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The prevalence of agranulocytosis and related death in clozapine-treated patients: a comprehensive meta-analysis of observational studies

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Abstract

Background. Clozapine treatment increases the risk of agranulocytosis, but findings on the epidemiology of agranulocytosis have been inconsistent. This meta-analysis examined the prevalence of agranulocytosis and related death in clozapine-treated patients.

Methods. A literature search in the international (PubMed, PsycINFO, and EMBASE) and Chinese (WanFang, Chinese National Knowledge Infrastructure, and Sinomed) databases was conducted. Prevalence estimates of agranulocytosis and related death in clozapine-treated patients were synthesized with the Comprehensive Meta-Analysis program using the random-effects model.

Results. Thirty-six studies with 260 948 clozapine-treated patients published between 1984 and 2018 were included in the meta-analysis. The overall prevalence of agranulocytosis and death caused by agranulocytosis were 0.4% (95% CI 0.3–0.6%) and 0.05% (95% CI 0.03–0.09%), respectively. The prevalence of agranulocytosis was moderated by sample size, study quality, year of publication, and that of data collection.

Conclusions. The prevalence of clozapine-associated agranulocytosis is low. Agranulocytosis-related death appears rare.

Introduction

As a highly efficacious atypical antipsychotic, clozapine is recommended for treatment-resistant schizophrenia in most of the world (Crilly, 2007). Following a 1975 report in Finland of 16 cases of clozapine-related agranulocytosis resulting in eight deaths due to infection (Idanpaan-Heikkila *et al*., 1975), clozapine was withdrawn in many countries. However, since the landmark study in 1988 demonstrating its safety with strict blood monitoring (Kane *et al*., 1988), clozapine has been approved by the Food and Drug Administration of the USA followed by the majority of health authorities for patients with treatment-resistant schizophrenia (Alvir *et al*., 1993) because of its superior efficacy in improving psychotic symptoms (Wahlbeck *et al*., 1999; Volavka *et al*., 2002; Siskind *et al*., 2016), aggressive, hostile or self-harming behaviors (Volavka *et al*., 2004; Faay *et al*., 2018), substance abuse (Arranz *et al*., 2018), and reducing the risk of hospitalization (Land *et al*., 2017) and overall mortality (Vermeulen *et al*., 2018).

Despite its better efficacy compared to all other antipsychotics for treatment-resistant schizophrenia, clozapine is still under-utilized in many countries because of its severe side effect profile, particularly the concern about the development of agranulocytosis (Oyesanmi *et al*., 1999). According to the Clozaril Patient Monitoring System (CPMS), the cumulative incidence of agranulocytosis related to clozapine was 0.8% at 1 year and 0.93% at 1.5 years; more than 80% of patients developed agranulocytosis in their first 3 months of treatment (Alvir *et al*., 1993). Between 1993 and 1996, the rate of agranulocytosis was 0.9% in Australia (Copolov *et al*., 1998). The general consensus is that patients receiving clozapine need regular white blood cell monitoring, particularly during the first 18 weeks of clozapine administration (Bastani *et al*., 1989). Due to the stringent blood monitoring, the rate of

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agranulocytosis was significantly reduced to 0.38% in the 5 years after its re-introduction (Honigfeld, 1996).

In a recent meta-analysis, the incidence of severe clozapine-associated neutropenia, defined as an absolute neutrophil count (ANC) <500 ul, was 0.9%, while the fatality rate of severe neutropenia was 2.1% (Myles *et al.*, 2018). In recent years, under strict blood monitoring, both the risk of agranulocytosis and the clozapine-related death rate have been significantly reduced. A thorough search of the literature could not locate any meta-analysis on the prevalence of agranulocytosis and death related to clozapine.

Clozapine has been widely prescribed in China without interruption since 1976 even when it was withdrawn from the market throughout the world. A nationwide survey of psychotropic medications in China found that clozapine was prescribed for 39.7, 32.5, and 26.4% of schizophrenia patients in 2002, 2006, and 2012, respectively (Li *et al.*, 2015). Many prevalence studies of clozapine-associated agranulocytosis have been published in Chinese language journals, which are not generally accessible to non-Chinese readership.

This meta-analysis examined the prevalence of agranulocytosis and related death and their associated factors in clozapine-treated patients.

Methods

Inclusion and exclusion criteria

Studies that fulfilled the following criteria were included: (a) cross-sectional or cohort studies (only baseline data of cohort studies were extracted) reporting accessible data on the prevalence of agranulocytosis or data that could generate a prevalence figure of agranulocytosis in clozapine-treated patients; (b) published in English or Chinese languages. Case reports and case series, prescription surveys, and reports with very small sample size were excluded.

