Clozapine-associated neutropenia and agranulocytosis in Argentina (2007–2012)

María V. Balda[a], Osvaldo U. Garay[b], Rosa M. Papale[a], Inés Bignone[a], Viviana G. Bologna[a], Andrés Brandolini[a], Cintia R. Prokopez[a], Juan I. Balasini[c], Ross J. Baldessarini[f] and Federico M. Daray[d,e]

The risks of severe leukopenia and agranulocytosis have varied over time and among geographical regions and cultures, with little information available on South American populations. Accordingly, we reviewed and analyzed data from a 6-year experience monitored by an Argentine national registry to which reporting of adverse events reports is required. We analyzed data for 2007–2012 from the pharmacovigilance program of the Argentine drug-regulatory agency (ANMAT) using standard bivariate and multivariate statistical methods and survival analysis. We identified 378 cases of adverse hematological events over 6 years among an average of 12 305 individuals/year treated with clozapine (308 ± 133 mg/day) to estimate the mean annualized rates of leukopenia [0.19 (95% confidence interval [CI] 0.11–0.27)], neutropenia [0.38 (95% CI 0.34–0.43)], and agranulocytosis [0.05 (95% CI 0.02–0.08)] % per year [median latency 2 (95% CI 1.3–2.1) months]; fatalities related to agranulocytosis averaged 4.2 (95% CI 0.0–9.2) per 100 000 treated individuals/year. Factors associated significantly and independently with agranulocytosis were female sex, older age, and use of other drugs in addition to clozapine. With monitoring by international standards, recent risks of clozapine-associated agranulocytosis in Argentina were lower, but fatality rates were higher than that in other regions of the world. Risk factors include the use of multiple psychotropic drugs, female sex, and older age. *Int Clin Psychopharmacol* **30:109–114**

International Clinical Psychopharmacology 2015, **30**:109–114

Keywords: agranulocytosis, Argentina, clozapine, leukopenia, pharmacovigilance

[a]Administración Nacional de Medicamentos, Alimentos y Tecnología Médica (ANMAT), Avenida de Mayo 869 (C1084AAD), [b]Instituto de Efectividad Clínica y Sanitaria (IECS), Dr Emilio Ravignani 2024, [c]Secretaría de Política Económica, Ministerio de Economía y Finanzas Públicas, [d]III Cátedra de Farmacología, Facultad de Medicina, Universidad de Buenos Aires, Paraguay 2155, 9th floor, [e]Consejo Nacional de Investigaciones Científicas y Técnicas (CONICET), Buenos Aires, Argentina and [f]International Consortium for Bipolar & Psychotic Disorders Research, McLean Hospital, Harvard Medical School, Boston, Massachusetts, USA

Correspondence to Federico M. Daray, MD, III Cátedra de Farmacología, Facultad de Medicina, Universidad de Buenos Aires, Paraguay 2155, Piso 9, C1121ABG Buenos Aires, Argentina
Tel: +54 11 496 20300; fax: +54 11 496 20300; e-mail: fdaray@hotmail.com

Received 15 August 2014 **Accepted** 29 October 2014

Introduction

Clozapine is the prototypical 'atypical' or 'second-generation' antipsychotic drug, with a relatively low risk of most neurological effects on posture and motility (other than akathisia) that are typical of older neuroleptic agents (Baldessarini and Frankenburg, 1991; Lieberman, 1998). It also appears to be more effective for the treatment of patients diagnosed with schizophrenia than other antipsychotics (Baldessarini and Frankenburg, 1991; Lieberman, 1998). However, clozapine has several important adverse effects, some of which are life-threatening. These include dose-dependent risk of epileptic seizures, potentially severe inhibition of bowel function, and possible carditis and cardiomyopathy (Baldessarini, 2013). However, prevalent and particularly dangerous adverse effects associated with clozapine are blood dyscrasias that include leukopenia, neutropenia, and agranulocytosis, with the risk of fatalities (Baldessarini and Frankenburg, 1991; Copolov *et al.*, 1998; Lieberman, 1998; Lambertenghi Deliliers, 2000; Miller, 2000; Haddad and Sharma, 2007). These hematological risks led to the removal of the drug from clinical use in the 1980s. However, the combination of superior antipsychotic efficacy of clozapine and arrangements to monitor white blood cell (WBC) counts regularly during its clinical use, as well as limiting its use to patients who have failed at least two other adequate trials of pharmacologically dissimilar antipsychotic drugs led to its return to international markets in the 1990s (Alvir *et al.*, 1993; Copolov *et al.*, 1998; Lambertenghi Deliliers, 2000).

