

Prevalence of drug-drug interactions (DDIs) involving clozapine: a systematic review

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Systematic Review

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Abstract

Background

Clozapine is a highly effective drug for managing treatment-resistant schizophrenia. Established haematological safety concerns are mitigated through mandatory blood testing and specialist prescribing; however, clozapine also carries a high risk of drug-drug interactions (DDIs) due to complex pharmacokinetics, polypharmacy, and fragmented prescribing and dispensing. While individual interactions are well described, the overall prevalence of DDIs involving clozapine has not yet been systematically synthesised.

Aims

To determine the prevalence of DDIs involving clozapine in adult populations, and to characterise how interactions are identified and reported across clinical settings.

Methods

A systematic search of MEDLINE, PubMed, Cochrane, EMBASE, EBSCO CINAHL, and Scopus databases was conducted from inception to July 2025 (PROSPERO registration 07/10/23). Studies reporting frequency of potential DDIs involving clozapine in adult populations were included. Data extraction took place 11/2023-01/2024 and 15th to 30th July 2025. Risk of bias was assessed using the JBI checklist for prevalence studies. Due to methodological heterogeneity a narrative synthesis was completed. Percentage of DDIs involving clozapine and rate of clozapine DDIs per 1,000 participants were calculated where possible.

Results

Fourteen studies comprising 150,119 participants from 14 countries across care settings were included. Studies employed various DDI screening tools and outcome measures. In 12 studies reporting total DDIs, interactions involving clozapine accounted for between 1.2% and 18.8% of all identified DDIs. Thirteen studies permitted estimation of clozapine DDI rates, which varied markedly (0.5 to 3,300 per 1,000 participants), reflecting differences in populations, denominators, and detection methods. Clozapine DDIs were usually classified within higher-risk categories and commonly involved antidepressants, other antipsychotics, sedatives, and medications for coexisting diseases.

Conclusions

Potential DDIs involving clozapine are common across care settings, particularly mental health. These findings highlight the need for improved medication review processes and greater integration of prescribing and dispensing systems to reduce preventable harm.

1. Introduction

Clozapine, an atypical antipsychotic, is the most effective treatment for treatment-resistant schizophrenia¹. Despite its efficacy, it is considered a high-risk medication, due to its narrow therapeutic index and well-established potential to cause serious adverse effects^{2,3}. Haematological risks, particularly agranulocytosis, are managed through mandatory blood monitoring and structured prescribing systems in many countries. However, clozapine remains underutilised globally, with substantial variation in prescribing rates observed between countries and healthcare systems⁴.

Alongside its recognised haematological risks, clozapine is associated with additional and clinically important risk of drug-drug interactions (DDIs)⁵. Its metabolism via cytochrome P450 enzymes (primarily CYP1A2 and CYP3A4), combined with the high prevalence of polypharmacy in people with treatment-resistant schizophrenia increases susceptibility to both pharmacokinetic and pharmacodynamic interactions^{6,7}. In clinical practice, patients prescribed clozapine frequently have multiple comorbidities, including cardio-metabolic disease, and complex medication regimens, increasing the likelihood of co-prescribing interacting medications^{8,9,10}. These interactions may result in toxicity, reduced therapeutic efficacy, or serious adverse outcomes including sedation, seizures, and cardiovascular complications.

Drug-drug interactions are a major contributor to preventable medication-related harm, with prescribing identified as the stage at which most issues occur¹¹. This risk is further increased in patients treated with clozapine due to the involvement of multiple prescribers across specialist mental health services and general healthcare, spanning both primary and secondary care settings. Although clozapine prescribing is highly regulated in most jurisdictions, the structure of these safety-focused systems may inadvertently contribute to fragmented care. Established barriers to optimal clozapine use include administrative burden, limited integration of care pathways, and lack of coordinated systems to support prescribing and monitoring across settings¹². This fragmentation may limit the potential for comprehensive medication review and reduce opportunity to detect and manage DDIs effectively.

While individual DDIs involving clozapine are well described in the product literature and interaction databases, there is limited understanding of how frequently these combinations of interacting medications occur in routine clinical practice. In particular, the prevalence of DDIs involving clozapine across different healthcare settings, populations, and methods of detection has not been systematically synthesised.

1.1 Aim

The aim of the review was to determine the prevalence of DDIs involving clozapine in adult populations, and to characterise how these interactions are identified and reported across clinical settings.

2. Methods

2.1 Study Design

This systematic review of prevalence studies was conducted in line with JBI guidance for systematic reviews of prevalence data and reported in line with the PRISMA guidelines^{13, 14}. The review was prospectively registered on PROSPERO¹⁵

PROSPERO ID: CRD42023470314, registered 7 October 2023, data extraction commenced on 10th November 2023 until 15th January 2024, and again from 15th to 30th July 2025.

