THERAPEUTIC ADVANCES in
Drug Safety

Original Research

Alert prescribing of clozapine: a comparison of five drug–drug interaction sources

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Ther Adv Drug Saf

2024, Vol. 15: 1–9

DOI: 10.1177/20420986241233842

Abstract

Introduction: Clozapine, an antipsychotic used in the treatment of schizophrenia, is known for its serious side effects. In order to promote patient safety, drug–drug interaction (DDI) databases can be consulted by clinicians. In this study, the degree of consensus between five sources on DDIs with clozapine is determined.

Methods: The summary of product characteristics of clozapine, Delphicare interaction database, Stockley's interaction checker, the Lexicomp interaction database, and the interaction database of Clinical Pharmacology are included. By comparing the original categories assigned to interactions with clozapine by the included DDI sources, a degree of consensus between sources is determined. Furthermore, based on the combined information, an evaluation on the severity of each potential interaction is made.

Results: One hundred eighty-three potential DDIs with clozapine are retrieved from the five included sources. A consensus between sources is found in 47.5% ($n = 87$) of DDIs.

Conclusion: This study shows major discrepancies between five different sources on DDIs with clozapine. The potential impact of the use of one specific database on patient safety and prescribing behavior could prove to be problematic.

Plain language summary

A comparison of five sources on drug–drug interactions with clozapine: emphasizing the discrepancies between sources and determining the degree of severity of potential drug–drug interactions

Clozapine is an antipsychotic agent advised to be used in the treatment of schizophrenia after two failed adequate treatments with other antipsychotics. A reluctance towards prescribing clozapine is described in literature, mainly because of its potential life threatening side effects. In assuring patient safety, evaluating potential interactions with other drugs are a key aspect in the risk assessment of clozapine. Drug–drug interaction (DDI) databases are developed to assist clinicians in this assessment.

In this study we compare five sources on DDI with clozapine. Major discrepancies are found between sources with a consensus found in less than half of all included DDIs.

It is hypothesized that these discrepancies can contribute to excessive caution or to negligence in prescribing clozapine. The impact of relying one specific database in the risk assessment of DDIs with clozapine could thus prove to be potentially problematic.

Based on the comparison of the included sources, a conclusion was made on the severity of each unique potential DDI with clozapine. The results are shown in the appendix of supplementary materials.

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Keywords: clozapine, drug–drug interactions, interaction databases

Received: 14 November 2023; revised manuscript accepted: 4 February 2024.

Introduction

Clozapine is an atypical antipsychotic agent and the treatment of choice in refractory schizophrenia.[1–3] Practical guidelines suggest its use after two failed adequate trials with other antipsychotic agents in patients suffering from schizophrenia.[4,5] At this moment, there are no alternative treatments available with a comparable efficacy in treatment resistant schizophrenia.[6–8] Clozapine is known for its greater tolerability and lower intrinsic risk of extrapyramidal side effects as compared to other antipsychotic agents.[9] However, it is also known to be underused out of fear for other adverse drug reactions (ADRs), some of which are life-threatening.[4,6] Among these serious ADRs associated with clozapine are agranulocytosis and myocarditis. The risk of agranulocytosis can be managed by WBC counts and absolute neutrophil counts in monthly blood tests.[10,11] Myocarditis can be prevented by slow titration of clozapine.[12] Despite the existence of these safety measures it is described that fear of ADR keeps clinicians from prescribing clozapine to those most in need of an effective antipsychotic agent and literature even suggests the existence of 'clozaphobia'.[4,12,13] To counter this, a rational use of clozapine is promoted based on knowledge about pharmacokinetics, therapeutic drug monitoring, and slow titration.[12]

To obtain rational use of clozapine, drug–drug interactions (DDIs) should be taken into account. DDIs can influence the therapeutic efficacy and ADR of clozapine. DDIs involving pharmacokinetics can cause fluctuations in plasma levels of clozapine. Clozapine depends on the cytochrome P450 (CYP) enzymes for its metabolism. More specifically, CYP1A2, CYP2D6, and CYP3A4 are among the enzymes known to be involved in the metabolism of clozapine.[14,15] CYP inducing or inhibiting drugs can alter clozapine plasma levels when combined with clozapine.[16,17] Alternatively, DDIs with clozapine can occur on a pharmacodynamic level. An example of an additive interaction is the combination of bupropion, a norepinephrine–dopamine reuptake inhibitor, with clozapine. The combination is stated to lower the threshold for seizures.[18] Thus, a clinician should be alert to potential DDIs when combining clozapine with other drugs.

