



# A meta-analysis of controlled studies comparing the association between clozapine and other antipsychotic medications and the development of neutropenia

Australian & New Zealand Journal of Psychiatry  
2019, Vol. 53(5) 403–412  
DOI: 10.1177/0004867419833166

© The Royal Australian and  
New Zealand College of Psychiatrists 2019  
Article reuse guidelines:  
sagepub.com/journals-permissions  
journals.sagepub.com/home/anp



Nicholas Myles<sup>1,2</sup> , Hannah Myles<sup>3</sup>, Shelley Xia<sup>4</sup>, Matthew Large<sup>4,5</sup>,  
Robert Bird<sup>6,7</sup>, Cherrie Galletly<sup>3,8,9</sup>, Steve Kisely<sup>2,10</sup> ,  
and Dan Siskind<sup>2,11</sup>

## Abstract

**Background:** In most countries, clozapine can only be prescribed with regular monitoring of white blood cell counts because of concerns that clozapine has a stronger association with neutropenia than other antipsychotics. However, this has not been previously demonstrated conclusively with meta-analysis of controlled studies.

**Methods:** The aim of this study was to assess the strength of the association between clozapine and neutropenia when compared to other antipsychotic medications by a meta-analysis of controlled studies. An electronic search of Medline (1948–2018), PsycINFO (1967–2018) and Embase (1947–2018) using search terms (clozapine OR clopine OR clozaril OR zaponex) AND (neutropenia OR agranulocytosis) was undertaken. Random-effects meta-analysis using Mantel–Haenszel risk ratio was used to assess the strength of the effect size.

**Results:** We located 20 studies that reported rates of neutropenia associated with clozapine and other antipsychotic medications. The risk ratio was not significantly increased in clozapine-exposed groups compared to exposure to other antipsychotic medications (Mantel–Haenszel risk ratio = 1.45, 95% confidence interval = [0.87, 2.42]). This also applied to severe neutropenia (absolute neutrophil count < 500 per  $\mu\text{L}$ ) when compared to other antipsychotics (Mantel–Haenszel risk ratio = 1.65, 95% confidence interval = [0.58, 4.71]). The relative risk of neutropenia associated with clozapine exposure was not significantly associated with any individual antipsychotic medication.

**Conclusion:** Data from controlled trials do not support the belief that clozapine has a stronger association with neutropenia than other antipsychotic medications. This implies that either all antipsychotic drugs should be subjected to haematological monitoring or monitoring isolated to clozapine is not justified.

## Keywords

Clozapine, neutropenia, agranulocytosis, antipsychotic, meta-analysis

<sup>1</sup>Division of Haematology, SA Pathology, Adelaide, SA, Australia

<sup>2</sup>School of Medicine, The University of Queensland, St Lucia, QLD, Australia

<sup>3</sup>Discipline of Psychiatry, The University of Adelaide, Adelaide, SA, Australia

<sup>4</sup>Department of Psychiatry, Prince of Wales Hospital, Kensington, NSW, Australia

<sup>5</sup>School of Psychiatry, UNSW Sydney, Kensington, NSW, Australia

<sup>6</sup>Division of Cancer Services, Princess Alexandra Hospital, Woolloongabba, QLD, Australia

<sup>7</sup>School of Medicine, Griffith University, Nathan, QLD, Australia

<sup>8</sup>Mental Health, Ramsay Health Care, Gilberton, SA, Australia

<sup>9</sup>Department of Mental Health, Northern Adelaide Local Health Network, Elizabeth, SA, Australia

<sup>10</sup>Departments of Psychiatry, Community Health and Epidemiology, Dalhousie University, Halifax, NS, Canada

<sup>11</sup>Metro South Addiction and Mental Health Service, Woolloongabba, QLD, Australia

## Corresponding author:

Nicholas Myles, SA Pathology, Level 3 Royal Adelaide Hospital, 1 Port Rd, Adelaide, SA 5006, Australia.

Email: nicholas\_myles@hotmail.com

## Introduction

Clozapine is an atypical antipsychotic medication indicated for treatment-refractory schizophrenia (Siskind et al., 2016). The most feared side-effect is idiosyncratic severe neutropenia. Clozapine-associated neutropenia was first recognised in Finland in the 1970s following several fatal cases (Idanpaan-Heikkila et al., 1977). Extrapolation from this cluster to the broader population of patients on clozapine in Finland led to the belief that rates of severe neutropenia were substantially higher than those seen with the historical comparator medication, chlorpromazine. This early data have led to the belief of an important causal association specific to clozapine exposure (Amsler et al., 1977).

As a result, haematological monitoring is mandatory in most countries for patients on clozapine (Nielsen et al., 2016), which is not a requirement for other antipsychotic medications. However, beyond historical comparisons to haematological safety data of first-generation antipsychotics, the relative risk of neutropenia attributable to clozapine is not known despite the availability of safety data from randomised and other controlled trials of clozapine that use other antipsychotic medications as a comparator. Importantly, neutropenia has been reported as an idiosyncratic side-effect of antipsychotic medications other than clozapine (Melkersson and Dahl, 2004; Ruhé et al., 2001) and it is plausible that part of the risk of neutropenia associated with clozapine is a class effect of antipsychotics or results from a vulnerability carried by patients with psychosis.

We therefore compared the incidence of neutropenia in independent cohorts of subjects exposed to clozapine and other first- or second-generation antipsychotics to determine the risk of neutropenia specifically associated with clozapine exposure.

## Methods

The methods are based on the Preferred Reporting Items for Systematic Review and Meta-Analyses (PRISMA; Moher et al., 2009). The PROSPERO registration number is CRD42017056201.