2.2 Eligibility Criteria

Studies were deemed eligible if the population included adults prescribed clozapine with other medicines. Studies with a mixed adult and paediatric populations were included if it was clear at least 75% of the population were adults. Studies were not restricted to those reporting clozapine DDIs exclusively. Studies were included if they reported the number of drug-drug interactions involving clozapine or provided sufficient data to allow prevalence to be calculated. The reporting outcomes varied depending on the study focus.

The CoCoPop (condition, context and population) approach for prevalence reviews recommended by JBI was followed¹³. In this review, the condition of interest was drug-drug interactions involving clozapine, the context was unrestricted, and the population was adult patients prescribed clozapine.

2.3 Search Strategy

A comprehensive literature search was conducted with the assistance of an information specialist from the RCSI library. Electronic databases searched included OVID MEDLINE, PubMed, Cochrane Library, EMBASE, EBSCO CINAHL and Scopus from inception to July 2025.

The search strategy combined terms relating to clozapine, drug-drug interactions, and prevalence. The following key terms were used:

- Clozapine OR Clozaril OR Denzapine OR Zaponex OR Leponex OR desmethylclozapine OR norclozapine.
- "drug-interaction*" OR "drug-drug interaction*" OR "concomitant drug*" OR "co-prescribed"
- prevalence OR rate OR incidence

These terms were combined using Boolean operators. Search strategies were adapted for each database as appropriate. Full search strategies for each database are provided in the supplementary materials (Supplementary Table S1). The search was initially conducted in October 2023 and was updated in July 2025 to identify additional eligible studies.

2.4 Data Collection and Data Extraction

Records identified from each database were imported to Rayyan (a web-based systematic review screening tool) and deduplication was conducted. Titles and abstracts were independently screened by two reviewers (LF & GH). Full-text articles were assessed independently by two reviewers for eligibility. Disagreements were resolved through discussion and, where necessary, consultation with a third reviewer (FM).

A standardised data extraction form was developed in Microsoft Excel. This was piloted on three papers and revised before conducting data extraction. Data extraction was conducted by one reviewer (LF) with an independent check by a second reviewer (GH) to ensure accuracy and consistency. Extracted data included citation details (authors, location and year of publication) and study characteristics (study design, setting, time period, data source, sample size, participant characteristics). Data relating to DDIs were also extracted, including the method used to identify DDIs, severity classification of DDs, number of DDIs involving clozapine, number of overall DDIs and any reported or calculable measures of prevalence.

2.5 Quality Appraisal

The JBI Critical Appraisal Checklist for studies reporting prevalence data was completed independently by two reviewers (LF & GH) for each study¹⁶. Discrepancies were reviewed by a third reviewer (FM). This tool evaluates methodological quality across domains including sampling, measurement of condition, and statistical analysis.

2.6 Data Analysis

A narrative synthesis was conducted due to heterogeneity in study design, populations, and reporting of drug-drug interactions. Study characteristics were summarised descriptively including location, study design, setting and population. The methods for identifying DDIs and severity classification of DDIs were described for each study.

Given the variation in outcome reporting across studies, multiple definitions of prevalence were used. Where studies reported both the total number of DDIs and the number involving clozapine, the proportion of DDIs involving clozapine was calculated. Where sufficient data were available, rates of clozapine DDIs

per 1,000 participants were estimated. These metrics were calculated where possible for all studies, regardless of whether studies only assess clozapine-specific or restricted categories of interactions.

Further synthesis of secondary outcomes examined clozapine DDIs by classification of interaction severity, and the classes of co-prescribed medications involved in DDIs with clozapine.

3. Results

A total of 2,424 records were screened after deduplication, with 47 full-text articles assessed for eligibility in 2023. Of these, 12 papers met the inclusion criteria. The search was updated in July 2025 to identify additional eligible studies. This yielded a further 65 records, of which three were assessed at full text and two met the inclusion criteria. In total, 14 studies were included in this review, comprising 150,119 participants. Reasons for exclusion at full-text stage are provided in the supplementary materials (Supplementary Table 2). A PRISMA flow diagram illustrating the study selection process is shown in Fig. 1.

3.1 Quality Appraisal

Overall, the included studies were of good methodological quality. Inadequate sample size was identified for three of the studies considering a sufficient sample to precisely estimate prevalence of DDIs, however this was not the primary aims of the studies. The response rate criterion was not applicable for the included studies, as data were derived from prescription records, chart reviews, or administrative datasets. A summary of the quality appraisal is presented in the supplementary materials (Supplementary Table 3).