In order to support clinicians in everyday practice with the risk assessment of combining drugs with clozapine, various DDI databases can be consulted. Moreover, DDI databases are often implemented in a hospitals computerized physician order entry (CPOE) as a clinical decision support system to generate alerts when potentially harmful combinations are prescribed. Although designed to assist a clinician or pharmacist in the evaluation of the safety of a drug combination, DDI databases tend to over-alert clinicians.[19]

Because of the reluctant attitude toward prescribing clozapine due to potential life-threatening ADR, solid information on potential DDI is vital to support cautious prescribing of clozapine in the vulnerable population suffering from treatment resistant schizophrenia. Over-alerting clinicians could however contribute to 'clozaphobia' and lead to poorer outcomes for patients. In our study, we compare the categorization systems of five DDI sources and investigate the degree of consensus between the sources on DDIs with clozapine. Furthermore, an evaluation of the severity of each included DDI with clozapine is made based on information of all sources. In this way, we aim to investigate the potential impact of different sources on risk assessment and contribute to alert prescribing of clozapine.

Methods

Data sources: Five DDI sources of which four subscription DDI databases and the summary of product characteristics (SmPC) of clozapine[20] are investigated. Databases were chosen because of their common use in hospital software in Belgium. Included DDI databases are the Belgian Pharmaceutical Association (APB) Delphicare interaction database,[21] Stockley's interaction checker by the British Royal Pharmaceutical Society,[22] the Lexicomp interaction database owned by Wolters Kluwer,[23] and the interaction

database of Clinical Pharmacology owned by Elsevier.[24] The extensive list of potential DDIs with clozapine is composed by adding all potential DDIs stated by at least one of the included databases.

Data extraction: Drugs involved in the included DDIs with clozapine are sorted by Anatomic Therapeutic Classification code. Drug class and generic molecules, the DDI mechanism, and potential health risk are added. For each drug, the assigned severity category of each DDI source is added. Definitions of the categories presented by the different sources are shown in Table 1.

Assignment of color labels: To be able to compare the five sources with different categorizing systems for potential DDIs, a color label is assigned to each category of the original DDI source (Table 1). A red label is assigned when the definition of the category resulted in a contraindication. A green label is assigned when the category mentions that the interaction is potentially safe or no action is needed. Every possible category in between is assigned an orange label.

Determining consensus between sources

Potential DDIs with information from only one source are not assessed. Information from at least two out of five sources on potential DDI is needed in order to decide on a consensus. Considering each unique DDI, a consensus is concluded when the respective categories of each of the original sources are all assigned the same color label (Table 2).

Evaluation of the severity of the DDI

An evaluation on the severity of each unique DDI is made by comparing the respective color categories from the included sources in the excel file, by two separate researchers (Table 3). Sources without information on a DDI are excluded from the evaluation. When at least half of the sources categorize the DDI as a contraindication (red label), the DDI is evaluated as 'contraindicated' and a red label is assigned in conclusion. When all sources categorize the DDI as safe, the DDI is evaluated as 'safe' and a green label is assigned in conclusion. When at least one source categorizes the DDI as a potential harmful interaction, the DDI is evaluated as 'caution needed' and an orange label is assigned in conclusion.

The initial analysis is performed by a pharmacist (VA) and repeated by a psychiatrist (DHM) in order to reach consensus.

Results

A total of 183 potential DDIs with clozapine are retrieved from five DDI sources. 27.3% ($n=50$) of DDIs are only reported by one ($n=17$) or two ($n=33$) sources (Table 4). The APB Delphicare interaction database ($n=99$) and the database of Clinical Pharmacology ($n=108$) report the lowest number of DDIs. The SmPC ($n=147$) and the Lexicomp interaction database ($n=145$) report the highest number of DDIs.

Determining consensus between sources

In 9.3% ($n=17$) of the included DDIs consensus is not determined because there is information from only one source (Table 5). A consensus between the five included sources on DDI is found in 47.5% ($n=87$) of all included DDIs. In 43.2% ($n=79$) of all included DDIs, no consensus is found. Table 6 illustrates the prevalence of the different combinations of categories from the original sources when there is no consensus found.