In Argentina, as in other countries, clozapine was initially marketed in the early 1970s (Bergman *et al.*, 2011). In 1977–1992, as a result of deaths from agranulocytosis reported in Finland (1975), the use of clozapine in Argentina was restricted to institutional use and primarily for the treatment of schizophrenia patients. Following studies led by John Kane (US Clozaril Multicenter Trial), clozapine was released in the USA in 1989 and reintroduced in Europe in the 1990s. In 1992, Argentina also resumed marketing of clozapine and implemented the first national program for monitoring clozapine-treated patients, as proposed by the manufacturer Sandoz (currently Novartis) Corporation. In 1996, a year after the

DOI: 10.1097/YIC.0000000000000060

establishment of the Argentine National Administration of Drugs, Food and Medical Technology (ANMAT), the regulatory agency made these procedures official (Bergman *et al.*, 2011). Clozapine is currently provided by four pharmaceutical corporations in Buenos Aires, Argentina (Fabra, IVAX-Argentina, Novartis, and Rospaw), all of which require a program of consistent hematological monitoring overseen by the ANMAT. This program (Argentine Clozapine Monitoring System) requires a normal baseline WBC count and absolute neutrophil count (ANC) before starting treatment, with weekly retesting for 18 weeks and monthly thereafter. More frequent blood counts are obtained if a patient presents with mild leukopenia (WBC count of 3500–3000 cells/μl or ANC of 2000–1500 cells/μl of blood). Moderate (WBC count of 3000–2000 cells/μl, ANC 1500–1000 cells/μl) or severe leukopenia (WBC count < 2000 cells/μl, ANC < 1000 cells/μl), or agranulocytosis (ANC ≤ 500 cells/μl) requires that clozapine be discontinued. With severe leukopenia, blood counts are obtained daily until no longer severely reduced, and agranulocytosis requires expert consultation with a hematologist (ANMAT, 2000).

The risks of adverse hematological effects associated with clozapine treatment may vary among ethnic groups and countries (Atkin *et al.*, 1996; Munro *et al.*, 1999), making reports from different regions across the world of interest. Data from national registers of hematological adverse events associated with clozapine treatment have been reported from North America (Alvir *et al.*, 1993; Honigfeld *et al.*, 1998), Europe (Atkin *et al.*, 1996; Honigfeld *et al.*, 1998; Munro *et al.*, 1999; Lambertenghi Deliliers, 2000; Lahdelma and Appelberg, 2012), Australia–New Zealand (Miller and Cutten, 1997), and East Asia (Kang *et al.*, 2006), but not from Latin America or the Caribbean. Accordingly, the present study aimed to estimate the yearly incidence rates of major hematological adverse effects associated with clinical use of clozapine and to examine the potential risk factors associated with them, on the basis of data from patients in the Argentine Clozapine Monitoring System overseen by ANMAT and available between 2007 and 2012.

Methods

Data collection

Data for the 6 years sampled, 2007–2012, were obtained for all reported cases of adverse, clozapine-associated hematological events reported by doctors or by pharmaceutical manufacturers to the ANMAT, and recorded by their Pharmacovigilance Department. Notification of ANMAT of hematological adverse events during treatment with clozapine is mandatory (ANMAT, 2000). For each reported case, we sought information on age, sex, mean daily dose of clozapine, duration of treatment until the onset of blood dyscrasia, types and doses of other medicines being used with clozapine, and cases involving infections or deaths. Estimates of the total number of patients at risk by being prescribed clozapine were provided by the four companies marketing the drug in Argentina (Fabra, IVAX-Argentina, Novartis, and Rospaw). The study was authorized by ANMAT, and involved anonymous and aggregate reporting of findings.