3.2 Characteristics of included studies

The 14 included studies were conducted across a range of geographical regions, including Europe, North America, and Asia, reflecting diverse healthcare systems and prescribing practices. The study settings for the included studies varied considerably and included psychiatric inpatient and outpatient services, general hospital settings, nursing homes and a specialised clozapine clinic. Eight studies reported data from specialist psychiatric settings^{17,18,19,20,21,22,23,29}. Two studies reported data from multiple nursing homes^{25,26}, and four studies reported on data sourced in primary care and general hospital inpatient and outpatient settings^{24,27,28,30}.

Most of the studies (n = 13) employed cross-sectional study designs^{17–24, 26–30}, with one retrospective longitudinal cohort study conducted in a nursing home context²⁵. Study duration ranged from 1 day to 14 years, reflecting variation in study design and data sources. Sample sizes for the individual studies varied widely. Studies utilising claims data or datasets from larger studies or monitoring programmes had sample sizes ranging from 4,467 to 84,607^{19,22,23,28}. Studies undertaken in clinical settings ranged from 112 to 1,987 participants^{17,18,20,21,24,25,26,27,29,30}. Where reported, mean age ranged from 38.3 years to 83.7 years. Participant gender was reported for twelve studies, and percentage of female participants ranged from 33% to 81%.

Approaches used to identify DDIs varied between studies. Some studies relied on clinical review of prescriptions or primary literature, and others employed one or more of a wide range of interaction screening tools and databases, including commercially available resources such as Micromedex, Drugs.com, Stockley's, and Lexicomp® (now known as UpToDate® Lexidrug), as well as locally developed or study-specific systems. Ten studies used unique tools not shared with other included studies highlighting substantial heterogeneity. Two studies used the Drugs.com interaction checker^{21,27}, while two other studies reported using Lexicomp®^{17,29}. One study used both Stockley's and Lexicomp¹⁷. Characteristics of studies are described in Table 1.

Table 1
Study Characteristics

Study & Year	Location	Study design	Timeframe & Study Period	Setting	Sample size	Age years (Mean)	% Female	Data source & DDI screening tool used
Psychiatric Setting								
Barrett et al., 2018	Ireland	Retrospective cross-sectional study	One month May to June 2017	Outpatient clozapine clinic	112	43.9	33%	Prescription review (clozapine + other medication) Lexicomp interaction checker ^a & Stockley's interaction checker ^b
Collins et al., 2022	USA	Retrospective cross-sectional study	Fifteen months July 2021 to Oct 2022	Psychiatric clinic	129	43.1	0%	Chart review Primary literature on DDIs
Guo et al., 2012	USA	Retrospective cross-sectional study	Four years January 2000 to December 2003	Prescription claims data (adults with a schizophrenia diagnosis and on at least one antipsychotic)	27,909	42.5	48.2%	Claims database Facts and comparisons 4.0 interaction classification ^c
Haeuys et al., 2011	Germany, Switzerland, Austria, Belgium & Hungary	Retrospective cross-sectional study	Fourteen years 1994 to 2008	Psychiatric hospital	84,607	51*	55%	Prescription review Software interaction alerts Zurich Interaction System (ZHIAS)) incorporating the Operational Classification of Drug Interactions (ORCA)
Javelot et al., 2012	France	Cross-sectional study	Two days October 5 2011 October 5 2012	Psychiatric hospital	711	21%Elderly (> 65)	Not reported	Chart review Drug-drug interaction software
Kirilochev et al., 2019	Russian Federation	Cross-sectional study	Not specified	Psychiatric hospital	500	62	64%	Chart review Website Drugs.com interaction checker ^d
Toto et al., 2021	Germany	Cross-sectional study	Eleven months October 2017 to September 2018	Psychiatric hospitals	27,396	47	46%	Electronic hospital record review Reported DDIs resulting in increased anticholinergic burden
Vedaprakash et al, 2023	Vedaprakash et al, 2023	Cross-sectional study	Seven months January 2023 to July 2023	Outpatient psychiatric clinic	606	49.7	56%	Prescription review Lexicomp interaction checker ^a
Nursing home setting								
Hosia-Randell et al., 2008	Helsinki, Finland	Cross-sectional study	One day February 2003	Nursing home	1,987	83.7	81%	Chart review Swedish, Finnish, Interaction X-referencing (SFINX) interaction database
Liperoti et al., 2017	7 EU countries & Israel	Retrospective longitudinal cohort study	Two years 2009–2011 (follow up at 12 months)	Nursing home	604	82.9	72%	Subset of data from another study DDI classification proposed by Bleakley ^e
General hospital or mixed setting								
* Median age reported								