### Searches

We conducted systematic searches of Medline, PsycINFO and Embase using the search terms (clozapine OR clopine OR zaponex OR clozaril) AND (neutropenia OR agranulocytosis) (Figure 1). Abstracts and titles were reviewed for papers reporting on neutropenia in subjects on clozapine compared to those on other antipsychotic medications. Two authors (N.M. and S.X.) examined full text papers for inclusion. The reference lists of included studies and review articles of comparative trials were hand searched for additional studies not identified by electronic searches.

### Inclusion and exclusion criteria

Studies were included if they examined cohorts of subjects exposed to clozapine compared to another cohort exposed to a comparator antipsychotic medication (either first or second generation), reported in a peer-reviewed publication. Studies had to have monitored subjects from initiation of clozapine or the comparator medication. Studies were restricted to randomised controlled trials and cohort studies. We included all age groups with no language restriction.

### Exclusion criteria

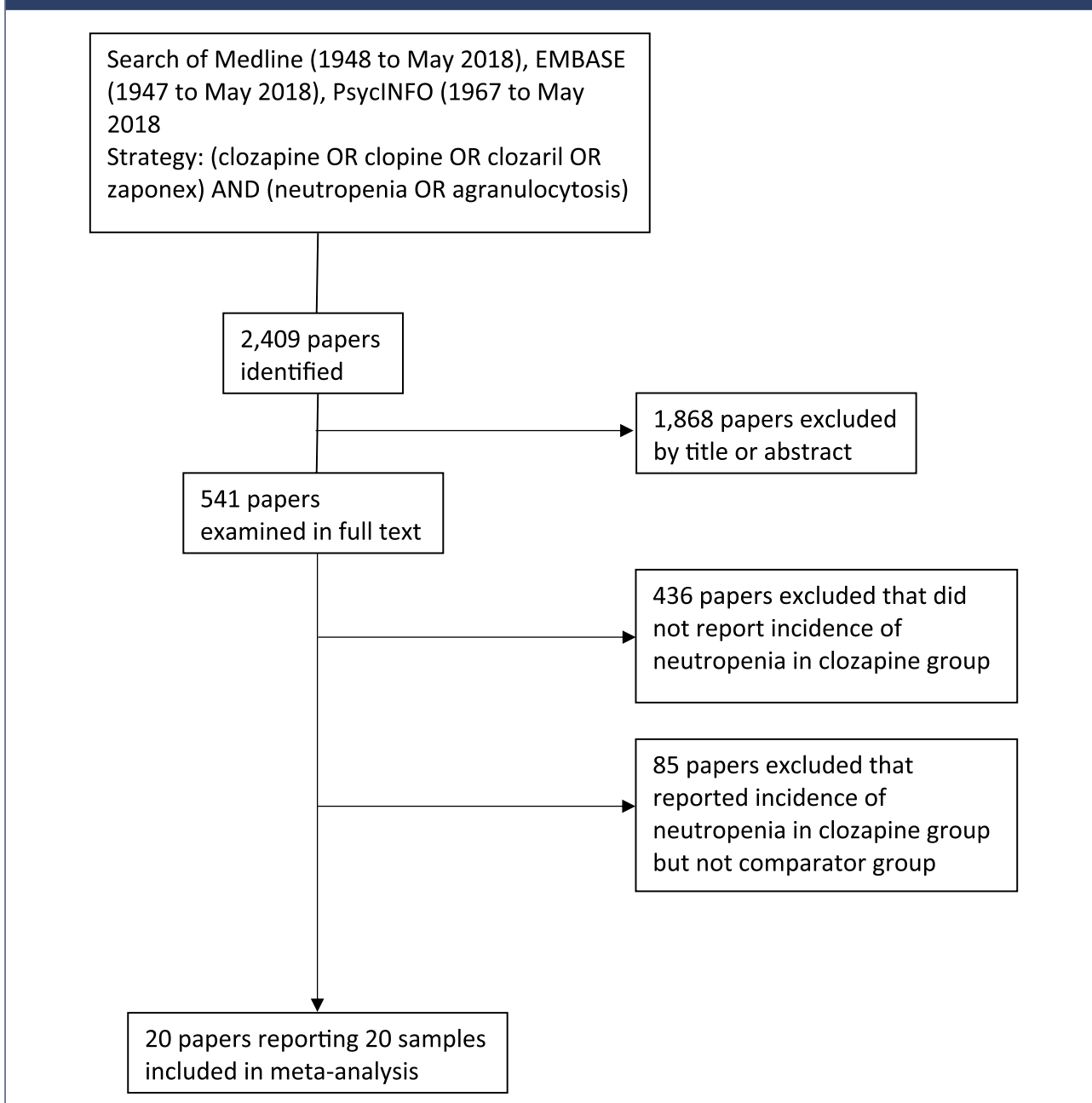
This meta-analysis was designed to compare single-agent clozapine to other individual antipsychotic medications; studies examining clozapine augmented with additional antipsychotic medications were excluded. Studies were also excluded if they reported cross-sectional data about neutropenia among those exposed to clozapine and a comparator medication because the risk of clozapine-associated neutropenia peaks during the first month of treatment (Myles et al., 2018) and the retrospective methodology would be expected to bias towards to a lower rate of neutropenia due to early drop out.