Although the Council for International Organisations of Medical Sciences (CIOMS) (2001) defined agranulocytosis as neutrophil count of $<0.1 \times 10^9$/L, currently the traditional criteria (neutrophil count of $<1.0 \times 10^9$/L or $<0.5 \times 10^9$/L) are still used to define agranulocytosis in clinical guidelines on blood monitoring for clozapine, particularly in China. The two traditional criteria were used in the studies included in the current meta-analysis. In order to reflect actual clinical practice and remain consistent with the included studies, in this meta-analysis, the term 'agranulocytosis' was defined according to the earlier diagnostic criteria of the CIOMS (Bankowski *et al.*, Reprinted, 2000).

Search strategy

Two reviewers (XHL and XMZ) systematically and independently searched major international (PubMed, PsycINFO, and EMBASE) and Chinese (WanFang, Chinese National Knowledge Infrastructure, and Sinomed) databases from their inception up to 8 June 2018 with the following search terms: (Clozapine OR Clozaril OR Leponex) AND (agranulocytosis OR 'granulocyte deficiency' OR agranulocytopenia OR aleucocytosis OR aleukocytosis OR hypoleucocytosis OR leucopenia OR leukopenia OR neutropenia OR 'sudden death' OR 'unexpected death' OR mortality OR death). In addition, a manual search was conducted by reviewing the reference lists of relevant meta-analyses and reviews.

Data extraction

Data extraction was independently performed by two reviewers (XHL and XMZ) who screened the titles and abstracts first, and later read the full texts. If more than one article were published using the same dataset, only the article with complete data was included. Any inconsistencies in data extraction were discussed or resolved by involving a third reviewer (YTX).

Quality assessment

Following the methodology of other studies (Cooper *et al.*, 2007; Pringsheim *et al.*, 2014), two researchers (XHL and XMZ) independently assessed the quality of studies with the methodological quality checklist that comprised eight items (Boyle, 1998). Each study was scored from 0 to 8. The score of 7–8 was considered as 'high quality', 4–6 as 'moderate quality', and 0–3 as 'low quality'. Any disagreement in the assessment was discussed and resolved involving a third investigator (WWR). Table 3 shows the details of the quality assessment of the studies.

Statistical analyses

The Comprehensive Meta-Analysis Version 2 (http://www.meta-analysis.com) was used to analyze data. The pooled prevalence estimates of agranulocytosis and their 95% confidence intervals (95% CI) were calculated using the random-effects models. The I^2 statistic was calculated to measure heterogeneity (Higgins *et al.*, 2003). When high heterogeneity was present ($I^2 > 50\%$), sensitivity and subgroup analyses were performed to explore the sources of heterogeneity. Publication bias was assessed with the funnel plot, and the Begg's and Egger's tests (Egger *et al.*, 1997). The level of significance was set at 0.05 (two-sided).

Results

Study characteristics and quality assessment

Thirty-six (13 in English and 23 in Chinese) of the 5176 potentially eligible articles met the inclusion criteria and were included in the analyses (Figure 1). Table 1 shows the characteristics of these 36 studies on 260 948 subjects. They were conducted between 1984 and 2018 across 12 countries in five continents: Asia (25 studies: 23 in China; one each in Korea and Saudi Arabia), Europe (six studies: one each in UK and Ireland, Hungary, Iceland, Italy, Denmark, and the Slovak Republic), North America (three studies in the USA), South America (one study in Argentina) and Oceania (one study in Australia). Sample sizes ranged from 147 to 99 502; the mean age of patients varied between 15.0 and 51.2 years. Eight studies were based on clozapine monitoring systems.

One study reported on two samples: clozapine alone and clozapine plus lithium (Gan and Chen, 1995). Clozapine-associated agranulocytosis occurred from 26.07 days to 4 years after exposure to clozapine. Thirteen studies (Fan *et al.*, 1992; Zhu *et al.*, 1992; Peacock and Gerlach, 1994; Gan and Chen, 1995; Lv *et al.*, 1997; Copolov *et al.*, 1998; Deng *et al.*, 1999; Zhao *et al.*, 1999; Xu *et al.*, 2001; Gaszner *et al.*, 2002; Kang *et al.*, 2006; Pecenak *et al.*, 2009; Balda *et al.*, 2015) reported the mean length of clozapine exposure when agranulocytosis occurred (9.8 weeks); of them, nine studies reported the mean length with standard deviations (S.D.) (5.4w ± 3.3w) (Fan *et al.*, 1992; Zhu *et al.*, 1992; Gan and Chen, 1995; Lv *et al.*, 1997; Copolov *et al.*, 1998; Deng