Study & Year	Location	Study design	Timeframe & Study Period	Setting	Sample size	Age years (Mean)	% Female	Data source & DDI screening tool used
Psychiatric Setting								
Nikolic et al., 2013	Serbia	Cross-sectional study	One month November 2011	Prescription database outpatient prescriptions	4467	62.8	58%	Prescription database Drug Interaction Facts by David S Tatro ^f
Sah et al., 2023	Southern India	Cross-sectional study	Three years January 2019 to December 2021	Tertiary care teaching hospital (patients with rheumatoid arthritis)	598	47.8	77%	Prescription review Micromedex interaction checker ^g
Sengul et al., 2014	Denizli, Turkey	Cross-sectional study	Not specified	Outpatient clinic for psychotic disorders & General hospital	240	38	41%	Prescription review Website Drugs.com interaction checker ^d
Sinclair et al., 2010	United Kingdom	Cross-sectional study	Three months December 2006 to February 2007	General hospital & psychiatric units (inpatients prescribed one or more psychotropic drugs)	253	Gen. hosp 69.9 Psych. 46.9	42%	Prescription review Computer based protocol identified DDIs
* Median age reported								

a: Lexicomp now known as Lexidrug UpToDate Inc. <https://online.lexi.com>.

b: Preston, C.L. Stockley's Drug Interactions. 2016.

c: Drug Facts & Comparisons 4.0 [online] Drug Comparison Tools | UpToDate Lexidrug | Wolters Kluwer

d: www.drugs.com/drug_interactions.html

e: Interactions classified by potential adverse effect in categories as proposed by Bleakley S.³¹

f: Tatro D. Drug Interaction Facts 10th Edition United States; Facts and Comparisons 2010

g: <https://www.micromedexsolutions.com>

3.3 Outcomes

Prevalence of DDIs with clozapine

All included studies reported data on drug-drug interactions involving clozapine. In twelve studies reporting both DDIs and clozapine-specific interactions as a percentage of total interactions, the proportion of DDIs involving clozapine ranged from 1% to 28%. The proportion varied by setting. Studies in psychiatric settings reported higher proportions ranging from 2.8% to 28%^{17,18,19,20,21,22,23,29}, while studies in general hospital or mixed settings reported lower proportions^{24,27,28,30} (1.2% to 3.2%). The lowest proportions were reported in nursing home populations^{25,26} (1% and 1.4%).

Rates of clozapine DDIs per 1,000 participants was estimated for thirteen studies^{17,18,20,21,22,23,24,25,26,27,28,29,30}. One study in a dedicated clozapine clinic reported the substantially higher rates (2,900 to 3,300 per 1,000 participants) reflecting differences in the study population¹⁷. Among the other twelve studies the rate of DDIs per 1,000 participants ranged from 0.5 to 303. Higher rates were reported in psychiatric settings^{17,18,20,21,22,23,29} (4.2 to 303 per 1,000 participants), while lower rates were reported in nursing home populations^{25,26} (0.5 and 6.6 per 1,000 participants). Studies conducted in general hospital or mixed populations had intermediate rates^{24,27,28,30} (18.3 to 63.2 per 1,000 participants). The results relating to prevalence of DDIs with clozapine are outlined in Table 2.

Table 2
Prevalence of DDIs with clozapine

Study	No. of participants	No. of DDIs Identified	Number of DDIs with Clozapine	Clozapine DDIs as a % of all DDIs	Rate of clozapine DDIs per 1000 participants	Setting & Scope of DDIs assessed
Psychiatric Setting						
Barrett et al. 2018	112	n/a ⁱ	325 ^a 370 ^b	n/a ⁱ	2,900-3,300 ^c	Outpatient clozapine clinic DDIs with clozapine
Collins et al. 2022	129	146	12	8.2%	93	Psychiatric clinic Psychotropic DDIs
Guo et al. 2012	27,909	14,213	2,769	19.4%	99	Prescriptions claims data (adults with a schizophrenia diagnosis and on at least one antipsychotic) Antipsychotic DDIs
Haueis et al. 2011	84,607	2,308 ^d	648 ^e	28% ^f	n/a ⁱ	Psychiatric hospital, All DDIs
Javelot et al. 2012	711	107	3	2.8%	4.2	Psychiatric hospital, All DDIs
Kirillochev et al, 2019	500	1352	73	5.4%	146	Psychiatric hospital, All DDIs
Toto et al, 2021	27,396	1738 ^h	171	n/a ⁱ	6.2	Psychiatric hospital Anticholinergic specific DDIs
Vedaprakash et al, 2023	606	1366	184	13.46%	303	Outpatient psychiatric clinic All DDIs
Nursing home setting						
Hosia-Randell et al. 2008	1987	96 ^g	1	1.04%	0.5	Nursing homes, All DDIs
Liperoti et al, 2017	604	278	4	1.4%	6.6	Nursing homes Antipsychotic DDIs
General hospital or mixed setting						
Nikolic et al, 2013	4467	2558	82	3.2%	18.35	Prescription database outpatient prescriptions, All DDIs
Sah et al, 2023	598	1492	19	1.2%	31.7	Tertiary care teaching hospital All DDIs
Sengul et al. 2014	240	417	21	5.03%	87.5	Psychiatric outpatient clinics & general hospital Psychotropic DDIs
Sinclair et al, 2010	253	380	16	4.2%	63.2	General hospital & Psychiatric Units Psychotropic DDIs