### Definition of neutropenia and clozapine use

The definition of neutropenia was an absolute neutrophil count (ANC) of less than 1500 neutrophils per microlitre ( $\mu\text{L}$ ) which is the highest threshold used in clozapine monitoring guidelines globally (Nielsen et al., 2016). Severity of neutropenia was stratified as mild (1000–1500 per  $\mu\text{L}$ ), moderate (500–1000 per  $\mu\text{L}$ ) and severe ( $<500$  per  $\mu\text{L}$ ). These thresholds are based on the common terminology criteria for adverse events (CTCAE) toxicity reporting guidelines for haematological toxicities (National Cancer Institute, 2009). Studies were excluded if they did not report a threshold for neutropenia. However, if an event was reported as agranulocytosis, this was considered to be a threshold of at least  $<500$  per  $\mu\text{L}$ . Studies that reported mean neutrophil counts between cohorts as the only outcome were not considered for analysis. We did not set a threshold for the frequency of monitoring for neutropenia in primary studies. Most cohort studies relied on registry-mandated monitoring guidelines for clozapine-associated neutropenia with events in comparator groups based on incidental identification of neutropenia. By contrast, monitoring in randomised controlled trials (RCTs) is likely to be more systematic in both clozapine and comparator medication groups. While inclusion of both study types is prone to observation bias, this was considered in the risk of bias assessments.

Clozapine and other antipsychotic medication use were considered to be the regular prescription for the duration of each study and the only prescribed antipsychotic agent. No minimum dose threshold of clozapine or comparator

Figure 1. PRISMA flow diagram of search methodology.



antipsychotic medication was used for inclusion of studies. The mean dose of clozapine and comparator antipsychotic medications were converted to chlorpromazine equivalents and reported as a ratio of the clozapine to comparator equivalent dose (Leucht et al., 2014) (see Table 1).

### Risk of bias assessment

Because both observational and randomised trials were included for analysis, we used the Newcastle–Ottawa scale

(Wells et al., 2009) to assess risk of bias across the following three domains: selection, comparability and outcome assessment. An overall score was calculated by assigning one point to each domain if a study satisfied all criteria within that domain, such that each study could score a maximum of three. Studies with a score of two or more were considered at low risk of bias, while those with a score of less than two were considered at higher risk of bias. The criteria associated with lower risk of bias within each domain are as follows:

Table 1. Characteristics of included studies.

Study name	Study and setting	Participants	Comparator medication	Clozapine to comparator dose ratio in chlorpromazine equivalents	Definition of neutropenia and f/u	Outcomes, events/sample size	Risk of bias
Azorin et al. (2001)	RCT, France and Canada, 1994–1996	Adults, non-treatment-refractory schizophrenia	Risperidone	1.17	ANC < 1500, 12 weeks	1/136 clozapine 3/134 risperidone	Low
Bondolfi et al. (1998)	RCT, Switzerland	Adults, treatment-refractory schizophrenia	Risperidone	0.53	ANC < 1000, 56 days	0/43 clozapine 1/43 risperidone	Higher
Fabrazzo et al. (2017)	Retrospective cohort, Italy, 1992–2011	Adults, schizophrenia and bipolar spectrum disorders	Any other antipsychotic agent	–	ANC < 1500, 18 weeks	3/135 clozapine 0/150 other antipsychotic	Low
Girgis et al. (2011)	RCT, China, 1995–1998	Adults, treatment-naïve first-episode schizophrenia	Chlorpromazine	–	ANC < 500, 9 years	1/80 clozapine 1/80 chlorpromazine	Low
Hong et al. (1997)	RCT, Taiwan, 1995	Adults, treatment-refractory schizophrenia	Chlorpromazine	0.39	ANC < 1500, 12 weeks	0/21 clozapine 0/19 chlorpromazine	Higher
Howanitz et al. (1999)	RCT, USA	Older adults (>55 years), non-treatment-refractory schizophrenia	Chlorpromazine	0.42	ANC < 500, 5 weeks	1/24 clozapine 0/18 chlorpromazine	Higher
Ingimarsson et al. (2016)	Retrospective cohort study, Iceland, 2000–2004	Adults admitted with schizophrenia	Any other antipsychotic agent	–	ANC < 500, 9 years	1/188 clozapine 4/400 other antipsychotic	Higher
Kane et al. (1988)	RCT, USA	Adults, treatment-refractory schizophrenia	Chlorpromazine	0.42	ANC < 500, 6 weeks	0/126 clozapine 0/142 chlorpromazine	Higher
Kumra et al. (1996)	RCT, USA	Paediatric, early onset (<12 years) treatment-refractory schizophrenia	Haloperidol	0.15	ANC < 1500, 6 weeks	5/10 clozapine 0/11 haloperidol	Higher
Kumra et al. (2008)	RCT, USA, 2001–2006	Paediatric (10–18 years), treatment-refractory schizophrenia	Olanzapine	0.46	ANC < 1500, 12 weeks	0/18 clozapine 1/21 olanzapine	Higher

(continued)

Table 1. (Continued)