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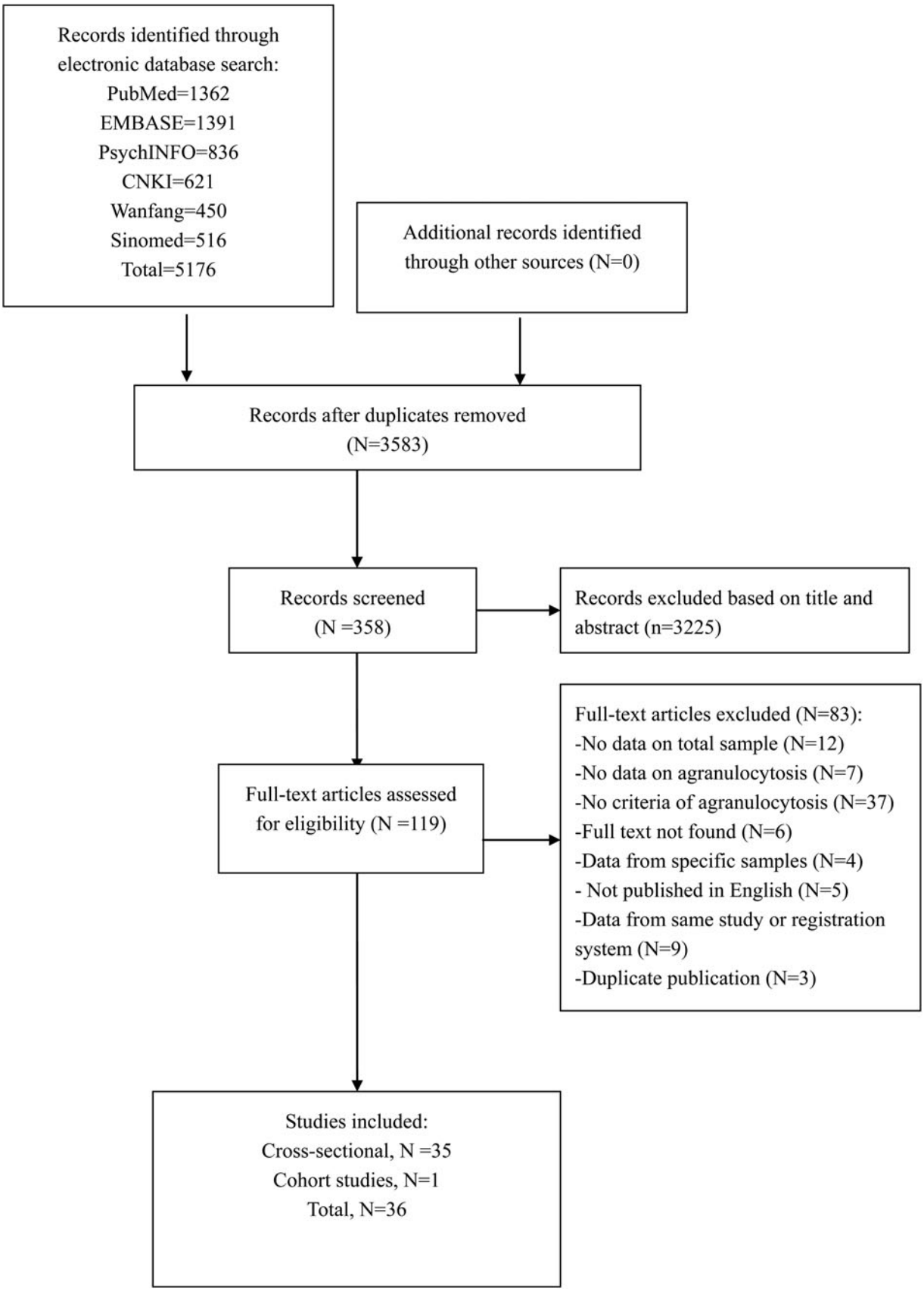

Fig. 1. PRISMA flow diagram.

