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Haematologic malignancies associated with clozapine *v.* all other antipsychotic agents: a pharmacovigilance study in VigiBase®

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Abstract

Background. Clozapine is mainly used in patients with treatment-resistant schizophrenia and may lead to potentially severe haematologic adverse events, such as agranulocytosis. Whether clozapine might be associated with haematologic malignancies is unknown. We aimed to assess the association between haematologic malignancies and clozapine using Vigibase®, the WHO pharmacovigilance database.

Methods. We performed a disproportionality analysis to compute reporting odds-ratio adjusted for age, sex and concurrent reporting of antineoplastic/immunomodulating agents (aROR) for clozapine and structurally related drugs (loxapine, olanzapine and quetiapine) compared with other antipsychotic drugs. Cases were malignant lymphoma and leukaemia reports. Non-cases were all other reports including at least one antipsychotic report.

Results. Of the 140 226 clozapine-associated reports, 493 were malignant lymphoma cases, and 275 were leukaemia cases. Clozapine was significantly associated with malignant lymphoma (aROR 9.14, 95% CI 7.75–10.77) and leukaemia (aROR 3.54, 95% CI 2.97–4.22). Patients suffering from those haematologic malignancies were significantly younger in the clozapine treatment group than patients treated with other medicines ($p < 0.001$). The median time to onset (available for 212 cases) was 5.1 years (IQR 2.2–9.9) for malignant lymphoma and 2.5 years (IQR 0.6–7.4) for leukaemia. The aROR by quartile of dose of clozapine in patients with haematologic malignancies suggested a dose-dependent association.

Conclusions. Clozapine was significantly associated with a pharmacovigilance signal of haematologic malignancies. The risk-benefit balance of clozapine should be carefully assessed in patients with risk factors of haematologic malignancies. Clozapine should be used at the lowest effective posology.

Introduction

Clozapine is an atypical antipsychotic drug mainly used in patients with treatment-resistant schizophrenia. Clozapine use has increased in most countries over the years, with a prevalence of clozapine consumption in 2014 ranging from 0.9 to 173.2 per 100 000 persons, depending on the country (Bachmann et al., 2017; Remington et al., 2017). Safety issues are common with clozapine, including severe haematologic adverse effects such as agranulocytosis (incidence of 1.0%) and neutropenia (incidence of 3.0%) (Rajagopal, 2005). Clozapine has also been associated with eosinophilia, anaemia, lymphopenia, leukocytosis and thrombocytopenia (Rajagopal, 2005).

The case of a schizophrenic patient with long-term use of clozapine and diagnosed with diffuse large B cell lymphoma was reported to our regional pharmacovigilance centre. Several cases of haematologic malignancies have also been reported recently in patients treated with clozapine (Leung, Barreto, & Thompson, 2018; Meltzer, 2016; Nielsen & Boysen, 2010). An increased risk of acute myeloid leukaemia associated with clozapine exposure was suspected in a cohort of 31 788 Danish patients with schizophrenia or schizo-affective disorders (Nielsen & Boysen, 2010). During a mean follow-up of 11.2 years, 3779 patients were exposed to clozapine, among whom four cases of acute myeloid leukaemia were identified, corresponding to a hazard ratio (adjusted for sex, age and antipsychotic exposure) of 8.31 (95% CI 2.28–

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38.46). In addition, in an Australian community mental health centre during an 11-year period, 5 out of 221 patients taking clozapine had developed non-Hodgkin's lymphomas, among whom two were Burkitt's lymphoma patients. The lymphomas occurred between ages 39 and 58, which the author believed to be younger than the general population and thus was likely associated with clozapine administration (Meltzer, 2016). Also, a study performed with the Expanded Rochester Epidemiologic Project on approximately 1.8 million unique individual patients in 27 counties of Minnesota with data on clozapine prescription information (2003–2015) and data on diagnosis (2010–2015) identified four cases of patients who developed lymphoma following clozapine exposure (Leung et al., 2018). Clozapine induced agranulocytosis is caused by the bioactivation of clozapine in an N-arylnitrenium ion (Jegouzo et al., 1999; Uetrecht, Zahid, Tehim, Mim Fu, & Rakhit, 1997). N-Arylnitrenium ions are recognised as active reactive intermediates in chemical carcinogenesis (Novak & Zhang, 2012). Clozapine formed N-arylnitrenium ions could therefore theoretically be a potent carcinogenic agent. Thus, the aim of the present study was to evaluate the association between haematologic malignancies and clozapine exposure using the World Health Organization (WHO) pharmacovigilance database VigiBase®. We also performed an extensive literature search to identify case reports of haematologic malignancies in clozapine-treated patients.