Study name	Study and setting	Participants	Comparator medication	Clozapine to comparator dose ratio in chlorpromazine equivalents	Definition of neutropenia and f/u	Outcomes, events/sample size	Risk of bias
McEvoy et al. (2006)	RCT (CATIE trial phase 2), USA, 2001–2004	Adult, schizophrenia non-responsive to atypical antipsychotic	Olanzapine, quetiapine, risperidone	0.48	ANC < 500, 18 months	1/45 clozapine 0/45 other AP	Low
Melzer et al. (2010)	RCT, USA, 1991–1996	Adult, non-treatment-refractory schizophrenia	Typical antipsychotics	0.74	ANC < 500, 24 months	1/40 clozapine 0/45 typical antipsychotics	Higher
Merims et al. (2006)	RCT, Israel	Older Parkinson's-associated psychosis	Quetiapine	0.11	ANC < 500, 22 weeks	1/14 clozapine 0/13 quetiapine	Higher
Midbari et al. (2013)	Retrospective cohort, Israel, 2005–2012	Paediatric (age: 6–12 years), early onset schizophrenia	Any other antipsychotic	–	ANC < 1500, 1 year	2/17 clozapine 1/19 other antipsychotic	Higher
Moresco et al. (2004)	RCT, Italy	Adult, treatment-refractory schizophrenia	Olanzapine	0.53	ANC < 500, 8 weeks	1/6 clozapine 0/9 olanzapine	Higher
Rosenheck et al. (1997)	RCT, USA, 1993–1995	Adult, treatment-refractory schizophrenia	Haloperidol	0.26	ANC < 1500, 12 months	8/205 clozapine 9/218 haloperidol	Higher
Shaw et al. (2006)	RCT, USA, 1998–2005	Paediatric, early onset (age: < 13 years) treatment-refractory schizophrenia	Olanzapine	0.51	ANC < 1500, 8 weeks	2/12 clozapine 1/13 olanzapine	Higher
Tollefson et al. (2001)	RCT, international	Adults, treatment-refractory schizophrenia	Olanzapine	0.44	ANC < 1500, 18 weeks	1/90 clozapine 0/90 olanzapine	Higher
Volavka et al. (2002)	RCT, USA, 1996–1997	Adult, treatment-refractory schizophrenia	Olanzapine, risperidone, haloperidol	0.40	ANC < 1500, 14 weeks	3/40 clozapine 3/117 other antipsychotic	Higher
Wahlbeck et al. (2000)	RCT, Finland	Adult, treatment-refractory schizophrenia	Risperidone	0.57	ANC < 1500, 10 weeks	1/10 clozapine 0/9 risperidone	Low

ANC: absolute neutrophil count; RCT: randomised controlled trial.

1. Selection
  - (a) Reporting on an adult population (18–60 years of age);
  - (b) Recruitment of clozapine and comparator groups from same population;
  - (c) Reported a measure of compliance with study medications;
  - (d) Pre-existing neutropenia excluded prior to study recruitment.
2. Comparability
  - (a) Neutropenia as an outcome specified in the methods;
  - (b) Protocolised haematological monitoring specified in both clozapine and comparator groups.
3. Outcome assessment (maximum of three points)
  - (a) Blinded assessment of outcomes;
  - (b) Follow-up greater than 18 weeks;
  - (c) Participant dropout less than 20% excluding patients who dropped out due to haematological toxicities.

### Data extraction

Two authors (N.M. and S.X.) independently extracted the data using a pro forma with disagreements resolved by joint examination of the papers. The effect size data were extracted based on the sample size of clozapine and control groups and the number of neutropenia events in each cohort into a pro forma electronic spreadsheet. There were nine disagreements in data extraction that were resolved by joint examination of the relevant articles. The following methodological characteristics of each study were recorded (see Table 1):

1. Risk of bias criteria (see Table 1 of supplementary appendix);
2. Age group assessed in each study: paediatric (<18 years), adult (18–60 years) and older age (>60 years);
3. Study design (RCT, cohort);
4. Comparator antipsychotic medication;
5. Severity of neutropenia as outlined above;
6. The mean dose of clozapine and mean dose of comparator medication, converted into chlorpromazine equivalents and reported as a ratio, in study participants.

### Meta-analysis

We used the Mantel–Haenszel method for meta-analytical estimation of risk ratios (MHRR) given the rarity of the outcomes, the number of zero events in the included studies and the differences in group sizes (Efthimiou, 2018). Non-fixed empirical continuity corrections (Sweeting et al., 2004) were used to impute data for studies with no events in both treatment groups. All analyses were performed

using Comprehensive Meta-Analysis version 2 (Biostat, Englewood, NJ). Between-study heterogeneity was assessed using the  $I^2$  statistic, and between-group heterogeneity was assessed using Q-value statistic. A random-effects meta-analysis was chosen for all analyses due to presumed differences in patient groups and study methods.

### Publication bias

Potential publication bias was assessed using Egger's test. We used Duval and Tweedie's trim-and-fill method to examine the possible effect of hypothetically missing samples.

### Sensitivity and subgroup analysis

We conducted sensitivity analyses by type of antipsychotic comparator, the threshold of neutropenia (stratified as  $ANC < 1500$  or  $ANC < 500$ ) and between studies with a higher and lower risk of bias. Subgroup analysis was undertaken between RCT and cohort studies.

## Results

### Searches

The number of samples included in each meta-analysis is outlined in Figure 1 and descriptions of each study in Table 1. A total of 20 papers were included, of which 17 studies were RCTs and 3 cohort studies. Risperidone was the comparator medication in three studies, chlorpromazine in four, haloperidol in two, olanzapine in four and combinations of multiple antipsychotic medications in four. Combinations of second-generation antipsychotic medications, combinations of first-generation antipsychotic medications and quetiapine alone were comparators in single studies, respectively.