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Table 1. Characteristics of studies included in the meta-analysis

First author (year) Ref	Country	Mean age (years)	Period of data collection (year and month)	Sample origin (from monitoring system)	Sampling methods	*N* (total)	Male, %	Diagnostic criteria	Criteria of agranulocytosis (neutrophil)	With blood monitoring [a]	Quality assessment score
Abanmy *et al.* (2014)	Saudi Arabia	38	2009.8–2012.8	No	NR	147	52.4	NR	$<1\times109$/L	Yes	5
Balda *et al.* (2015)	Argentina	NR	2007.1–2012.12	ANMAT	NR	73 831	NR	NR	$<0.5\times109$/L	Yes	6
Copolov *et al.* (1998)	Australia	35[b]	1993.6–1996.7	CPMS	NR	4061	65.8	NR	$<0.5\times109$/L	Yes	6
Kelly *et al.* (2007)	USA	NR	1989.1.1–1999.12.31	CAMP	NR	1875	NR	DSM-IV	$<0.5\times109$/L	Yes	5
Gerbino-Rosen *et al.* (2005)	USA	15.03	1992.6–2004.5	No	NR	172	61.0	NR	$<0.5\times109$/L	Yes	8
Gaszner *et al.* (2002)	Hungary	37.7	1986–2001	No	NR	750	46.1	DSM-IV	$<0.5\times109$/L	Yes	5
Honigfeld *et al.* (1998)	USA	NR	1990.2–1994.12	CNR	NR	99 502	NR	NR	$<0.5\times109$/L	Yes	5
Ingimarsson *et al.* (2016)	Iceland	51.2[c]	1986–2014	No	NR	201	NR	NR	$<0.5\times109$/L	No	5
Munro *et al.* (1999)	UK and Ireland	36.8	1990.1–1997.4	CPMS	NR	12 760	66.9	NR	$<0.5\times109$/L	Yes	5
Kang *et al.* (2006)	Korea	NR	1993.2–2004.2	CPMS	NR	6782	60.1	NR	$<0.5\times109$/L	Yes	5
Lambertenghi Deliliers (2000)	Italy	NR	1995–1999	ICLOS	NR	2404	63.0	DSM-IV	$<0.5\times109$/L	Yes	5
Lau and Yim (2015)	China	NR	1997.1–2012.12	No	NR	980	48.6	NR	$<0.5\times109$/L	Yes	5
Peacock and Gerlach (1994)	Denmark	38	Since 1985-?	No	NR	656	66.6	NR	$<0.5\times109$/L		5
Pecenak *et al.* (2009)	Slovak Republic	36.38	1995–2005	NR	NR	1077	51.3	NR	$<0.5\times109$/L	Yes	5
Sing *et al.* (2017)	China	NR	2004.1.1–2013.12.31	CDARS	NR	4551	NR	NR	$<0.5\times109$/L	No	5
Zeng *et al.* (1994)	China	NR	1992.5–1993.5	No	NR	245	NR	CCMD-2	$<1\times109$/L	No	5
Chen *et al.* (1991)	China	NR	1989.1–1990.9	No	NR	263	NR	NR	$<1\times109$/L	No	5
	China	33.7		No	Random	100	58.0	NR	$<1\times109$/L	Yes	5

Deng *et al.* (1999)			1985.5–1998.5								
Duan (2007)	China	NR	2002.6–2006.5	No	NR	2296	NR	CCMD-3	$<0.4\times109$/L	Yes	4
Fan *et al.* (1992)	China	34	1980–1991	No	NR	3113	68.7	NR	$<1\times109$/L	Yes	5
Gan and Chen (1995)	China	29.95	NR	No	NR	2641	41.0	NR	$<1\times109$/L	No	5
He *et al.* (2002)	China	NR	1990.1–1999.1	No	NR	3929	NR	CCMD-2-R and ICD-9	$<0.5\times109$/L	No	5
Ji and Gao (2005)	China	NR	1986.1–2003.1	No	NR	13 268	NR	CCMD-3	$<0.5\times109$/L	No	5
Liu (1996)	China	NR	1982.1–1995.5	No	NR	4586	NR	NR	$<1\times109$/L	No	5
Lu *et al.* (1990)	China	NR	1980–1988.12	No	NR	8476	NR	NR	$<1\times109$/L	Yes	5
Lv *et al.* (1997)	China	NR	1990–1995	No	NR	5012	50.8	NR	$<0.5\times109$/L	No	5
Wang and Liu (2005)	China	NR	2004.8–2004.10	No	NR	390	NR	CCMD-2-R	$<1\times109$/L	No	5
Wang (2002)	China	NR	1992–2001	No	NR	793	NR	CCMD-2-R	$<0.5\times109$/L	Yes	3
Xu (1984)	China	NR	1976–1982	No	NR	2096	NR	NR	$<1\times109$/L	No	5
Xu *et al.* (2001)	China	31.2	1990.11–1999.11	No	NR	302	66.2	NR	$<1\times109$/L	Yes	5
Yan and Wu (2014)	China	NR	2009.4–2012.4	No	NR	361	NR	CCMD-3	$<0.5\times109$/L	Yes	5
Yang and Zhang (1990)	China	31	1981.10–1987.12	No	NR	416	62.3	NR	$<1\times109$/L	No	5
Zhang *et al.* (1997)	China	31.52	NR	No	NR	210	80.5	NR	$<1\times109$/L	No	5
Zhao *et al.* (1999)	China	30.8	1992.1–1996.6	No	NR	260	76.2	NR	$<1\times109$/L	No	5
Zheng (2000)	China	29.12	1989–1999	No	NR	1782	79.8	NR	$<2\times109$/L	Yes	5
Zhu *et al.* (1992)	China	NR	1985.1–1990.1	No	NR	332	NR	NR	$<1\times109$/L	Yes	5