a & b: Study utilised two interaction references. a=Stockley's Drug Interaction checker b= Lexicomp drug interaction checker

c: Two interaction references used

d: Number of high danger DDIs from total number 270,660

e: Clozapine DDIs reported for high danger DDI category only

f: Percentage of high danger DDIs

g: Number of participants exposed to potential DDIs

h: Number of participants on combinations with anticholinergic potential:

i: Barrett et al only assessed for DDIs with clozapine therefore did not report an overall number of DDIs, Haueis et al reported the number of clozapine prescriptions in the study population, Toto et al reported the number of patients exposed to anticholinergic DDIs

DDI Severity Categorisation

Thirteen studies reported clozapine DDIs according to severity categories, although classification systems varied between studies^{17,19,20–30}. Four studies reported details of DDIs in only the most severe DDI rating category, and therefore all reported clozapine DDIs were in the most severe category^{19, 20, 22,26}. In the studies reporting multiple severity categories, 100% of clozapine DDIs appeared in the most severe category for three studies^{25,28,30}. Of the remaining studies four reported a majority of clozapine DDIs in the most severe category (38–81%)^{23,24,27,29}, one reported 41%²¹, while one reported 4–12% depending on the interaction checker used¹⁷.

The results relating to DDI severity categorisation are shown in Table 3

Table 3
DDI Severity Categorisation

Study	DDI Identification tool	Severity categories	Clozapine DDIs	Percentage of reported clozapine DDIs in each category	Clozapine DDIs as a percentage of all DDIs within each category
Barrett et al. 2018	Two Interaction checkers used Lexicomp (Lex.) & Stockley's (SIC) interaction checkers	1. Avoid Combination: Contra-Indicated(CI)/Life Threatening	Lex. 38 SIC 11	Lex. 12% SIC 4%	Lex. 12% SIC 4%
		2. Consider Therapy Modification/Dose Adjustment	Lex. 58 SIC 120	Lex. 18% SIC 43%	Lex. 18% SIC 43%
		3. Monitor Therapy	Lex. 226 SIC 146	Lex. 70% SIC 52%	Lex. 70% SIC 52%
Guo et al. 2012	Facts and comparisons 4.0 interaction classification	Major	2134	77%	15%
		Moderate	17	0.63%	0.10%
		Major or Moderate	618	22%	4.30%
Haeuis et al. 2011	DDI detection software ^a	MediQ high danger alerts	648	100%	28%
Hosia-Randell et al. 2008	(SFINX) interaction database ^b	Class D clinically significant, should be avoided	1	100%	0.10%
Javelot et al. 2012	Automated drug interaction detection ^c	Hazardous or contraindicated combination (HCDC)	3	100%	2.8%
Kirilochev et al, 2019	Website Drugs.com interaction checker		30	41%	19%
		Major			
		Moderate	43	59%	4%
Liperoti et al, 2017	Grouped by potential adverse effect of the interacting combination	Decreased BP & falls	0	0%	0%
		QT prolongation	0	0%	0%
		Sedation	4	100%	9%
		Inhibition of CYP450	0	0%	0%
		Anticholinergic effects	0	0%	0%
		Seizures	0	0%	0%
		Agranulocytosis	0	0%	0%
Nikolic et al, 2013	Drug Interaction Facts by David S Tatro	1 = clinically significant	82	100%	8.9%
		2 = clinically significant	0	0%	0%
Sah et al, 2023	Micromedex interaction checker	Contraindicated	19	100%	30.6%
		Moderate	0	0%	0%
		Minor	0	0%	0%
Sengul et al. 2014	Website Drugs.com interaction checker	QT prolongation, Major	8	38%	19%
		Bradycardia, hypotension, Major	7	33%	50%
		Drug level change, Moderate	6	28%	13%
Sinclair et al, 2010	DDI detection algorithm GeneMedRx ^d		13	81%	59%
		Major			
		Other Serious	3	19%	12%
Toto et al, 2021	Anticholinergic combinations	Potential clinical consequences of the combinations shown	171	100%	14%
Vedaprakash et al, 2023	Lexicomp interaction checker	Major	141	76%	89%
		Moderate	43	23%	4%
		Minor	0	0%	0%