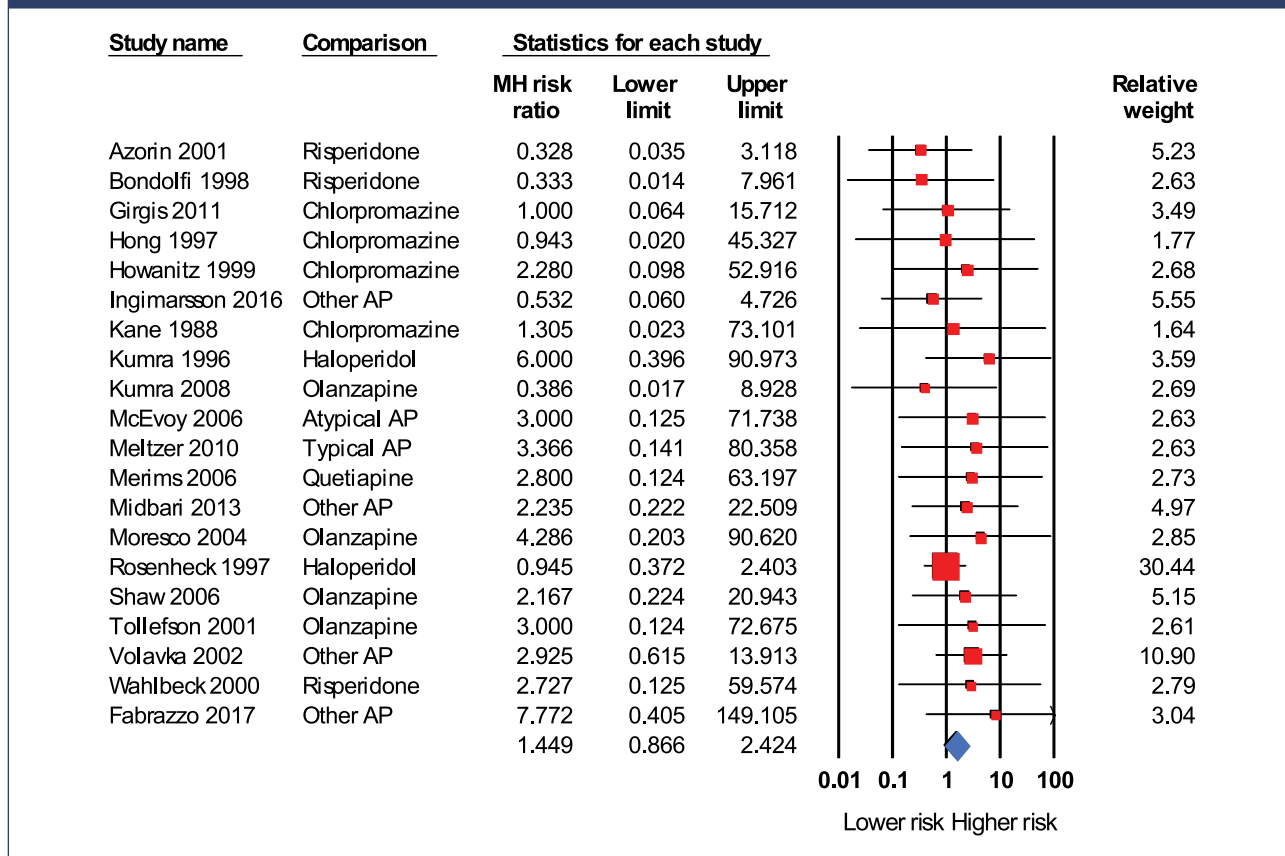
The total sample size of subjects exposed to clozapine was 1260 (mean number per sample = 63) comprising 2981 person-years. The total sample size of subjects exposed to comparator antipsychotics was 1596 (mean number per sample = 80) comprising 4942 person-years. The crude neutropenia event rate was 2.6% in clozapine-exposed patients (1.1 events per 100 person-years) and 1.5% in subjects exposed to comparator antipsychotics (0.49 events per 100 person-years). Median follow-up was 3.5 (range = 1–108) months.

The meta-analysis reported here deviates from the registered PROPSERO protocol in that we were unable to report an analysis of mean time to neutropenia and mean neutrophil count at time of neutropenia due to sparsity of data and an inability to perform meaningful analysis.

### Meta-analysis

Meta-analysis of 20 samples indicated a MHRR of neutropenia of 1.45 (95% confidence interval [CI] = [0.87, 2.42]; see Figure 2), and studies with zero events in at least one

**Figure 2.** Forest plot. Lower absolute MH risk ratio indicates a lower relative risk of neutropenia in clozapine-exposed subjects relative to comparator-exposed subjects (i.e. 'lower risk' denotes a lower risk of neutropenia in clozapine-exposed subjects and 'higher risk' denotes a lower risk of neutropenia in comparator-exposed subjects).



AP: antipsychotic; MH: Mantel–Haenszel risk ratio.

treatment group contributed 26.5% to the relative weighting. There was no heterogeneity ( $Q = 9.8$ ,  $df(Q) = 19$ ,  $p = 0.96$ ,  $I^2 = 0$ ).

Subgroup analyses specified in the registered PROSPERO protocol (proportion of males, geographical region, mean age of subjects and year of data collection) were not conducted as there was a lack of heterogeneity in the summary analysis. Meaningful analysis of differences in between-study heterogeneity would therefore have been futile.

Sensitivity analysis by neutropenia severity, comparator agent and study quality made little difference to the effect size although CIs were wide (see Table 2). The MHRR for an ANC threshold of  $<500$  was 1.65 (95% CI = [0.58, 4.71]), while that for a threshold of  $<1500$  was 1.46 (95% CI = [0.80, 2.67]). Sensitivity analysis restricted to a comparison of clozapine to specific antipsychotic comparators gave a MHRR of 1.89 (95% CI = [0.46, 7.74]) for olanzapine, 1.53 (95% CI = [0.30, 7.81]) for haloperidol, 1.30 (95% CI = [0.25, 6.88]) for chlorpromazine and 0.57 (95% CI = [0.12, 2.78]) for risperidone. Studies with a low risk of bias reported a similar MHRR of neutropenia compared to the summary effect (RR = 1.43, 95% CI = [0.41, 4.94]).

Subgroup analysis of study design demonstrated no significant impact on effect size ( $Q = 0.04$ ,  $df(Q) = 1$ ,  $p = 0.84$ ) between RCT (17 samples, MHRR = 1.42, 95% CI = [0.81, 22.47]) and cohort studies (3 samples, MHRR = 1.67, 95% CI = [0.39, 7.20]).