Statistical analysis

Categorical measures are reported as frequency or percentage, and compared using contingency tables (χ^2); continuous measures are reported as means ± SD and compared using ANOVA methods (*t*-test) or the Wilcoxon rank-sum test (Mann–Whitney *U*-statistic) for non-normally distributed continuous data. The incidence of adverse hematological effects was calculated as the number of cases per individuals at risk for receiving the drug, and is reported as means of yearly rates with 95% confidence intervals (CIs).

Logistic regression modeling [to provide odds ratios (ORs) and their CI] tested potential factors for a significant and independent association with agranulocytosis among patients receiving clozapine. Because of a lack of information on individuals treated with clozapine who were not known to have adverse hematological events, we compared those who developed agranulocytosis (38 cases) with those who developed other adverse hematological (leukopenia and neutropenia, 339 cases), considering the effects of sex, age, and use of drugs other than clozapine. Latency to agranulocytosis was estimated using Kaplan–Meier survival analysis. Statistical significance required two-tailed *P* value less than 0.05. Analyses used commercial statistical software STATA (version 13; StataCorp, College Station, Texas, USA).

Results

We identified 393 cases of clozapine-associated adverse hematological events reported to the Pharmacovigilance Department of ANMAT in the 6 years between January 2007 and December 2012 among an estimated total of 12 305 clozapine-treated individuals at risk per year (6-year total of 73 831). Of these 393 cases, 15 were excluded because of lack of insufficient information for adequate analysis, leaving a total of 378. These 378 cases included 460 reports of adverse hematological events (1.22 events/patient), including 137 reports of leukopenia, 285 of neutropenia, and 38 cases of agranulocytosis (Table 1). Across the 6 years, the computed mean annualized incidence (per 100 person-years at risk) was as follows: leukopenia, 0.191; neutropenia, 0.385; and agranulocytosis, 0.051 (Table 1).

Among cases of leukopenia, approximately one-third, each, were mild, moderate, or severe, and incidence was similar among women and men. However, the frequencies of neutropenia and agranulocytosis were significantly greater among women: agranulocytosis was almost twice as frequent in women (Tables 2 and 3).

Table 1 Rates of leukopenia and agranulocytosis among clozapine-treated Argentine patients (2007–2012)

		Incidence (% per year)			
Years	Treated patients	Leukopenia	Neutropenia	Agranulocytosis	Fatalities
2007	11 920	31/11 920 (0.260)	54/11 920 (0.453)	5/11 920 (0.042)	0/11 920 (0.0000)
2008	10 642	31/10 642 (0.291)	40/10 642 (0.376)	11/10 642 (0.103)	1/10 642 (0.0094)
2009	11 425	25/11 425 (0.219)	44/11 425 (0.385)	6/11 425 (0.052)	1/11 425 (0.0088)
2010	11 369	14/11 369 (0.123)	36/11 369 (0.317)	4/11 369 (0.035)	0/11 369 (0.0000)
2011	13 898	15/13 898 (0.108)	58/13 898 (0.417)	9/13 898 (0.065)	1/13 898 (0.0072)
2012	14 577	21/14 577 (0.144)	53/14 577 (0.364)	3/14 577 (0.021)	0/14 577 (0.0000)
Mean (95% CI)	12 305 (10 662–13 948)	0.191 (0.111–0.271)	0.385 (0.336–0.434)	0.051 (0.020–0.081)	0.0042 (0.0000–0.0092)

The average annual risk of agranulocytosis was 51 cases per 100 000 patients treated, and 8.24% of these were fatal.
The nominal total of patients treated with clozapine over the 6 years was 73 831, but with uncertainty on how many patients are represented in more than 1 year.
CI, confidence interval.

Table 2 Severity of clozapine-associated leukopenia and neutropenia

	Leukopenia risk [*n* (%)]		Neutropenia risk [*n* (%)]	
Severities	Men	Women	Men	Women
Mild	18 (30.5)	21 (30.0)	79 (47.3)	62 (41.3)
Moderate	22 (37.3)	24 (34.3)	54 (32.3)	49 (32.7)
Severe	19 (32.2)	25 (35.7)	20 (12.0)	15 (10.0)
Agranulocytosis	0 (0.00)	0 (0.00)	14 (8.38)	24 (16.0)
Total	59 (100)	70 (100)	167 (100)	150 (100)

Leukocyte count definitions are provided in the text.