CPMS, Clozaril Patient Management System; ANMAT, Argentine drug-regulatory agency; CAMP, Clozapine Authorization and Monitoring Program; CNR, The Clozaril National Registry; ICLOS, Italian Clozapine Monitoring System; CDARS, Clinical Data Analysis and Reporting System

CCMD-2-R, Chinese Classification of Mental Disorders, the Second Edition, Revised; CCMD-3, Chinese Classification of Mental Disorders, the Third Version; DSM, Diagnostic and Statistical Manual of Mental Disorders; ICD-9, International Classification of Disease, the Ninth version

[a]Having strict blood monitoring during the clozapine treatment

[b]Median age

[c]The mean age was derived from the number of 195 patients

et al., 1999; Zhao *et al.*, 1999; Xu *et al.*, 2001; Balda *et al.*, 2015). Four studies (Copolov *et al.*, 1998; Munro *et al.*, 1999; Kang *et al.*, 2006; Kelly *et al.*, 2007) reported that 53.7–87.5% of agranulocytosis occurred in the first 18 weeks of clozapine treatment. Insufficient data were available to calculate proportion of agranulocytosis in the first 12 months of clozapine exposure.

Several studies referred to the term 'incidence' (such as Copolov *et al.*, 1998; Honigfeld *et al.*, 1998; Munro *et al.*, 1999; Lambertenghi Deliliers, 2000; Kang *et al.*, 2006; Abanmy *et al.*, 2014; Balda *et al.*, 2015; Sing *et al.*, 2017), but, in fact, the figures reflected prevalence, i.e. the number of cases over a period, thus they were included in the analyses. The mean score of quality assessment was 5.1 (range: 4–8). One study (2.6%) was rated as 'high quality' (Gerbino-Rosen *et al.*, 2005) while the rest of 35 studies were rated as 'moderate quality' (Table 2).

The pooled prevalence of clozapine-associated agranulocytosis and related death

The prevalence of agranulocytosis ranged from 0.1% to 2.7% in the 36 studies with a pooled prevalence of 0.4% (95% CI 0.3–0.6%, $I^2 = 90.2\%$); i.e. one case of agranulocytosis in every 250 clozapine-treated patients.

In the 30 studies that reported deaths caused by clozapine-associated agranulocytosis ($n = 33$), the pooled prevalence of death was 0.05% (95% CI 0.03–0.09%, $I^2 = 63.6\%$; range: 0–0.8%); i.e. one in every 2000 clozapine-treated patients. Among patients with agranulocytosis, the pooled prevalence of death was 10.0% (95% CI 6.1–15.8%, $I^2 = 43.7\%$); i.e. one in every 10 patients.

Subgroup analysis

Table 3 shows the results of the subgroup analyses. The prevalence of agranulocytosis was not significantly associated with gender, Chinese studies, and geographic locations. The prevalence of agranulocytosis was 0.5% in men, 0.7% in women; 0.4% in Chinese and 0.5% in non-Chinese studies. Studies conducted in North and South America (0.2%) reported a lower prevalence than those in Asia (0.4%), Europe (0.5%), and Oceania (0.9%), without significant group difference. There were significant differences in the prevalence of agranulocytosis between studies with smaller sample size (0.8% in studies of sample size <1000) and larger sample size (0.3% in studies of sample size ⩾1000; $Q = 11.41$, $p = 0.001$). The trend of significant difference was found between studies with or without strict blood monitoring (0.5% *v.* 0.3%; $Q = 2.887$, $p = 0.089$). No significant differences were found between different periods of publication (before 1991 *v.* 1991 and after), and between clozapine alone *v.* clozapine + other psychotropic medications. Broad criteria of agranulocytosis (neutrophil<1.0×10^9/L) was associated with a slightly higher prevalence (0.5%) than those (0.4%) applying stringent criteria (neutrophil<0.5×10^9/L), but the difference was not significant ($p = 0.50$).