### Publication bias

Visual inspection of the funnel plot demonstrated publication bias towards studies reporting a higher risk of neutropenia (see Figure 1 of supplementary appendix). Duval and Tweedie's trim-and-fill method identified four hypothetically missing studies to the left of mean associated with an adjusted risk ratio of 1.21 (95% CI = [0.75, 1.98]).

### Discussion

Despite a data synthesis of 20 primary studies, we were not able to demonstrate a statistically significant increased relative risk of neutropenia associated with clozapine compared to other antipsychotic medications. Moreover, the

**Table 2.** Sensitivity analysis.

Analysis group	No. of samples	Effect size (MHRR)	95% CI	Standard error	Variance	Heterogeneity
<i>Summary effect</i>						
	20	1.45	[0.87, 2.42]	0.49	0.24	$I^2=0, p=0.96$
<i>Severity of neutropenia</i>						
ANC < 1.5	11	1.46	[0.80, 2.67]	0.54	0.29	$I^2=0, p=0.73$
ANC < 0.5	8	1.65	[0.58, 4.71]	1.24	1.54	$I^2=0, p=0.96$
<i>Stratified by antipsychotic type</i>						
Olanzapine	4	1.89	[0.46, 7.74]	1.76	3.08	$I^2=0, p=0.72$
Risperidone	3	0.57	[0.12, 2.78]	2.06	4.24	$I^2=0, p=0.51$
Chlorpromazine	4	1.30	[0.25, 6.88]	2.43	5.92	$I^2=0, p=0.98$
Haloperidol	2	1.53	[0.30, 7.81]	2.52	6.36	$I^2=40, p=0.20$
<i>Study quality</i>						
Low quality	4	1.17	[0.27, 4.98]	1.93	3.71	$I^2=0, p=0.81$
Moderate quality	11	1.51	[0.82, 2.80]	0.57	0.33	$I^2=0, p=0.86$
High quality	5	1.43	[0.41, 4.94]	1.45	2.09	$I^2=0, p=0.50$

MHRR: Mantel–Haenszel risk ratio; CI: confidence interval; ANC: absolute neutrophil count.

strength of the pooled association was weak (Rosenthal, 1996) casting doubt on whether clozapine is causally associated with neutropenia (Hill, 1965). Importantly, our finding of a weak and non-significant association between clozapine and neutropenia was similar across a range of individual antipsychotic comparator medications, different thresholds for neutropenia and among groups of studies with greater and lesser risk of bias.

While there have been reports of neutropenia associated with antipsychotic agents other than clozapine (Finkel et al., 1998; Ruhé et al., 2001), there is a widespread assumption that clozapine has specific, causal and clinically important haematological risks that do not apply to other antipsychotic medications. This assumption forms the basis for mandated haematological monitoring of clozapine. However, our results suggest that clozapine and other antipsychotic agents have a similar incidence of neutropenia, calling into question the rationale for stringent monitoring of clozapine and the lack of similar monitoring for other antipsychotic drugs. While our results challenge the rationale for haematological monitoring of clozapine, they provide insufficient evidence to support abandoning monitoring entirely. Further evidence reporting comparative rates of neutropenia as a primary outcome for clozapine and other antipsychotic agents is required before such an approach should be considered.

Conclusions about the haematological toxicity of clozapine should also be considered in the light of more

general difficulties in determining the clinical relevance of neutropenia associated with any medication. Neutropenia occurs as a benign and transient finding in the general population. One large cross-sectional epidemiological study of healthy participants reported a point prevalence of neutropenia at an ANC threshold of <1500 and <1000 between 0.38% and 4.5% and between 0.08% and 0.57%, respectively (Hsieh et al., 2007). As a result, it is plausible that repeated haematological monitoring over time might result in the observation of events that are not aetiologically related to the medication of interest. Clozapine-associated neutropenia is particularly prone to observation bias compared to other antipsychotics because of mandated haematological monitoring, potentially inflating the reported rates of clozapine-associated neutropenia. Conversely fatal clozapine-associated agranulocytosis is very rare, affecting about 1 in 8000 patients (Myles et al., 2018) while rates seen with other antipsychotic medications is unknown, hindering adequately powered research into comparative safety of different antipsychotics. Importantly, the crude clozapine-associated neutropenia rate in our meta-analysis is similar to large registry studies of clozapine (Alvir et al., 1993; Atkin et al., 1996; Munro et al., 1999) indicating that the comparator rate reported here is generalisable to the broader literature.

Complicating matters further, clozapine is prescribed in circumstances that might explain the apparent temporal relationship between clozapine exposure and neutropenia.



Clozapine is a second- or third-line therapy limited to patients who have failed trials of other antipsychotic medications. While such treatment-resistant patients might differ in their vulnerability to neutropenia for a variety of reasons, one major factor may be the cross-titration of clozapine with the preceding antipsychotic treatment. This early period of combination antipsychotic prescribing is likely to inflate the number of neutropenia cases attributed to clozapine in the first month of treatment (Myles et al., 2018) due to neutropenia cases occurring due to non-clozapine antipsychotic drugs. Finally, survivorship bias might also be at play in the apparent temporal relationship between clozapine and neutropenia. Patients who are prone to non-clozapine-related neutropenia are more likely to have neutropenia detected early in the course of clozapine prescribing, have their clozapine stopped and therefore do not develop later neutropenia. We believe that weakness of the association between clozapine and neutropenia as well as plausible alternative explanations for an apparent temporal relationship between clozapine exposure and neutropenia challenge conventional wisdom about clozapine toxicity.