Table 3 Risk of leukopenia with clozapine by sex and age

	Risks [cases (%)]					
	Leukopenia		Neutropenia		Agranulocytosis	
Age groups	Men	Women	Men	Women	Men	Women
<20	4 (6.45)	2 (2.77)	13 (8.61)	13 (10.5)	0 (0.00)	0 (0.00)
21–30	18 (29.0)	10 (13.9)	50 (33.1)	23 (18.5)	3 (21.4)	4 (16.7)
31–40	10 (16.1)	10 (13.9)	24 (15.9)	18 (14.5)	2 (14.3)	3 (12.5)
41–50	5 (8.06)	15 (20.8)	8 (5.30)	14 (11.3)	1 (7.14)	6 (25.0)
51–60	9 (14.5)	18 (25.0)	16 (10.6)	24 (19.4)	3 (21.4)	3 (12.5)
61–70	10 (16.1)	9 (12.5)	8 (5.30)	7 (5.64)	3 (21.4)	6 (25.0)
71–80	2 (3.22)	1 (1.39)	2 (1.32)	2 (1.61)	0 (0.0)	0 (0.00)
>80	4 (6.45)	7 (9.72)	30 (19.9)	23 (18.54)	2 (14.29)	2 (8.33)
Total	62	72	151	124	14	24

Cases of agranulocytosis represented 38/393 (9.67%) of all reported hematological abnormalities. Their average age was 46.8 ± 15.1 years, and clozapine was administered at an average daily total of 308 ± 133 mg for an average of 10.1 ± 6.1 weeks before agranulocytosis (Table 4). Additional medicines were received by 42.1% (16/38) of patients who developed agranulocytosis. Other antipsychotics and benzodiazepines were particularly prevalent (Table 5).

Agranulocytosis occurred within the first 3 months of therapy in 83.3% (25/30) of patients in whom latency could be documented and in 86.7% (26/30) within 6 months. The mean total daily dose of clozapine among patients developing agranulocytosis averaged 308 (95% CI 224–372) mg compared with 256 (95% CI 232–280) mg with lesser decreases of WBCs. An additional case of agranulocytosis occurred at 13 months of treatment, and another three were identified after 2 years or more of clozapine treatment. On the basis of survival analysis, the median latency to agranulocytosis was 2.00 (95% CI 1.34–2.06) months (Fig. 1). Of the four cases of agranulocytosis occurring later than 12 months of continuous treatment with clozapine, two were receiving other medications that have also been associated rarely with agranulocytosis (Oyesanmi *et al.*, 1999; Flanagan and Dunk, 2008). One patient was treated with clozapine (300 mg/day) and concomitant clonazepam and ranitidine, and the second patient with clozapine (500 mg/day) and clonazepam, clotiapine, haloperidol, and biperiden. The other two cases of late-onset agranulocytosis that were not on concomitant medication were on clozapine 350 and 400 mg/day.

Table 4 Characteristics of 38 patients with agranulocytosis during treatment with clozapine

Measures	Men	Women	Total
Age (years)	46.1 ± 16.3	47.2 ± 14.8	46.8 ± 15.1
Clozapine dose (mg/day)	271 ± 122	329 ± 139	308 ± 133
Clozapine use (weeks)	12.1 ± 5.7	8.9 ± 6.1	10.1 ± 6.1
Other medicines used (%)	50.0	37.5	42.1
Infection occurred (%)	29.0	54.0	41.5

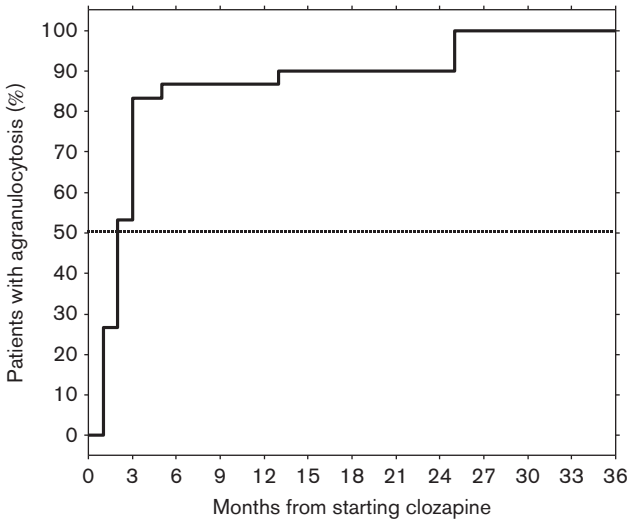
Data are presented as mean ± SD or percentages.