Meta regression of the prevalence of agranulocytosis caused by clozapine

Meta-regression analysis found a significant negative association between the publication period (before or being/after 1991) and the prevalence of agranulocytosis based on 36 studies ($\beta = -0.03$, 95% CI −0.05 to −0.02, $p < 0.001$). Years of data collection were negatively associated with prevalence of agranulocytosis in 33 studies with available data ($\beta = -0.03$, 95% CI −0.05 to −0.01, $p < 0.001$). Age showed a significant trend with agranulocytosis in 16 studies with available data ($\beta = 0.05$, 95% CI −0.002 to 0.11, $p = 0.06$), while study quality assessment had significant association with the prevalence of agranulocytosis ($\beta = -0.46$, 95% CI −0.66 to −0.26, $p = 0.00001$).

Publication bias and sensitivity analysis

Online Supplementary Figure S1 shows the funnel plot of all studies. Neither the funnel plot, nor the Egger's ($t = 0.049$, 95% CI −1.49 to 1.56; $p = 0.96$) and Begg's tests ($z = 1.35$, $p = 0.18$) found any publication bias. After excluding each study sequentially, the recalculated pooled results did not significantly change, indicating that there was no outlying study that significantly influenced the overall results.

Discussion

The pooled prevalence of clozapine-associated agranulocytosis in this meta-analysis was 0.4%, similar to the US registry studies in the 5 years post 1990 (0.38%) (Honigfeld, 1996). The pooled prevalence of death caused by clozapine-associated agranulocytosis was 0.05%, which is higher than the previously reported figure (0.012%) based on the national registry database of the US manufacturer of clozapine (Honigfeld, 1996). Comparison across studies should be made with caution due to different study designs and definitions of agranulocytosis. This was the first meta-analysis of prevalence of clozapine-associated agranulocytosis, therefore direct comparisons with other meta-analyses could not be performed.

A higher risk of agranulocytosis in Asian patients receiving clozapine is found in some (Munro *et al.*, 1999), but not in all studies (Shapiro *et al.*, 1999; Sing *et al.*, 2017). Gene sequence variations, such as HLA-DQB1 and HLA-A1, have been associated with an increased risk of clozapine-associated agranulocytosis (Lieberman *et al.*, 1990; Amar *et al.*, 1998; Valevski *et al.*, 1998; Lahdelma *et al.*, 2001; Dettling *et al.*, 2007; Athanasiou *et al.*, 2011; Kadasah *et al.*, 2011; Goldstein *et al.*, 2014; Legge *et al.*, 2017). Genetic variations between ethnic groups may be associated with different prevalence of clozapine-associated agranulocytosis. However, in this meta-analysis, the prevalence of clozapine-associated agranulocytosis in Asia was not significantly higher than in America, Europe, and Oceania.

The prevalence of agranulocytosis in studies with smaller sample size (0.8%) was significantly higher than in those with larger sample size (0.3%; $p = 0.001$). There is no explanation for this observation; it may well be that findings of studies with smaller sample size are not sufficiently stable (Cao *et al.*, 2017). No differences were found in the prevalence of agranulocytosis in studies published before and after 1991 (Crilly, 2007), when strict registry-based prescribing system for hematological monitoring was mandatory. This finding is consistent with that of a recent review (Myles *et al.*, 2018).

Studies using the broad diagnostic criteria of agranulocytosis (neutrophil < 1.0×10^9/L) had a higher pooled prevalence than those applying more stringent criteria (neutrophil < 0.5×10^9/L), although the difference did not reach significant level. Recent treatment guidelines recommended a flexible threshold for clozapine treatment, i.e. if the ANC ranges from 1.5×109/L to 0.5×109/L in patients with benign ethnic neutropenia, clozapine

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Table 2. The quality assessment