The potential implications of our findings for clozapine prescribing and monitoring mean that several limitations of our analysis need to be considered. First, neutropenia was not the primary outcome in the majority of included studies. Given neutropenia is a widely recognised side-effect of clozapine and given haematological monitoring of clozapine may not have been replicated exactly in comparator arms, there is a risk of observation bias towards a higher relative risk of neutropenia in the clozapine arm. Unfortunately, there were insufficient data in the primary literature to perform subgroup analysis according to methods of haematological monitoring in clozapine and comparator arms. Second, clozapine and comparator dosing were defined according to the protocols of included studies and regular prescription was assumed in our analysis. Realistically, many study participants may have discontinued or resumed treatment, especially in the observational studies. While this was accounted for by including a measure of compliance in risk of bias assessment, it remains a limitation to our analysis. Third, the rarity of events limits the power of primary research to detect differences in rates of neutropenia between clozapine and non-clozapine antipsychotic-exposed subjects. While a meta-analysis can greatly increase the power to detect small effect sizes, the small summary effect size we estimated does not conclusively prove the absence of a small but specific association between clozapine and neutropenia. Fourth, our research methods were affected by a number of studies that reported zero events in one or both treatment arms. While there is no clear consensus on how to best approach the analysis of zero-value studies, our approach using a MHRR is reasonable as it allows for the analysis of studies with zero events in a single treatment group and is suitable for analysis of datasets with sparse data and unbalanced cohort sizes

(Efthimiou, 2018). We also used non-fixed continuity corrections which involves the estimation of effect size data for studies with zero events in both treatment arms based on the effect size data in non-zero-event studies. This method is considered to be the most statistically robust approach to zero-event studies in meta-analysis (Sweeting et al., 2004) and avoids the unnecessary omission of useable data (Sankey et al., 1996). However, one of the trade-offs of this approach is a normalisation of between-study heterogeneity and an associated reduction in meta-analytic ability to detect differences between subgroups of studies.

The association between clozapine and neutropenia may be neither causal nor clinically meaningful, and belief in the toxicity of clozapine may be contributing to the under-use of clozapine, suboptimal treatment of many patients and resource wastage due to haematological monitoring. Further primary research with larger samples such as linked epidemiological registers of healthcare data and timely replication meta-analyses are warranted. Replication of our results might lead to a loosening of the restrictions and improved ease of prescribing the most effective treatment for schizophrenia to date.

### Declaration of Conflicting Interests

The authors declared no potential conflicts of interest with respect to the research, authorship and/or publication of this article.

### Funding

The authors received no financial support for the research, authorship and/or publication of this article.

### ORCID iDs

Nicholas Myles  <https://orcid.org/0000-0003-1561-581X>  
Steve Kisely  <https://orcid.org/0000-0003-4021-2924>

### Supplemental material

Supplemental material for this article is available online.

### References

- Alvir J, Lieberman JA, Safferman AZ, et al. (1993) Clozapine-induced agranulocytosis: Incidence and risk factors in the United States. *New England Journal of Medicine* 329: 162–167.
- Amsler H, Teerenhovi L, Barth E, et al. (1977) Agranulocytosis in patients treated with clozapine: A study of the Finnish epidemic. *Acta Psychiatrica Scandinavica* 56: 241–248.
- Atkin K, Kendall F, Gould D, et al. (1996) Neutropenia and agranulocytosis in patients receiving clozapine in the UK and Ireland. *British Journal of Psychiatry* 169: 483–488.
- Azorin JM, Spiegel R, Remington G, et al. (2001) A double-blind comparative study of clozapine and risperidone in the management of severe chronic schizophrenia. *American Journal of Psychiatry* 158: 1305–1313.
- Bondolfi G, Dufour H, Patris M, et al. (1998) Risperidone versus clozapine in treatment-resistant chronic schizophrenia: A randomized double-blind study. *American Journal of Psychiatry* 155: 499–504.
- Efthimiou O (2018) Practical guide to the meta-analysis of rare events. *Evidence Based Mental Health* 21: 72–76.

