Parkinson's disease: association with disease and drug choice during the first 5 years of antiparkinsonian drug treatment. *Eur. J. Clin. Pharmacol.* 58, 157–161. <https://doi.org/10.1007/s00228-002-0441-x>.
- van der Zalm, Y.C., Termorshuizen, F., Selten, J.P., 2019. Concerns about bias in studies on clozapine and mortality. *Schizophr. Res.* 204, 425–426. <https://doi.org/10.1016/j.schres.2018.08.017>.
- van der Zalm, Y., Termorshuizen, F., Sommer, I.E., Selten, J.P., 2020. Use of cardiovascular and antidiabetic drugs before and after starting with clozapine versus other antipsychotic drugs: a Dutch database study. *Int. Clin. Psychopharmacol.* 35, 36–41. <https://doi.org/10.1097/YIC.0000000000000292>.
- van der Zalm, Y., Foldager, L., Termorshuizen, F., Sommer, I.E., Nielsen, J., Selten, J.P., 2021. Clozapine and mortality: a comparison with other antipsychotics in a nationwide Danish cohort study. *Acta Psychiatr. Scand.* 143, 216–226. <https://doi.org/10.1111/acps.13267>.
- Varallo, F.R., Guimarães Sde, O., Abjaude, S.A., Mastroianni, P.deC., 2014. Causes for the underreporting of adverse drug events by health professionals: a systematic review. *Rev. Esc. Enferm. USP.* 48, 739–747. <https://doi.org/10.1590/s0080-623420140000400023> (Spanish).
- Veerman, S.R.T., Bogers, J.P.A.M., Cohen, D., Schulte, P.F.J., 2022. COVID-19: risks, complications, and monitoring in patients on clozapine. *Pharmacopsychiatry* 55, 48–56. <https://doi.org/10.1055/a-1562-2521>.
- Verdoux, H., Pambrun, E., 2014. Clozapine use pattern in persons with and without treatment for Parkinson's disease in real-world conditions: a naturalistic study in a community-based sample. *Acta Psychiatr. Scand.* 130, 487–497. <https://doi.org/10.1111/acps.12344>.
- Verdoux, H., Quiles, C., 2020. Educational needs and psychoeducation interventions in clozapine users: a narrative review. *Acta Psychiatr. Scand.* 142, 96–108. <https://doi.org/10.1111/acps.13172>.
- Verdoux, H., Pambrun, E., Cortaredona, S., Coldefy, M., Le Neindre, C., Tournier, M., Verger, P., 2016. Geographical disparities in prescription practices of lithium and clozapine: a community-based study. *Acta Psychiatr. Scand.* 133, 470–480. <https://doi.org/10.1111/acps.12554>.
- Verdoux, H., Quiles, C., Bachmann, C.J., Siskind, D., 2018. Prescriber and institutional barriers and facilitators of clozapine use: a systematic review. *Schizophr. Res.* 201, 10–19. <https://doi.org/10.1016/j.schres.2018.05.046>.
- Verdoux, H., Quiles, C., de Leon, J., 2019. Clinical determinants of fever in clozapine users and implications for treatment management: a narrative review. *Schizophr. Res.* 211, 1–9. <https://doi.org/10.1016/j.schres.2019.07.040>.
- Verdoux, H., Quiles, C., de Leon, J., 2024a. Risks and benefits of clozapine and lithium co-prescribing: a systematic review and expert recommendations. *Schizophr. Res.* <https://doi.org/10.1016/j.schres.2023.03.032> (Epub ahead of print).
- Verdoux, H., Quiles, C., de Leon, J., 2024b. Optimizing antidepressant and clozapine co-prescription in clinical practice: a systematic review and expert recommendations. *Schizophr. Res.* <https://doi.org/10.1016/j.schres.2023.10.003> (Epub ahead of print).
- Vermeulen, J.M., van Rooijen, G., van de Kerkhof, M.P.J., Sutherland, A.L., Correll, C.U., de Haan, L., 2019. Clozapine and long-term mortality risk in patients with schizophrenia: a systematic review and meta-analysis of studies lasting 1.1–12.5 years. *Schizophr. Bull.* 45, 315–329. <https://doi.org/10.1093/schbul/sby052>.
- Vesterby, A., Pedersen, J.H., Kaempe, B., Thomsen, N.J., 1980. Pludselig død under behandling med klozapin (Leponex) [sudden death during treatment with clozapine (Leponex)]. *Ugeskr. Laeger* 142, 170–171.

- Villasante-Tezanos, A.G., Rohde, C., Nielsen, J., de Leon, J., 2020. Pneumonia risk: approximately one-third is due to clozapine and two-thirds is due to treatment-resistant schizophrenia. *Acta Psychiatr. Scand.* 142, 66–67. <https://doi.org/10.1111/acps.13184>.
- Wakao, R., Taavola, H., Sandberg, L., Iwasa, E., Soejima, S., Chandler, R., Norén, G.N., 2019. Data-driven identification of adverse event reporting patterns for Japan in VigiBase, the WHO global database of individual case safety reports. *Drug Saf.* 42, 1487–1498. <https://doi.org/10.1007/s40264-019-00861-y>.
- Whiskey, E., Barnard, A., Oloyede, E., Dzahini, O., Taylor, D.M., Shergill, S.S., 2021. An evaluation of the variation and underuse of clozapine in the United Kingdom. *Acta Psychiatr. Scand.* 143, 339–347. <https://doi.org/10.1111/acps.13280>.
- Wimberley, T., MacCabe, J.H., Laursen, T.M., Sørensen, H.J., Astrup, A., Horsdal, H.T., Gasse, C., Støvring, H., 2017. Mortality and self-harm in association with clozapine in treatment-resistant schizophrenia. *Am. J. Psychiatry* 174, 990–998. <https://doi.org/10.1176/appi.ajp.2017.16091097>.
- Windfuhr, K., Turnbull, P., While, D., Swinson, N., Mehta, H., Hadfield, K., Hiroeh, U., Watkinson, H., Dixon, C., Flynn, S., Thomas, S., Lewis, G., Ferrier, I.N., Amos, T., Skapinakis, P., Shaw, J., Kapur, N., Appleby, L., 2011. The incidence and associated risk factors for sudden unexplained death in psychiatric in-patients in England and Wales. *J. Psychopharmacol.* 25, 1533–1542. <https://doi.org/10.1177/0269881110379288>.
- Yang, X., Chen, Y., Wang, H., Fu, X., Kural, K.C., Cao, H., Li, Y., 2021. Schizophrenia plays a negative role in the pathological development of myocardial infarction at multiple biological levels. *Front. Genet.* 12, 607690 <https://doi.org/10.3389/fgene.2021.607690>.
- Zoccali, R., Muscatello, M.R., Torre, D.L., Malara, G., Canale, A., Crucitti, D., D'Arrigo, C., Spina, E., 2003. Lack of a pharmacokinetic interaction between mirtazapine and the newer antipsychotics clozapine, risperidone and olanzapine in patients with chronic schizophrenia. *Pharmacol. Res.* 48, 411–414. [https://doi.org/10.1016/s1043-6618\(03\)00178-6](https://doi.org/10.1016/s1043-6618(03)00178-6).
- Zullino, D.F., Delessert, D., Eap, C.B., Preisig, M., Baumann, P., 2002. Tobacco and cannabis smoking cessation can lead to intoxication with clozapine or olanzapine. *Int. Clin. Psychopharmacol.* 17, 141–143. <https://doi.org/10.1097/00004850-200205000-00008>.