Table 5 Medicines used with clozapine among patients with agranulocytosis

Cases	Drugs
1	Clonazepam, ranitidine
2	Lamotrigine
3	Clonazepam, quetiapine
4	Diazepam, haloperidol, levomepromazine
5	Risperidone
6	Atenolol, biperiden, citalopram, enalapril, omeprazole, valproate
7	Clothiapine, haloperidol, lorazepam
8	Clonazepam, lamotrigine
9	Biperiden, clonazepam, clothiapine, haloperidol
10	Clonazepam, phenobarbital
11	Biperiden, clonazepam, haloperidol, risperidone, valproate
12	Antineoplastics, lipoic acid, valproate
13	Lithium carbonate
14	Clonazepam, olanzapine
15	Haloperidol, thioridazine, zopiclone
16	Biperiden, lamotrigine, valproate

Frequency of drug types ranked: other antipsychotics (31.7%) > other drugs (31.7%) > benzodiazepines (22.0) > anticonvulsants (14.6%). Data on doses were not available.

Fig. 1



Kaplan–Meier survival analysis of latency (months) to agranulocytosis from onset of clozapine treatment for 30 cases with reliable data on timing. The median latency (horizontal dotted line) is 2 months and 89.5% of cases occurred within 12 months.

There were 11 deaths among the 393 cases of blood dyscrasia during clozapine treatment (2.80%), but only 27.3% (3/11) or 0.76% (3/393 of blood dyscrasias) of these were associated with agranulocytosis. All three cases involved women (mean age 38 years) with sepsis. The other eight deaths were associated with neutropenia (four of these had moderate neutropenia, without clear information on other illnesses or causes of death), and one each with acute leukemia, cardiac arrest, acute pulmonary edema, or an unspecified lung disorder; these medical events may not be related to clozapine treatment specifically (Table 1). One patient who died was receiving phenobarbital and clonazepam as well as clozapine; all 10 others were administered clozapine as a monotherapy.

Multivariate logistic regression modeling indicated that the risk of agranulocytosis was greater among women than men (OR = 2.25, 95% CI 1.12–4.52; $P = 0.023$), with older age (OR = 1.22, 95% CI 1.02–1.45; $P = 0.027$), and among patients taking other psychotropic medicines (OR = 2.22, 95% CI 1.09–4.54; $P = 0.028$) (Table 6).

Table 6 Factors associated with agranulocytosis during clozapine treatment: multivariate logistic model

Factors	OR (95% CI)	χ^2	*P* value
Female sex	2.25 (1.12–4.52)	2.28	0.023
Older age	1.22 (1.02–1.45)	2.21	0.027
Other psychotropics used	2.22 (1.09–4.54)	2.19	0.028

Included independent variables were sex, age (in decade-intervals), and exposure to other psychotropics (yes/no).
CI, confidence interval; OR, odds ratio.