- Fabrazzo M, Prisco V, Sampogna G, et al. (2017) Clozapine versus other antipsychotics during the first 18 weeks of treatment: A retrospective study on risk factor increase of blood dyscrasias. *Psychiatry Research* 256: 275–282.
- Finkel B, Oyffe I and Sigal M (1998) Risperidone-associated agranulocytosis. *American Journal of Psychiatry* 155: 855–856.
- Girgis RR, Phillips MR, Li X, et al. (2011) Clozapine v. chlorpromazine in treatment-naïve, first-episode schizophrenia: 9-Year outcomes of a randomised clinical trial. *British Journal of Psychiatry* 199: 281–288.
- Hill AB (1965) The environment and disease: Association or causation? *Proceedings of the Royal Society of Medicine* 58: 295–300.
- Hong CJ, Chen JY, Chiu HJ, et al. (1997) A double-blind comparative study of clozapine versus chlorpromazine on Chinese patients with treatment-refractory schizophrenia. *International Clinical Psychopharmacology* 12: 123–130.
- Howanitz E, Pardo M, Smelson DA, et al. (1999) The efficacy and safety of clozapine versus chlorpromazine in geriatric schizophrenia. *Journal of Clinical Psychiatry* 60: 41–44.
- Hsieh MH, Everhart JE and Byrd-Holt DD (2007) Prevalence of neutropenia in the US population: Age, sex, smoking and ethnic differences. *Annals of Internal Medicine* 146: 486–492.
- Idanpaan-Heikkilä J, Alhava E, Olkinuora M, et al. (1977) Agranulocytosis during treatment with clozapine. *European Journal of Clinical Pharmacology* 11: 193–198.
- Ingimarsson O, Maccabe JH, Haraldsson M, et al. (2016) Neutropenia and agranulocytosis during treatment of schizophrenia with clozapine versus other antipsychotics: An observational study in Iceland. *BMC Psychiatry* 16: 441.
- Kane J, Honigfeld G, Singer J, et al. (1988) Clozapine for the treatment-resistant schizophrenic: A double-blind comparison with chlorpromazine. *Archives of General Psychiatry* 45: 789–796.
- Kumra S, Frazier JA, Jacobsen LK, et al. (1996) Childhood-onset schizophrenia. A double-blind clozapine-haloperidol comparison. *Archives of General Psychiatry* 53: 1090–1097.
- Kumra S, Kranzler H, Gerbino-Rosen G, et al. (2008) Clozapine and ‘high-dose’ olanzapine in refractory early-onset schizophrenia: A 12-week randomized and double-blind comparison. *Biological Psychiatry* 63: 524–529.
- Leucht S, Samara M, Heres S, et al. (2014) Dose equivalents for second generation antipsychotics: The minimum effective dose method. *Schizophrenia Bulletin* 40: 314–326.
- McEvoy JP, Lieberman JA, Stroup TS, et al. (2006) Effectiveness of clozapine versus olanzapine, quetiapine, and risperidone in patients with chronic schizophrenia who did not respond to prior atypical antipsychotic treatment. *American Journal of Psychiatry* 163: 600–610.
- Melkersson K and Dahl ML (2004) Adverse metabolic effects associated with atypical antipsychotic: Literature review and clinical implications. *Drugs* 64: 701–723.
- Meltzer HY, Bobo WV, Lee MA, et al. (2010) A randomized trial comparing clozapine and typical neuroleptic drugs in non-treatment-resistant schizophrenia. *Psychiatry Research* 177: 286–293.
- Merims D, Balas M, Peretz C, et al. (2006) Rater-blinded, prospective comparison: Quetiapine versus clozapine for Parkinson’s disease psychosis. *Clinical Neuropharmacology* 29: 331–337.
- Midbari Y, Ebert T, Kosov I, et al. (2013) Hematological and cardiometabolic safety of clozapine in the treatment of very early onset schizophrenia: A retrospective chart review. *Journal of Child and Adolescent Psychopharmacology* 23: 516–521.
- Moher D, Liberati A, Tetzlaff J, et al. (2009) Preferred reporting items for systematic reviews and meta-analyses: The PRISMA statement. *Annals of Internal Medicine* 151: 264–269.
- Moresco RM, Cavallaro R, Messa C, et al. (2004) Cerebral D2 and 5-HT2 receptor occupancy in Schizophrenic patients treated with olanzapine or clozapine. *Journal of Psychopharmacology* 18: 355–365.
- Munro J, O’Sullivan D, Andrews C, et al. (1999) Active monitoring of 12,760 clozapine recipients in the UK and Ireland: Beyond pharmacovigilance. *British Journal of Psychiatry* 175: 576–580.
- Myles N, Myles H, Xia S, et al. (2018) Meta-analysis examining the epidemiology of clozapine-associated neutropenia. *Acta Psychiatrica Scandinavica* 132: 101–109.
- National Cancer Institute (2009) *Common terminology criteria for adverse events v4.0*. Report for the National Institutes of Health, publication no. 09-7473, 28 May. Bethesda, MD: National Cancer Institute.
- Nielsen J, Young C, Ifteni P, et al. (2016) Worldwide differences in regulations of clozapine use. *CNS Drugs* 30: 149–161.
- Rosenheck R, Cramer J, Xu W, et al. (1997) A comparison of clozapine and haloperidol in hospitalized patients with refractory schizophrenia. *New England Journal of Medicine* 337: 809–815.
- Rosenthal J (1996) Qualitative descriptors of strength of association and effect size. *Journal of Social Service Research* 21: 37–57.
- Ruhé HG, Becker HE, Jessurun P, et al. (2001) Agranulocytosis and granulocytopenia associated with quetiapine. *Acta Psychiatrica Scandinavica* 104: 311–313.
- Sankey SSAWL, Fine MJ and Kapoor W (1996) An assessment of the use of the continuity correction for sparse data in metaanalysis. *Communications in Statistics – Simulation and Computation* 25: 1031–1056.
- Shaw P, Sporn A, Gogtay N, et al. (2006) Childhood-onset schizophrenia: A double-blind, randomized clozapine-olanzapine comparison. *Archives of General Psychiatry* 63: 721–730.
- Siskind D, McCartney L, Goldschlager R, et al. (2016) Clozapine versus first and second-generation antipsychotics in treatment-refractory schizophrenia: Systematic review and meta-analysis. *The British Journal of Psychiatry* 209: 385–392.
- Sweeting MJ, Sutton AJ and Lambert PC (2004) What to add to nothing? Use and avoidance of continuity corrections in meta-analysis of sparse data. *Statistics in Medicine* 23: 1351–1375.
- Tollefson GD, Birkett MA, Kiesler GM, et al. (2001) Double-blind comparison of olanzapine versus clozapine in schizophrenic patients clinically eligible for treatment with clozapine. *Biological Psychiatry* 49: 52–63.
- Volavka J, Czobor P, Sheitman B, et al. (2002) Clozapine, olanzapine, risperidone, and haloperidol in the treatment of patients with chronic schizophrenia and schizoaffective disorder. *American Journal of Psychiatry* 159: 255–262.
- Wahlbeck K, Cheine M, Tuisku K, et al. (2000) Risperidone versus clozapine in treatment-resistant schizophrenia: A randomized pilot study. *Progress in Neuro-psychopharmacology & Biological Psychiatry* 24: 911–922.
- Wells GA, Shea BO, Connell D, et al. (2009) The Newcastle–Ottawa Scale (NOS) for assessing the quality of nonrandomised studies in meta-analyses. Available at [http://www.ohri.ca/programs/clinical\\_epidemiology/oxford.asp](http://www.ohri.ca/programs/clinical_epidemiology/oxford.asp) (accessed 3 July 2017).