No.	Author (year)	Items								Score
		1. *Is the target population clearly defined?*	2. *Was either of the following ascertainment methods used [must be one or the other]? (1) probability sampling, or (2) entire population surveyed*	3. *Is the response rate>70%*	4. *Are non-responders clearly described?*	5. *Is the sample representative of the target population?*	6. *Were data collection methods standardized?*	7. *Were validated criteria used to assess for the presence/ absence of disease?*	8. *Are the estimates of prevalence given with confidence intervals and in detail by subgroup (if applicable)?*	
1.	Abanmy *et al.* (2014)	1	1	1	0	1	0	1	0	5
2.	Balda *et al.* (2015)	1	1	1	0	1	0	1	1	6
3.	Copolov *et al.* (1998)	1	1	1	0	1	0	1	1	6
4.	Kelly *et al.* (2007)	1	1	1	1	1	0	1	0	6
5.	Gerbino-Rosen *et al.* (2005)	1	1	1	1	1	1	1	1	8
6.	Gaszner *et al.* (2002)	1	1	1	0	1	0	1	0	5
7.	Honigfeld *et al.* (1998)	1	1	1	0	1	0	1	0	5
8.	Ingimarsson *et al.* (2016)	1	1	1	0	1	0	1	0	5
9.	Munro *et al.* (1999)	1	1	1	0	1	0	1	0	5
10.	Kang *et al.* (2006)	1	1	1	0	1	0	1	0	5
11.	Lambertenghi Deliliers (2000)	1	1	1	0	1	0	1	0	5
12.	Lau and Yim (2015)	1	1	1	0	1	0	1	0	5
13.	Peacock and Gerlach (1994)	1	1	1	0	1	0	1	0	5
14.	Pecenak *et al.* (2009)	1	1	1	0	1	0	1	0	5
15.	Sing *et al.* (2017)	0	1	1	0	1	0	1	1	5
16.	Zeng *et al.* (1994)	1	1	1	0	1	0	1	0	5
17.	Chen *et al.* (1991)	1	1	1	0	1	0	1	0	5
18.	Deng *et al.* (1999)	1	1	1	0	1	0	1	0	5
19.	Duan (2007)	1	1	1	0	1	0	0	0	4
20.	Fan *et al.* (1992)	1	1	1	0	1	0	1	0	5
21.	Gan and Chen (1995)	1	1	1	0	1	0	1	0	5
22.	He *et al.* (2002)	1	1	1	0	1	0	1	0	5
23.	Ji and Gao (2005)	1	1	1	0	1	0	1	0	5

(*Continued*)

Table 2. (*Continued.*)

No.	Author (year)	Items								Score
		1. *Is the target population clearly defined?*	2. *Was either of the following ascertainment methods used [must be one or the other]? (1) probability sampling, or (2) entire population surveyed*	3. *Is the response rate>70%*	4. *Are non-responders clearly described?*	5. *Is the sample representative of the target population?*	6. *Were data collection methods standardized?*	7. *Were validated criteria used to assess for the presence/ absence of disease?*	8. *Are the estimates of prevalence given with confidence intervals and in detail by subgroup (if applicable)?*	
24.	Liu (1996)	1	1	1	0	1	0	1	0	5
25.	Lu *et al.* (1990)	1	1	1	0	1	0	1	0	5
26.	Lv *et al.* (1997)	1	1	1	0	1	0	1	0	5
27.	Wang and Liu (2005)	1	1	1	0	1	0	1	0	5
28.	Wang (2002)	1	1	1	0	1	0	1	0	5
29.	Xu (1984)	1	1	1	0	1	0	1	0	5
30.	Xu *et al.* (2001)	1	1	1	0	1	0	1	0	5
31.	Yan and Wu (2014)	1	1	1	0	1	0	1	0	5
32.	Yang and Zhang (1990)	1	1	1	0	1	0	1	0	5
33.	Zhang *et al.* (1997)	1	1	1	0	1	0	1	0	5
34.	Zhao *et al.* (1999)	1	1	1	0	1	0	1	0	5
35.	Zheng (2000)	1	1	1	0	1	0	1	0	5
36.	Zhu *et al.* (1992)	1	1	1	0	1	0	1	0	5