Discussion

The use of clozapine in Argentina can be estimated as the ratio of the number of cases included in the national clozapine registry to the national population or 12 305/40 000 000 (31/100 000/year). This ratio for other countries is as follows: Australia, 18; UK–Ireland, 20; Republic of Korea, 27; and USA, 31 (Copolov *et al.*, 1998; Munro *et al.*, 1999; Kang *et al.*, 2006; Honigfeld *et al.*, 1998). That is, the use of clozapine in Argentina is similar to that in Europe, the USA, and other countries. Reports on the basis of data from national registries of patients treated with clozapine in Australia, UK–Ireland, Italy, and the USA indicated an average, cumulative incidence over several years of clozapine-associated agranulocytosis of 0.80% of patients treated (Alvir *et al.*, 1993; Atkin *et al.*, 1996; Miller and Cutten, 1997; Copolov *et al.*, 1998; Munro *et al.*, 1999; Lambertenghi Deliliers, 2000). Data from the national clozapine registry in the USA (Honigfeld *et al.*, 1998) estimated a lower incidence of agranulocytosis, 0.38% (382/99 502), over 5 years. More recently, a Finnish national agency (Lahdelma and Appelberg, 2012) estimated the risk of agranulocytosis on the basis of cases and on the total amounts of drug sold in 1 year (assuming a typical daily dose of 300 mg/patient, dispensed monthly) to estimate the number of patients at risk. On the basis of the assumptions applied, these estimates yielded an average incidence of 0.11% per year, with a range 0.02–0.20% per year. This rate is lower than those of 0.38–0.80% in earlier reports (Cohen *et al.*, 2012), but is a yearly rate rather than a cumulative incidence over several years. In the present study, we estimated an annualized rate of agranulocytosis of 0.05% per year (Table 1). Although this value is lower than the previously reported cumulative incidence, the range of annualized rates includes our finding. In addition to the Finnish 1-year incidence of agranulocytosis of 0.11% (Lahdelma and Appelberg, 2012) and Australian annual incidence of 0.06% (Drew, 2013), UK–Ireland data (Munro *et al.*, 1999) found a cumulative incidence of agranulocytosis of 0.73% over 7 years, or about 0.10% per year (Munro *et al.*, 1999), and the US estimate was 0.38% over 5 years, or 0.08% per year (Honigfeld *et al.*, 1998). These experiences suggest that annual rates of agranulocytosis of about 1/1000 clozapine-treated patients, or somewhat less, are not unreasonable.

In our sample of 38 patients with agranulocytosis, there were three (7.89%) fatalities considered to be related to agranulocytosis or nearly twice the fatality rates of 3–4% of cases of agranulocytosis in other studies already cited. The reported variation in the estimates of the incidence of agranulocytosis and of its association with fatal outcomes probably reflects differences in case identification and determination of causes of death, whereas our impression is that monitoring and treatment of agranulocytosis in Argentina appear to be similar to practices in other countries (ANMAT, 2000). Other factors, such as

ethic mixes, age, proportion of women patients, daily doses of clozapine, and others, may also be involved.

The risk of developing agranulocytosis is clearly the highest during the initial months of treatment (Atkin *et al.*, 1996; Miller and Cutten, 1997; Copolov *et al.*, 1998; Lambertenghi Deliliers, 2000; Lahdelma and Appelberg, 2012), consistent with our finding of the greatest risk within the first 3 months of clozapine treatment (83% of cases), with a median latency of 8 weeks (Fig. 1). Of the three unusually late cases of agranulocytosis appearing later than 1 year, two involved other drugs with some risk of agranulocytosis, including clonazepam, clothiapine, haloperidol, and ranitidine (Vial *et al.*, 1991; Oyesanmi *et al.*, 1999; Arana, 2000; Flanagan and Dunk, 2008).

Cases of agranulocytosis included more than twice as many women as men (Table 6), but this association is not adjusted for the relative proportions of women and men at risk so as to define the relative sex-specific risk. A higher risk of clozapine-related agranulocytosis in women was reported by Alvir and colleagues in the USA (Alvir *et al.*, 1993), but was not found in three other, more recent studies in Australia (Copolov *et al.*, 1998), UK and Ireland (Munro *et al.*, 1999), Italy (Lambertenghi Deliliers, 2000), or Korea (Kang *et al.*, 2006). We also found that the risk of agranulocytosis increased at older ages (Table 6) as has been noted previously (Alvir *et al.*, 1993; Atkin *et al.*, 1996; Copolov *et al.*, 1998; Munro *et al.*, 1999; Lahdelma and Appelberg, 2012). The mean daily dose of clozapine associated with agranulocytosis in the present study was 308 mg or well within the recommended range of 150–450 mg. Moreover, although the numbers are small, the daily dose of clozapine was not associated with the risk of agranulocytosis in the present sample, as has been reported in previous studies (Alvir *et al.*, 1993; Atkin *et al.*, 1996; Miller and Cutten, 1997; Munro *et al.*, 1999; Lambertenghi Deliliers, 2000; Lahdelma and Appelberg, 2012). The lack of dose dependency is consistent with the prevalent view that idiosyncratic responses underlie the unknown mechanisms contributing toward agranulocytosis and that these are not likely to represent direct drug toxicity on WBC formation (Baldessarini and Frankenburg, 1991).