- a: incorporating interface for mass analysis using the Clinical Decision Support Software (CDSS) MediQ and a multidimensional classification Zurich Interaction System (ZHIAS), incorporating the Operational Classification of Drug Interactions (ORCA).
- b: Swedish, Finnish, Interaction X-referencing (SFINX) interaction database.
- c: Automated drug interaction detection using the drug -drug interaction database of the French Agency for Medicinal Products
- d: Classified based on potential to change plasma drug concentratio

Interacting drugs

Thirteen studies reported the medications co-prescribed with clozapine that were associated with potential drug-drug interactions^{17,19,20–30}. Commonly prescribed psychiatric medications were identified most frequently. Six studies identified interactions with other antipsychotics^{17,19,21,24,27,29}, and anxiolytics/sedatives were also reported for six studies^{17, 24,26,27,28,29}. Four studies identified antidepressants^{17,19,23,24}, while antiseizure drugs were identified in four studies^{17, 20,23,25}, and three studies identified anticholinergics^{17,21,22}. Medications used to treat other health conditions, including antibiotics/antifungals, gastrointestinal agents, analgesics, anti-hyperglycaemic drugs and central nervous system agents used in the management of Parkinson's disease were identified in three studies^{17,23, 30}.

The results relating to co-prescribed interacting drugs are shown in Table 4

Table 4
Co-prescribed drugs identified as potentially interacting with clozapine

Study	Study Setting	Drug classes co-prescribed with clozapine identified in highest or second highest DDI severity category					
		Antidepressant	Antipsychotic	Anxiolytic & Sedative	Antiseizure	Anticholinergic	Antibiotic & Antifungal
Barrett et al. 2018	Psychiatric	Citalopram Fluoxetine Mirtazapine* SSRIs*	Amisulpride Chlorpromazine* Fluphenazine Flupenthixol Haloperidol* Olanzapine Quetiapine	Benzodiazepines* Zolpidem*	Carbamazepine Phenytoin	Inhaled antimuscarinic	Ciprofloxacin Macrolides [‡] Trimethoprim
Guo et al. 2012†	Psychiatric	Citalopram Fluoxetine Fluvoxamine Sertraline			Carbamazepine Phenytoin Phenobarbital		Ciprofloxacin
Haueis et al. 2011†	Psychiatric	Fluvoxamine	Olanzapine Pimozide				
Hosia-Randell et al. 2008†	NH			Benzodiazepines [#]			
Javelot et al. 2012†	Psychiatric				Carbamazepine		
Kirillochev et al, 2019	Psychiatric		Haloperidol			Trihexyphenidyl*	
Liperoti et al, 2017	NH				Carbamazepine		
Nikolic et al, 2013†	General			Benzodiazepines			
Sah et al, 2023	General						Fluconazole
Sengul et al. 2014	Psychiatric		Risperidone Quetiapine Haloperidol Aripiprazole Fluphenazine	Benzodiazepines			
Sinclair et al, 2010†	General & Psychiatric	Fluoxetine*	Haloperidol	Lorazepam			
Toto et al, 2021	Psychiatric					Pirenzepine [¶] Biperiden [¶]	
Vedaprakash et al, 2023	Psychiatric		Haloperidol Quetiapine	Clonazepam Tetra-hydropalmatine			

* Drug identified in second highest severity category for DDIs

† Study reported only DDIs in highest severity category or highest & second highest severity categories

¶ No severity categories shown as study identified combinations of anticholinergic drugs resulting in DDI

DDI combinations categorised by potential adverse effect of the interaction

4. Discussion

This systematic review demonstrates that DDIs involving clozapine are reported across a range of clinical settings, with considerable variation in reported prevalence. Among studies reporting total DDIs, the proportion ranged from 1.2% to 18.8%, and estimated rates ranged from 0.5 to 3,300 per 1,000 participants. This wide variation is likely due to differences in study populations, prescribing patterns, and methods used to identify and classify interactions rather than reflecting true differences in underlying risk. It also highlights the challenges of quantifying the burden of clozapine DDIs across healthcare systems and the lack of standardisation in approaches to DDI identification and classification^{32,33,34}.