Table 3. Subgroup analysis of pooled prevalence of agranulocytosis

Subgroups	Categories (No. of studies)	Events	Sample size	Pooled prevalence (%)	95% CI (%)	I^2 (%)	p within subgroup	Q (p across subgroups)
Gender	Male (6)	62	10 631	0.5	0.3–0.8	66.373	<0.001	0.63 (0.42)
	Female (6)	50	7707	0.7	0.4–1.1	52.246	<0.001	
China	Yes (23)	147	56 730	0.4	0.3–0.6	74.036	<0.001	0.63 (0.43)
	No (13)	643	204 218	0.5	0.3–0.8	95.415	<0.001	
Geographic location	Asia (25)	205	63 659	0.4	0.3–0.6	81.825	<0.001	2.36 (0.50)
	North and South America (4)	429	175 380	0.2	0.1–0.6	97.871	<0.001	
	Europe (6)	119	17 848	0.5	0.2–1.1	0	0.501	
	Oceania (1)	37	4061	0.9	0.2–5.2	0	1.0	
Sample size	<1000 (17)	46	6578	0.8	0.5–1.2	44.451	0.025	11.41 (0.001)
	⩾1000 (19)	744	254 370	0.3	0.2–0.4	93.880	<0.001	
Publication year	Before 1991 (3)	28	10 988	0.3	0.1–0.8	43.461	0.171	0.38 (0.54)
	1991-(33)	762	249 960	0.4	0.3–0.6	90.817	<0.001	
Criteria of agranulocytosis	Neutrophil < 0.5×10^9/L (20)	718	235 261	0.4	0.3–0.6	93.579	<0.001	0.45 (0.50)
	Neutrophil < 1×10^9/L (16)	72	25 687	0.5	0.3–0.8	75.470	<0.001	
Concomitant medication[a]	Clozapine alone (9)	49	17 748	0.7	0.3–1.2	75.334	<0.001	3.14 (0.21)
	Having concomitant medications (16)	101	95 241	0.3	0.2–0.5	90.815	<0.001	
Having strict blood monitoring	Yes (16)	662	207 472	0.5	0.4–0.8	94.969	<0.001	2.887 (0.089)
	No (20)	128	53 476	0.3	0.2–0.5	39.584	0.036	

[a]Gan and Chen (1995), had two samples (clozapine alone; clozapine + lithium)

could still be continued since people with persistent or episodic neutropenia usually do not progress to agranulocytosis (Bastiampillai *et al.*, 2016). Following the recommended flexible threshold of neutrophil count would allow more patients to benefit from clozapine treatment (Sultan *et al.*, 2017).

Consistent with previous findings (Alvir *et al.*, 1993; Atkin *et al.*, 1996; Lieberman and Alvir, 1992; Munro *et al.*, 1999), age seemed to be significantly associated with the prevalence of agranulocytosis ($\beta = 0.05$, $p = 0.06$). This may be due to the higher vulnerability to hematopoietic toxicity associated with clozapine in older patients (Munro *et al.*, 1999). Combining clozapine with other psychotropic medications increases the risk of agranulocytosis (Peacock and Gerlach, 1994; Lau and Yim, 2015), which was not confirmed in this meta-analysis. This could be partly due to the small number of studies with concomitant medications with clozapine.

A negative association between publication period and the prevalence of agranulocytosis was found. In earlier times, regular blood monitoring for clozapine was not mandatory in certain parts of the world, such as China, due to insufficient training or economic reasons. Hence, mild-to-moderate clozapine-associated neutropenia was not identified early leading to higher risk of agranulocytosis. Unexpectedly, the time frame of data collection was negatively associated with the prevalence of agranulocytosis ($\beta = -0.03$, $p < 0.001$). The possible explanation is that most cases of agranulocytosis occur in the first 18 weeks of exposure to clozapine. Since many patients were only included in the clozapine monitoring system after they had been taking clozapine for a period of time, which is common in China, the most vulnerable period for agranulocytosis was not captured and the prevalence of agranulocytosis was consequently lower. Furthermore, a negative association between low study quality and the prevalence of agranulocytosis was found.

There are several limitations of this meta-analysis. First, several included studies were based on clozapine monitoring systems with various timespan, thus the prevalence of agranulocytosis in specific timeframes could not be calculated. Second, in order to reflect actual clinical practice, two diagnostic criteria of agranulocytosis (neutrophils of $<1.0 \times 10\text{^}9/L$ or $<0.5 \times 10\text{^}9/L$) were applied. However, this did not significantly influence the prevalence of agranulocytosis according to the subgroup analyses. Third, similar to other recent meta-analyses (Winsper *et al.*, 2013; Long *et al.*, 2014; Mata *et al.*, 2015; Li *et al.*, 2016), high heterogeneity still remained in certain subgroup analyses which is difficult to avoid in meta-analysis of observational surveys. The heterogeneity was probably associated with factors that were not examined in most included studies, such as clozapine doses, treatment stage and duration, psychiatric comorbidities, and concurrent use of other psychotropic medications. Fourth, different periods of data collection and quality of studies could

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moderate the pooled prevalence of agranulocytosis. However, meta-regression analysis did not find any significant moderating effect of the period of data collection on the primary results.

In conclusion, this meta-analysis found that the prevalence of clozapine-associated agranulocytosis is low. Death due to agranulocytosis following exposure to clozapine appeared to be rare.

Supplementary material. The supplementary material for this article can be found at https://doi.org/10.1017/S0033291719000369.

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