Methods

Study design

We performed a retrospective pharmacovigilance cohort study in Vigibase®, the WHO global individual case safety report (ICSR) database (Bate, Lindquist, & Edwards, 2008). This database contains more than 18 million ICSRs (hereafter, the reports) received from 130 country members since 1967. Reports include administrative information (country, type of report, qualification of reporter), patient data (sex, age), medication data [drug name (s), role (suspect, concomitant, interacting), start and stop dates, indication and dose], adverse drug reaction (ADR) data (type of adverse effect, date of onset, WHO assessment causality, outcome) and time to onset between medications and reactions (online Supplementary Methods S1). The study protocol was registered on ClinicalTrials.gov, NCT04074213.

Setting and participants

Reports were extracted from inception up until the 3rd of March 2019. Reports were eligible if they contained at least one liable antipsychotic drug (online Supplementary Methods S1 and S2). This setting was chosen to improve the comparability between cases and non-cases, i.e. to limit the indication bias.

Outcomes

The primary outcome was the association between clozapine and haematologic malignancies (including both lymphomas and leukaemia). Secondary outcomes were the dose-effect relationship between clozapine and haematologic malignancies; the association between haematologic malignancies and the three other mainly used antipsychotics included in the same chemical subgroup than clozapine, (olanzapine, quetiapine and loxapine), to investigate a class effect; the association between myelodysplastic syndrome (MDS) and all four drugs.

Variables

Lymphomas and leukaemia cases were identified with the Medical Dictionary for Regulatory activities terms (online Supplementary Methods S3). Clozapine and the other drugs exposure was identified with the Anatomical and Therapeutic Chemical classification and/or their international non-proprietary name (online Supplementary Methods S2 and S4).

Data on potential confounders such as age (categorised '<18 years old (yo)', '18–44 yo', '45–64 yo', '65–74 yo', '>75 yo'), sex, the presence of concurrent reporting of at least one antineoplastic or immunomodulating agents was collected (online Supplementary Methods S1). The clozapine daily dose was extracted from clozapine reports and was divided into quartiles.

Descriptive study in VigiBase®

We described the clinical features of clozapine-related haematologic malignancies according to the main clinical subtypes. Descriptive analysis encompassed acute lymphocytic and myeloid leukaemia, chronic lymphocytic and myeloid leukaemia, Hodgkin's disease and non-Hodgkin's lymphomas (online Supplementary Methods S1, S5–S8). In the haematologic malignancy population treated with clozapine, for each subtype, we reported the reports completeness score, demographic parameters (age, sex), dose, time to onset from the clozapine start date and mortality rate. We also compared the sex and age of clozapine-associated reports of each subtype of haematologic malignancies with all other reports including liable medicines (of all pharmacological classes) in the full database population. The choice of the full database population to compare age and sex was guided by the fact that the number of potential confounders (some of which are caused by missing data) for the reporting of haematologic malignancies would be averaged by analysing a high number of patients (Faillie, 2019).

Literature search

We performed a comprehensive and extensive literature search in MEDLINE and Google Scholar for all articles (regardless of the language) from inception to 12 March 2019, including reporting cases of lymphomas and leukaemia associated with the use of clozapine (online Supplementary Methods S1).