It may be important that 41.5% of the present cases of clozapine-associated agranulocytosis also involved additional psychotropic or other medicines (Table 5), and that such combinations were reported more than twice as often among those who developed agranulocytosis than those who did not (Table 6). A similar association was found in the Finnish study (Lahdelma and Appelberg, 2012) and in some case reports (Pantelis and Adesanya, 2001; Madeb *et al.*, 2002; Cohen and Monden, 2013). Complex treatment regimens would be expected among treatment-resistant patients with chronic psychotic illnesses who, indeed, are typical candidates for clozapine treatment. Drugs with some risk of blood dyscrasias include other antipsychotics, anticonvulsants, and benzodiazepines (Oyesanmi *et al.*, 1999; Duggal and Singh, 2005; Flanagan and Dunk, 2008; Demler and Trigoboff, 2011; Nooijen *et al.*, 2011; De Leon *et al.*, 2012; Vila-Rodriguez *et al.*, 2013). The association of agranulocytosis with polytherapy that includes clozapine has important implications for clinical practice and encourages simplification of treatment regimens, especially when clozapine is being used as a primary antipsychotic treatment.

The limitations of this study include the lack of some information in the national database used, including unambiguous counts of nonrepeated individuals at risk over the entire 6-year sampling period, details of ethnicity and other demographic and clinical characteristics of patients, and potential uncertainties related to the diagnosis of blood dyscrasias, complications, and causes of death. Also unavailable were characteristics of patients taking clozapine who did not develop leukopenia or agranulocytosis.

In conclusion, we found a relatively low incidence of agranulocytosis compared with studies from other international regions. This low cumulative and annualized incidence may reflect longer experience in the safe clinical application of clozapine or ascertainment errors associated with rare events. Notably, the risk of agranulocytosis was associated with female sex and with the simultaneous use of other medicines with clozapine in a population at a high risk for treatment resistance and polytherapy. It is also important to note that the observed fatality rate associated with agranulocytosis was higher than has been reported in studies from other regions, and despite routine application of a rigorous WBC monitoring protocol for the use of this unusually effective but potentially toxic drug.

Acknowledgements

The pharmaceutical companies Fabra, IVAX-Argentina, Novartis, and Rospaw generously provided data, and the Argentine National Administration of Drugs, Food and Medical Technology (ANMAT) allowed us access to their pharmacovigilance reports.

M.V. Balda received research fellowship 'Ramón Carrillo-Arturo Oñativia' from Comisión Nacional Salud Investiga, Ministerio de Salud y Acción Social de la Nación, Argentina. F.M. Daray is a research member of Argentine National Scientific and Technical Research Council (CONICET). R.J. Baldessarini received support from a Bruce J. Anderson Foundation grant and from the McLean Private Donors Research Fund.

Conflicts of interest

There are no conflicts of interest.

References

Alvir JM, Lieberman JA, Safferman AZ, Schwimmer JL, Schaaf JA (1993). Clozapine-induced agranulocytosis. Incidence and risk factors in the United States. *N Engl J Med* **329**:162–167.

Argentine National Administration of Drugs, Food and Medical Technology (ANMAT) (2000). *Report 935: Approval of an updated monitoring program for ambulatory and hospiralized patients treated with clozapine [in Spanish]*. Buenos Aires: ANMAT.

Arana GW (2000). An overview of side effects caused by typical antipsychotics. *J Clin Psychiatry* **61 (Suppl 8)**:5–11, discussion 12–13.

Atkin K, Kendall F, Gould D, Freeman H, Liberman J, O'Sullivan D (1996). Neutropenia and agranulocytosis in patients receiving clozapine in the UK and Ireland. *Br J Psychiatry* **169**:483–488.

Baldessarini RJ (2013). *Chemotherapy in psychiatry*. New York: Springer Press.

Baldessarini RJ, Frankenburg FR (1991). Clozapine. A novel antipsychotic agent. *N Engl J Med* **324**:746–754.