The higher proportions of clozapine DDIs reported in psychiatric settings compared with general hospital, outpatient, and nursing home populations likely reflect greater clozapine use and higher levels of polypharmacy in these settings^{35,36,37}. Augmentation of clozapine with other antipsychotics or antidepressants is a recognised strategy in treatment refractory cases^{38–41}. However, DDIs involving clozapine were identified across all care settings, including in general medical and nursing home populations, meaning these interactions are not confined to specialist care. This finding is clinically important because patients prescribed clozapine frequently receive treatment for other conditions^{42,43,44} across multiple healthcare settings, meaning medications with potential to interact with clozapine may be initiated outside of specialist mental health services where awareness of clozapine-specific interaction risks may be lower^{45,46}.

Differences in clozapine prescribing, dispensing and monitoring protocols between countries may contribute to the variation in DDIs prevalence identified in this review^{47,48}. A recent study of global clozapine use demonstrated substantial variation in access to clozapine, prescribing practices, and mandatory blood monitoring requirements⁴. Although these systems are designed to support safe prescribing, they may inadvertently contribute to fragmentation of care. Fragmented systems are commonly identified as a barrier to effective mental healthcare delivery^{49–52}. In some countries clozapine prescribing and dispensing remains siloed, due to regulatory requirements and specialist supply arrangements⁵³, limiting opportunity for comprehensive medication list review and identification of DDIs. Even where shared care records are available, the accuracy of the information relating to clozapine within such records may be suboptimal⁵⁴. An audit of National Health Service Summary Care Records (SCR) in the United Kingdom identified deficiencies in recording of clozapine prescriptions on patient SCRs, with clozapine documented in only 58% of records in 2019 and 72% of cases in 2021⁵⁵. Incomplete recording of clozapine treatment may increase the risk that interacting medications are prescribed without full awareness of existing treatment.

The findings of this review may become increasingly relevant as efforts continue internationally to improve access to clozapine and address its longstanding underutilisation. Despite being recognised as the most effective treatment for treatment-resistant schizophrenia^{1,56}, clozapine remains substantially underprescribed in many countries^{57–61}. Recent changes to clozapine monitoring requirements, including extension of mandatory haematological monitoring intervals for stable patients in some jurisdictions, are intended to reduce treatment burden and facilitate wider use of clozapine^{62,63}. While these developments may improve access to treatment, they may also reduce the frequency of contact with specialist clozapine services. Although the evidence supports less fragmented care and recommendations for dedicated multidisciplinary clozapine services as strategies to increase clozapine use and improve clozapine services^{12,64,65}, the impact of reduced monitoring may result in a greater proportion of routine contact occurring in primary care, community pharmacy, and general medical settings. In the context of the findings of this review, this increases the importance of ensuring healthcare professionals outside specialist mental health services are aware of clinically significant clozapine interactions and have access to accurate and complete medication records.

The interacting medications identified in this review reflect the complex clinical needs of patients prescribed clozapine^{66,67}. Potential DDIs involved both psychiatric medications, including other antipsychotics, antidepressants and benzodiazepines, and medicines used to manage other health conditions, including antibiotics, analgesics and gastrointestinal agents. This pattern is consistent with the high burden of psychiatric and other co-morbidities reported in people with serious mental illness and highlights the need for comprehensive medication review across all healthcare settings^{68,69}.

The review identified interacting psychiatric drug classes that are commonly co-prescribed with clozapine in routine clinical practice. Other antipsychotics may be used as augmentation strategies, especially in treatment-refractory cases^{70,71}, while antidepressants and benzodiazepines are frequently used to manage coexisting symptoms and comorbid conditions^{72,73,74}. Many of the non-psychiatric medications may be initiated by clinicians outside specialist mental health services, including several prescribed for short duration. The identification of antibiotics, analgesics, and non-prescription gastrointestinal medications such as domperidone as interacting drugs reinforces the finding that clinically important clozapine DDIs are not limited to specialist psychiatric care. These findings highlight the importance of routine DDI screening even for medication combinations that are familiar and commonly prescribed, as appropriate management may require dose adjustment, increased monitoring, patient counselling, or selection of alternative therapies^{75,76,77}. This further emphasises the importance of awareness of clozapine DDIs among community pharmacists and patients as well as prescribers.

Our review demonstrates that co-prescription of clozapine with other medications can result in DDIs with varying degrees of severity and clinical significance. Despite variation in classification frameworks, clozapine DDIs were consistently identified within the top two highest risk categories across studies^{17,19,20–30}. In the studies showing the potential clinical outcome of these highest risk categories serious adverse effects such as bradycardia²⁷, QT prolongation^{17,27} and delirium and death²⁴ were reported for clozapine DDIs. The consistent identification of clozapine DDIs within higher-risk categories highlights the importance of recognising and appropriately managing these interactions in clinical practice.