Statistical analysis

A disproportionality analysis was used to evaluate the associations between drugs and reactions in Vigibase® (Faillie, 2019). Disproportionality analysis compares the proportion of reports of an ADR reported for a single drug with the proportion of reports of the same ADR for all other drugs or for a selected panel of control drugs. Briefly, if the proportion of an ADR in patients exposed to the drug of interest is greater than the proportion of the same ADR in patients not exposed to that drug, then a disproportionality association exists between the drug of interest and the ADR and is a potential signal for safety (Chavant, Favrelière, Lafay-Chebassier, Plazanet, & Pérault-Pochat, 2011; Montastruc, Sommet, Bagheri, & Lapeyre-Mestre, 2011). In the present study, the reporting odds-ratio (ROR) and its 95%

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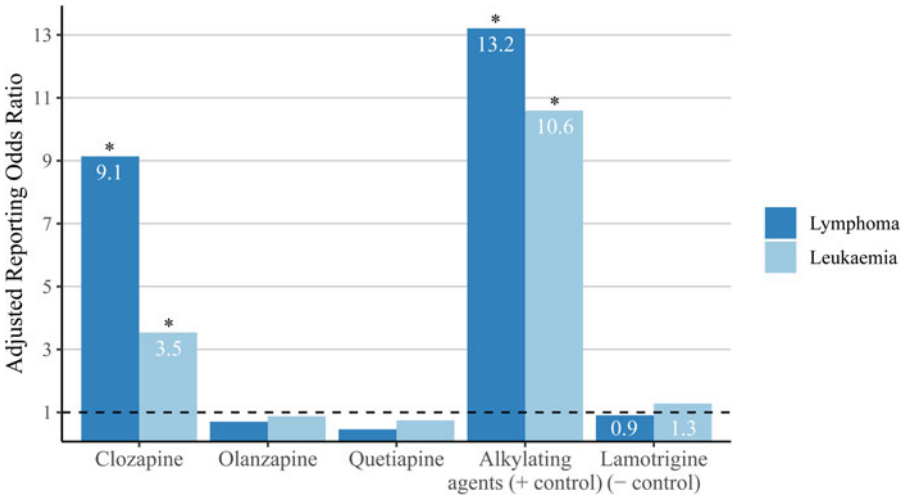

Fig. 1. Adjusted reporting OR VigiBase® for haematologic malignancies associated with antipsychotic drugs until 3 March 2019. Adjustment factors were age, sex and concurrent reporting of anticancer or immunomodulating agents (except for alkylating agents). *indicates a significant association between the drug and the haematologic malignancy.

confidence interval (CI) were used to evaluate disproportionality. Because the ROR was found to be more reliable when at least three to five cases of an ADR were reported for a drug, we chose to compute the ROR only for drugs that reported at least five cases of haematologic malignancies (Evans, Waller, & Davis, 2001). Adjusted RORs (aRORs) were computed with a multivariate logistic regression model. Adjustment variables were age, sex and concurrent reporting of at least one antineoplastic or immunomodulating agents. In disproportionality analysis, positive controls are drugs or drug classes established to provoke the ADR of interest, and negative controls are drugs that are known not to provoke the ADR. We chose the alkylating agents (online Supplementary Methods S4) as a positive control and lamotrigine as a negative control in the primary analysis population (reports with at least one antipsychotic). A lower end of the 95% CI of the aROR >1 was deemed significant. Student's *t* test and χ^2 test were used to compare the baseline characteristics of clozapine-associated haematologic malignancies reports with the other medicine-associated haematologic malignancies reports. Sensitivity analyses included the ROR computation in the full Vigibase® population, with no report selection, and data mining available in Vigilyze®.