Bergman M, Bignone I, Bisio A, Bologna V, Sabatini A (2011). Risk minimization evolution of agranulocytosis caused by the administration of pharmaceutical products containing Clozapine in Argentina. *Vertex* **22**:94–97.

Cohen D, Monden M (2013). White blood cell monitoring during long-term clozapine treatment. *Am J Psychiatry* **170**:366–369.

Cohen D, Bogers JP, van Dijk D, Bakker B, Schulte PF (2012). Beyond white blood cell monitoring: screening in the initial phase of clozapine therapy. *J Clin Psychiatry* **73**:1307–1312.

Copolov DL, Bell WR, Benson WJ, Keks NA, Strazzeri DC, Johnson GF (1998). Clozapine treatment in Australia: a review of haematological monitoring. *Med J Aust* **168**:495–497.

De Leon J, Santoro V, D'Arrigo C, Spina E (2012). Interactions between antiepileptics and second-generation antipsychotics. *Expert Opin Drug Metab Toxicol* **8**:311–334.

Demler TL, Trigoboff E (2011). Are clozapine blood dyscrasias associated with concomitant medications? *Innov Clin Neurosci* **8**:35–41.

Drew L (2013). Clozapine and agranulocytosis: re-assessing the risks. *Australas Psychiatry* **21**:335–337.

Duggal HS, Singh I (2005). Psychotropic drug-induced neutropenia. *Drugs Today (Barc)* **41**:517–526.

Flanagan RJ, Dunk L (2008). Haematological toxicity of drugs used in psychiatry. *Hum Psychopharmacol* **23 (Suppl 1)**:27–41.

Haddad PM, Sharma SG (2007). Adverse effects of atypical antipsychotics: differential risk and clinical implications. *CNS Drugs* **21**:911–936.

Honigfeld G, Arellano F, Sethi J, Bianchini A, Schein J (1998). Reducing clozapine-related morbidity and mortality: 5 years of experience with the Clozaril National Registry. *J Clin Psychiatry* **59 (Suppl 3)**:3–7.

Kang BJ, Cho MJ, Oh JT, Lee Y, Chae BJ, Ko J (2006). Long-term patient monitoring for clozapine-induced agranulocytosis and neutropenia in Korea: when is it safe to discontinue CPMS? *Hum Psychopharmacol* **21**:387–391.

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.

Lambertenghi Deliliers G (2000). Blood dyscrasias in clozapine-treated patients in Italy. *Haematologica* **85**:233–237.

Lieberman JA (1998). Maximizing clozapine therapy: managing side effects. *J Clin Psychiatry* **59 (Suppl 3)**:38–43.

Madeb R, Hirschmann S, Kurs R, Turkie A, Modai I (2002). Combined clozapine and valproic acid treatment-induced agranulocytosis. *Eur Psychiatry* **17**:238–239.

Miller DD (2000). Review and management of clozapine side effects. *J Clin Psychiatry* **61 (Suppl 8)**:14–17, discussion 18–19.

Miller PR, Cutten AE (1997). Haematological side effects of clozapine: patient characteristics. *N Z Med J* **110**:125–127.

Munro J, O'Sullivan D, Andews C, Arana A, Mortimer A, Kerwin R (1999). Active monitoring of 12,760 clozapine recipients in the UK and Ireland. Beyond pharmacovigilance. *Br J Psychiatry* **175**:576–580.

Nooijen PM, Carvalho F, Flanagan RJ (2011). Haematological toxicity of clozapine and some other drugs used in psychiatry. *Hum Psychopharmacol* **26**:112–119.

Oyesanmi O, Kunkel EJ, Monti DA, Field HL (1999). Hematologic side effects of psychotropics. *Psychosomatics* **40**:414–421.

Pantelis C, Adesanya A (2001). Increased risk of neutropaenia and agranulocytosis with sodium valproate used adjunctively with clozapine. *Aust N Z J Psychiatry* **35**:544–545.

Vial T, Goubier C, Bergeret A, Cabrera F, Evreux JC, Descotes J (1991). Side effects of ranitidine. *Drug Saf* **6**:94–117.

Vila-Rodriguez F, Tsang P, Barr AM (2013). Chronic benign neutropenia/agranulocytosis associated with non-clozapine antipsychotics. *Am J Psychiatry* **170**:1213–1214.