The variety of DDI screening tools used and variability in DDI severity classification across the included studies is a limitation of the review. Similar challenges have been reported in other DDI studies, where lack of standardised classification systems and the wide range of available screening tools and approaches limit comparison between studies⁷⁸. The disparity in risk classification tools used also affects interpretation as the same medication combination may be assigned different levels of severity depending on the screening tool^{79,80,81}. This was illustrated in one study included in this review

where two different DDI checkers applied to the same medication lists produced different results¹⁷. Such variation may contribute to both over- and under-identification of DDIs in research and clinical practice.

Although all studies did report DDIs involving clozapine, identification of DDIs was not the primary outcome in all studies. Therefore, reporting was not always comprehensive, with some presenting detailed results for only selected severity categories, particularly higher-risk interactions. This may have resulted in underestimation of the total number of DDIs involving clozapine. In addition, the population denominator was not consistently reported across studies. Some reported the number of participants prescribed clozapine, while others report numbers of prescriptions, and others identified clozapine DDIs from claims or prescribing datasets. This limited direct comparison of prevalence estimates between studies and restricted the ability to determine the exact prevalence of DDIs among people prescribed clozapine. Notwithstanding these limitations, to our knowledge, the review provides the first synthesis of the prevalence of DDIs involving clozapine across a range of healthcare settings and highlights clinically important considerations for the safe management of patients prescribed clozapine.

5. Conclusion

This review demonstrates that DDIs involving clozapine are reported across a range of healthcare settings and that many are classified within higher-risk categories. The findings highlight that clinically significant clozapine DDIs are not confined to specialist mental health services and may arise wherever patients receive treatment for coexisting physical or mental health conditions.

Fragmented models of care and limitations in access to complete medication records may reduce opportunities to identify and manage DDIs effectively. As efforts continue internationally to improve access to clozapine and reduce barriers to treatment, robust systems for medication reconciliation, DDI screening, and communication across healthcare settings will become increasingly important.

Further research is needed to better characterise the prevalence and clinical impact of DDIs among people prescribed clozapine and to identify strategies that support safer prescribing and monitoring practices.

Declarations

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LF: Conceptualization, Data curation, Formal analysis, Investigation, Methodology, Project administration, Validation, Visualization, Writing – original draft.

GH: Data curation, Investigation, Methodology, Validation, Writing – review & editing.

MF: Conceptualization, Methodology, Supervision, Writing – review & editing.

FM: Conceptualization, Data curation, Formal analysis, Methodology, Supervision, Validation, Writing – review & editing.

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Figures

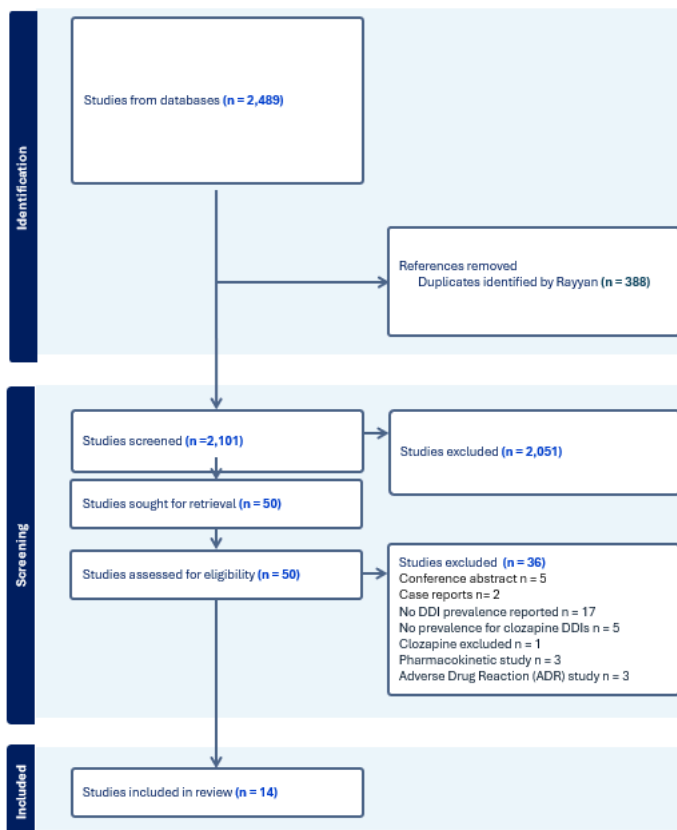


Figure 1

PRISMA Flow Diagram

Supplementary Files

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- [TableS1Searchstrategybydatabase.docx](#)
- [TableS2Excludedstudies.docx](#)
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