Results

Disproportionality analysis in VigiBase®

Among the 18 745 674 reports in Vigibase®, 913 780 (4.87%) reported at least one antipsychotic and were selected as our primary analysis population. In the primary analysis population, clozapine was reported in 140 226 (15.35%) reports. There were 493 malignant lymphoma cases, 275 leukaemia cases and 1658 MDS cases in clozapine-associated reports. Clozapine was suspected in respectively 485 (98.4%), 271 (98.5%) and 1651 (99.6%) of these reports and indication was reported in respectively 312 (63.3%), 148 (53.8%) and 1375 (82.9%) of the reports, with clear schizophrenia indication in respectively 247 (50.1%), 112 (40.7%) and 603 (36.4%) of the reports (online Supplementary Table S1). Figure 1 and Table 1 show the result of the disproportionality analysis. Clozapine was significantly associated with a higher reporting of lymphoma (aROR 9.13, 95% CI 7.75–10.77) and leukaemia (aROR 3.54, 95% CI 2.97–4.22) compared to other antipsychotics. Clozapine was also associated with a higher reporting of MDS. There was no significant association between lymphoma, leukaemia or MDS and quetiapine, olanzapine and loxapine. The alkylating agents (positive control) had a significant association with lymphoma, leukaemia and MDS. Lamotrigine (negative control) had no significant association. Results were consistent across the sensitivity analyses in the full database population with all other liable medications as the control group (online Supplementary Table S2) and in the data mining available in Vigilyze® (online Supplementary Table S3).

The daily dose of clozapine was available in 53 541 reports (37.1%). Figure 2 and Table 2 show the evolution of the aROR of lymphoma and leukaemia (aROR relative to the first quartile) for each quartile of daily dose of clozapine. There was a significant association between the clozapine daily dose and the reporting of lymphoma and leukaemia ($p < 0.001$ for both). When compared to the first quartile (daily dose ⩽150 mg), the aROR for leukaemia progressively increased: 1.11 (95% CI 0.56–2.19) in the (150–300] mg quartile, 2.22 (95% CI 1.11–4.44) in the (300–425] mg quartile and 2.6 (95% CI 1.39–4.87) in the fourth quartile (daily dose >425 mg). Similarly, when compared to the first quartile, the aROR for lymphoma was 3.06 (95% CI 1.75–5.35) in the (150–300] mg quartile, 3.42 (95% CI 1.84–6.35) in the (300–425] mg quartile and 5.52 (95% CI 3.18–9.57) in the >425 mg quartile. A dose-effect relationship was not observed for MDS (online Supplementary Table S4).

Descriptive analysis in VigiBase®

In clozapine-associated reports, the mean patient age was 49.5 ± 11.7 years old (yo) for the lymphoma reports and 50.5 ± 14.3 yo for the leukaemia reports ($p = 0.57$ for age difference between lymphoma and leukaemia reports). This age was significantly lower than the mean age reported for lymphoma (55.0 yo; $p < 0.001$) and leukaemia (57.4 yo; $p < 0.001$) in the full database population with all other medicines reported in Vigibase®. In the haematologic malignancy population, clozapine-associated lymphoma and leukaemia cases were more likely to be reported in men than were all other medicine-associated lymphoma and leukaemia cases (73.3% *v.* 50.8% and 66.4% *v.* 53.4%, respectively, $p < 0.001$ for both). Mortality rates were 16.6% and 16.7% at the time of reporting in clozapine-associated lymphoma and leukaemia reports, respectively (Table 3).

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Table 1. Disproportionality analysis in Vigibase®: search for an over-reporting of haematologic malignancies with clozapine, loxapine, olanzapine, quetiapine, alkylating agents and lamotrigine compared to all other antipsychotics

	Leukaemia			Malignant lymphoma			Myelodysplastic syndrome			Total reports in Vigibase®[a]
	N	aROR	95% CI	*N*	aROR	95% CI	*N*	aROR	95% CI	
Clozapine	275	3.54	(2.97–4.22)	493	9.14	(7.75–10.77)	1658	2.82	(2.64–3.02)	140 225
Loxapine	2	[b]		3	[b]		18	0.55	(0.33–0.93)	4839
Olanzapine	68	0.88	(0.66–1.16)	63	0.70	(0.53–0.94)	331	0.61	(0.54–0.69)	83 379
Quetiapine	85	0.75	(0.59–0.95)	69	0.46	(0.34–0.61)	314	0.39	(0.34–0.44)	115 072
Alkylating agents (positive control)	60	10.59	(7.92–14.17)	77	13.21	(10.18–17.13)	325	10.02	(8.82–11.37)	4806
Lamotrigine (negative control)	30	1.28	(0.88–1.87)	26	0.91	(0.59–1.40)	198	1.16	(0.99; 1.35)	31 017

N, number of reports; aROR, adjusted reporting odds ratios.
Multivariate analysis: results were adjusted on age, sex and concomitant report of antineoplastic and immunomodulating agents.
[a]Primary analysis population: reports with at least one antipsychotic (*n* = 913 780).
[b]Disproportionality analysis were computed if at least five cases were reported.

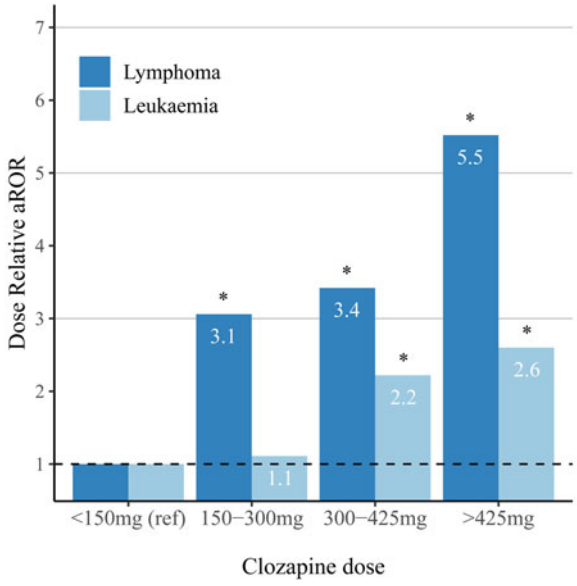

Fig. 2. Dose-effect relationship on the reporting of haematologic malignancies in clozapine ICSRs in Vigibase®. The daily dose of clozapine is divided into quartiles. The results are expressed relative to the first quartile of the daily dose of clozapine (<150 mg, reference). aROR, adjusted reporting odds-ratio. *Indicates significant 2-by-2 differences.

The median daily dose of clozapine in the leukaemia group was 350 mg. The median daily dose of clozapine used in the malignant lymphoma group was 400 mg (Table 3). The median time to onset from clozapine initiation was 5.1 years (IQR 2.2–9.9) in malignant lymphoma ICSRs (available for 131 patients) and 2.5 years (IQR 0.6–7.4) in the leukaemia ICSRs (available for 81 patients) (Table 3).

Literature search

Of the 1616 articles yielded by the search, 109 were assessed for eligibility and 20 were retained (online Supplementary Fig. S1 shows the flow diagram of the study selection process). These 20 publications reported a total of 30 lymphomas or leukaemia in patients treated with clozapine. The median age was 46 yo, and 81% of the patients were males. The median time to onset was 7 years (IQR 5–10.5). The clozapine median daily dose was 400 mg (online Supplementary Tables S5 and S6).

Discussion

In our study, performed under real-life conditions, we found a significant association between clozapine and haematologic malignancies, with a possible dose-effect relationship. Our results did not suggest a class effect.

Interestingly, the results of the literature search were consistent with our data regarding the various types of lymphoma/leukaemia, clozapine dose, sex ratio, age and time to onset (online Supplementary Table S5). Furthermore, it is important to note that to our knowledge, schizophrenia has not been associated with an increased risk of haematologic malignancies and could even be protective against cancer development, including leukaemia and lymphoma (Ji et al., 2013).

While men and women have a similar prevalence of schizophrenia (Li, Ma, Wang, Yang, & Wang, 2016), there are important gender differences in clozapine prescription. Indeed, it has been reported in several studies that, similarly to our data, males represented between 63.1% and 78.6% of the patients treated with clozapine (de Silveira et al., 2015; Taylor, 2004). Thus, we propose that sex is not a risk factor for clozapine-induced haematological disorders. Conversely, the mean age of patients treated with clozapine and suffering from haematologic malignancies was significantly lower than the mean age reported in patients treated with other medicines, with the notable exception of the ALL because the median age of diagnosis of ALL is approximately 8 years old (Snodgrass et al., 2018), while patients treated with clozapine are ordinarily adults. In our data, the mean age of clozapine-treated patients suffering from lymphoma (Hodgkin's and non-Hodgkin's) or leukaemia (chronic myeloid or lymphocytic; acute myeloid leukaemia) appeared to be lower than those observed in the general population (Hallek, Shanafelt, & Eichhorst, 2018; Höglund, Sandin, & Simonsson, 2015;

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Table 2. ROR and aROR according to clozapine daily dose (divided into quartiles), in ICSRs of leukaemia and in ICSRs of lymphoma. Daily dose of clozapine available in 53 541 reports

		Leukaemia				Lymphoma			
		Univariate analysis		Multivariate analysis		Univariate analysis		Multivariate analysis	
		ROR	95% CI	aROR	95% CI	ROR	95% CI	aROR	95% CI
Daily dose (mg)	⩽150	1	–	1	–	1	–	1	–
	(150–300)	0.99	(0.54–1.84)	1.11	(0.56–2.19)	2.36	(1.42–3.94)	3.06	(1.75–5.35)
	(300–425)	1.7	(0.91–3.19)	2.22	(1.11–4.44)	2.35	(1.33–4.16)	3.42	(1.84–6.35)
	>425	1.71	(0.96–3.04)	2.6	(1.39–4.87)	4.07	(2.48–6.67)	5.52	(3.18–9.57)
Age (+10 years ROR)		1.03	(1.02–1.04)	1.04	(1.03–1.06)	1.03	(1.02–1.04)	1.05	(1.03–1.06)
Sex (male)		1.15	(0.74–1.77)	1.29	(0.81–2.06)	2.49	(1.72–3.61)	3.69	(2.45–5.56)
Antineoplastics and immunomodulating agents		3.86	(1.56–9.52)	3.42	(1.24–9.44)	14.52	(9.79–21.52)	20.14	(13.09–30.98)

Multivariate analysis: results were adjusted on age, sex and concomitant report of antineoplastic and immunomodulating agents.

Juliusson et al., 2009; Smith et al., 2015). The peak incidence of schizophrenia for males and females is in the 15–24 yo decade (Messias, Chen, & Eaton, 2007). The time to onset of lymphoma/leukaemia after clozapine initiation ranged from 2.5 years (IQR 0.6–7.4) for leukaemia to 5.1 years (IQR 2.2–9.9) for malignant lymphoma in our study. The younger age at diagnosis for haematologic malignancies in clozapine ICSRs compared to haematologic malignancies in the literature could be in favour of a clozapine-induced adverse effect. The possible dose-dependent effect on the adjusted reporting of haematologic malignancies in our study is consistent with the *in vitro* dose-dependent toxicity of the clozapine-formed nitrenium ion (Gardner, Zahid, MacCrimmon, & Uetrecht, 1998; Pereira & Dean, 2006) and would reinforce the hypothesis of a clozapine-induced adverse effect.

Bioactivation of clozapine in a nitrenium ion by the myeloperoxidase-hydrogen peroxide system of the activated neutrophils (Jegouzo et al., 1999; Uetrecht et al., 1997) and the cytochrome P450 (CYP) is the initial step in the haematological toxicity of both clozapine and olanzapine (Gardner et al., 1998; Sikora, Adamus, & Marcinek, 2007; Williams, Pirmohamed, Naisbitt, Uetrecht, & Park, 2000). Myeloperoxidase is expressed early in myeloid precursors in the bone marrow (Koeffler, Ranyard, & Pertcheck, 1985), and bone marrow stroma highly express various CYP, among which CYP3A4 appears to be the most important (Alonso et al., 2015). Bioactivation of clozapine in a nitrenium ion induces a central toxicity: dose-dependent inhibition of stromal viability at therapeutically relevant concentrations (Pereira & Dean, 2006) and dose-dependent toxicity to human leukocytes (Gardner et al., 1998).

It is also very important to note that the N-arylnitrenium ions, of which clozapine-formed nitrenium ions are a part, are recognised as the active reactive intermediates in chemical carcinogenesis caused by arylamines and food-derived heterocyclic arylamines (Novak & Zhang, 2012). These N-arylnitrenium ions react with DNA and proteins and are very carcinogens (Novak & Zhang, 2012). Furthermore, human T lymphocytes can express CYP1 activity and bioactivate heterocyclic aromatic amines in nitrenium ions that form DNA adducts (Bellamri et al., 2016; Singh et al., 2010). As nitrenium ions have been demonstrated to be efficient at targeting single-stranded DNA, nitrenium ion-based antitumour drugs are currently under development (Novak & Zhang, 2012).

In our data, quetiapine, olanzapine and loxapine did not appear to be associated with haematologic malignancies. Indeed, despite very similar chemical structures, only clozapine and olanzapine possess nitrogen at position 5. The presence of sulphur (quetiapine) or oxygen (loxapine) at this latter position precludes the formation of a nitrenium ion (Jegouzo et al., 1999; Williams et al., 2000). Although both clozapine and olanzapine have the ability to form a nitrenium ion, it has been shown that the nitrenium ion formed from clozapine was more toxic at an equimolar dose than the nitrenium ion formed from olanzapine (Gardner et al., 1998; Ng, Kennar, & Uetrecht, 2014). Furthermore, while they have a similar molecular mass (327 g/mol for clozapine and 312 g/mol for olanzapine), the therapeutic dose of olanzapine is much lower than that of clozapine.

The bioactivation of clozapine by neutrophils or their precursors and/or by lymphocytes and/or stroma cells produces a reactive and potentially carcinogenic nitrenium ion. This nitrenium ion could form DNA adducts and be deleterious on haematologic cells, depending on the genetics of each individual. We hypothesize that this deleterious effect on the haematologic cells might in the long term induce the outcome of haematologic malignancies in susceptible patients, particularly in those with certain antioxidant system impairing polymorphisms, already identified as a genetic risk factor of clozapine-induced agranulocytosis (Opgen-Rhein & Dettling, 2008; Ostrousky et al., 2003; van der Weide et al., 2017). Still, clozapine is a broad spectrum ligand with a pharmacologic profile which substantially differs of other antipsychotic agents (Schaus & Bymaster, 1998). Thus, the hypothesis that hematologic malignancies would be a result of clozapine pharmacological off-target properties cannot be ruled out.

Limitations

Our study had some mandatory limitations due to the use of a pharmacovigilance database. Underreporting is the most important limitation in pharmacovigilance but fortunately does not change the results and significance of disproportionality analysis (Montastruc et al., 2011). Also, the probability that the suspected

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Table 3. Characteristics of patients in haematologic malignancies ICSRs in Vigibase®, from 1967 until 3 March 2019

			Leukaemia					Malignant lymphoma		
			Total	LAL	LAM	LCL	LCM	Total	HL	NHL
Age	Patients treated with clozapine	N (avail.)	218	6	20	34	12	415	57	192
		Mean age in years (IQR)	50.5	46.2	44.6	52.8	40.9	49,5	42.9	51.2
	Patients treated with other medicines	N (avail.)	18 057	1064	4888	1330	1560	15 462	1381	7809
		Mean age in years (IQR)	57.4	39.3	57.0	64.2	51.7	55	46.8	58.4
	p value		<0.001*	0.39	0.001*	<0.001*	0.026*	<0.001*	0.12	<0.001*
Sex	Patients treated with clozapine	N (avail.)	256	9	24	42	13	478	64	219
		Males (%)	170 (66.4)	6 (66.7)	18 (75.0)	32 (76.2)	10 (76.9)	350 (73.2)	47 (73.4)	162 (74.0)
	Patients treated with other medicines	N (avail.)	24 101	1305	6008	2002	2172	20 733	1804	10 094
		Males (%)	12 878 (53.4)	728 (55.8)	3101 (51.6)	1160 (57.9)	1215 (55.9)	10 536 (50.8)	952 (52.8)	5325 (52.8)
	p value		<0.001*	0.51	0.02*	0.02*	0.13	<0.001*	0.001*	<0.001*
Time to onset	N (avail.)		81	2	6	12	3	131	17	56
	Years (IQR)		2.5 (0.6–7.4)	5.3 (2.7–7.8)	8.3 (7.6–9.1)	7.3 (3.2–10.0)	7.1 (3.7–12.1)	5.1 (2.2–9.9)	4.3 (3.0–8.1)	5.7 (1.6–10.0)
Dose	N (avail.)		92	3	7	15	5	179	23	90
	Median daily dose of clozapine in mg (IQR)		350	400	300	500	500	400	400	400
All cause death in clozapine-associated reports (%)*			16.7%	11.1%	20.8%	0.0%	15.3%	16.6%	11.5%	14.9%
Completeness score (IQR)			0.40 (0.28–0.257)	0.51 (0.42–0.65)	0.48 (0.31–0.86)	0.46 (0.28–0.63)	0.48 (0.41–0.75)	0.44 (0.28–0.63)	0.41 (0.31–0.63)	0.44 (0.28–0.63)

HL, Hodgkin's lymphomas; IQR, InterQuartile range; LAL, leukaemias acute lymphocytic; LAM, leukaemias acute myeloid; LCL, leukaemias chronic lymphocytic; LCM, leukaemias chronic myeloid; N (avail.), total number of reports of patients treated with clozapine with available age; NHL, non-Hodgkin's lymphomas.
*Significant.

adverse effect is drug-related is not the same in all cases. Despite being a valuable tool to detect safety signals, disproportionality analysis of spontaneous reports also has some inherent limitations: the data may be of low quality due to missing information, and the causal relationship between the reported drug and the ADR is not proved (Egberts, Meyboom, & van Puijenbroek, 2002; Garbe & Suissa, 2014); however, in the present case, a plausible underlying mechanism including the formation of a nitrenium ion was identified. Furthermore, the reporting pattern of ADRs may differ between new and old drugs, with the most vigorous monitoring being at the time of marketing and shortly thereafter. Rather, it offers a rough indication of the signal strength used to generate hypotheses for unknown potential ADRs (Faillie, 2019). It's very important to note that because of under-reporting of adverse events, pharmacovigilance data cannot be used to determine incidence rates of adverse effects (Sharrar & Dieck, 2013). The adjustment on age, sex and coreporting of antineoplastic and immunomodulating agents allowed us to limit the confounding bias. Furthermore, the significant results obtained with the positive control, 'Alkylating agents', well-known to be carcinogenic, was another guarantee of validity despite not covering all possible confounding. We also did not have information on the history of smoking or drug abuse of the patients, while substance abusers are more at risk of developing haematologic malignancies. Fortunately, we could limit this bias by restricting the primary analysis population to people treated with antipsychotics, where the prevalence of smokers and substance use disorders should be comparable between clozapine and other drug users.

Conclusions

This study highlighted a significant safety signal between clozapine and haematologic malignancies, with a possible dose-dependent effect and fundamental data supporting a causal association. As this study was based on pharmacovigilance data, a causal relationship between clozapine exposure and occurrence of haematologic malignancies cannot be assumed with certainty. Still, we think that in daily practice, psychiatrists should control the complete blood count with caution to detect potential MDS or haematologic malignancies in clozapine-treated patients. In patients with potential risk factors of haematologic malignancies (i.e. immunodeficiency, tobacco smoking, substance abuse, exposure to ionising radiation, radon, pesticides, benzene and other organic solvents), the risk-benefit balance of clozapine should be carefully assessed, and clozapine should be used at the lowest effective posology.

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Ethical standards. All applicable international, national and/or institutional guidelines for the care and use of animals were followed.

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