Discrepancies in DDI categorization between sources are found. The SmPC of clozapine states that 31.3% ($n=46$) of the 147 potential DDIs mentioned are contraindicated. In the APB Delphicare interaction database, Stockley's interaction checker, the Lexicomp interaction database, and the database of Clinical Pharmacology, this is respectively 56.7% ($n=55$), 3.8% ($n=5$), 11.0% ($n=16$), and 3.7% ($n=4$) of potential DDIs with clozapine.

Evaluation of the severity of the DDI

Of all DDIs, 11.5% ($n=21$) are evaluated as contraindicated after the assessment of the five sources on each unique DDI. About 0.5% ($n=1$) of DDIs are assessed as safe, indicating that all five sources consider the potential DDI as safe or have no information about the interaction. The remaining 88.0% ($n=161$) of DDIs are labeled orange in conclusion, indicating that caution is needed. These results are shown in the Appendix of Supplemental Materials.

Table 1. Color labels assigned to the different interaction severity levels of the five original sources.

Delphicare	Grade 1	Severe consequences likely – contraindication
	Grade 2	Severe consequences likely – contraindicated in some cases
	Grade 3	Severe consequences possible – contraindicated out of precaution
	Grade 4	Concomitant use not recommended
	Grade 5	Monitoring and/or changes required
	Grade 6	Monitoring and/or changes required in some cases
	Grade 7	Monitoring and/or changes required out of precaution
	Grade 8	No action required
Stockley	A life-threatening or contraindicated combination	
	Dosage adjustment or close monitoring is needed	
	Give guidance about possible adverse effects and/or consider some monitoring	
	No interaction, or no interaction of clinical significance	
Lexicomp	X	Avoid combination
	D	Consider therapy modification
	C	Monitor therapy
	B	No action needed
	A	No known interaction
Clinical Pharmacology	Level 1: Severe	Contraindicated. Rare exceptions may exist
	Level 2: Major	Combination may be contraindicated in a select group of patients. Further therapy and/or an alteration in therapy may be necessary. The patient should be monitored for possible manifestations of the interaction
	Level 3: Moderate	The use of these medications together may result in unintended clinical effects. Depending on the clinical situation, alterations in therapy may be required. The patient should be monitored for possible manifestations of the interaction
	Level 4: Minor	The use of these medications together does not usually result in clinically significant interactions. Alterations in therapy or monitoring are not usually required
SmPC	Contraindication	
	Monitor/use with caution	

SmPC, summary of product characteristics.

Discussion

This study compares categorization systems of different DDI sources and investigates the degree of consensus on the severity of potential DDIs with clozapine. Five well-known sources are included; the SmPC of clozapine, the Delphicare interaction database, Stockley's interaction checker, the Lexicomp interaction database, and

Table 2. Determination of consensus.

Psychopharmaca	SmPC	Delphicare	Stockley	Uptodate	Clinical Pharmacology	
Anticholinergics		5		C	Moderate	Consensus
Olanzapine		3		C	Major	No consensus

In the example of anticholinergics, categories assigned by the different sources on DDI were all assigned the same color label; thus, consensus was concluded. In the example of olanzapine, the respective categories were not assigned the same color label; thus, no consensus was concluded.
SmPC, summary of product characteristics.

the interaction database of Clinical Pharmacology. These sources provide a categorizing system of potential DDIs to support a clinician in the decision making process. Furthermore DDI databases are often implemented in hospital CPOE to alert clinicians in case of a potential DDI.

Because of the potential life-threatening ADR of clozapine,[11] solid data on potential DDIs is essential to ensure patient safety. This information is needed to help clinicians avoid contraindicated combinations or monitor drug combinations with a potentially harmful DDI. At the same time, it is hypothesized that over-alerting as a cause of a DDI categorization system can result in the clinician avoiding a drug. Because of the 'clozaphobia' described in recent literature this may especially be a problem when it comes to clozapine treatment.[12] This could prove problematic for the highly vulnerable population of patients suffering from treatment resistant schizophrenia. It is argued that the delicate pharmacological consideration asks for consistent information on DDIs. In what follows we investigate consistency of DDI sources by evaluating the degree of agreement between different sources on DDI with clozapine.

Determining consensus between sources

A first important indication of the discrepancies between sources is that more than a quarter of the included DDIs ($n=183$) are reported by only one or two sources. There are major differences in the number of DDIs reported between sources with only 27.3% ($n=50$) of included DDIs reported by all sources. This finding already emphasizes the potential impact of the choice of a DDI database on prescribing behavior.

These discrepancies are confirmed by the comparison of categories of the five included DDI sources. A consensus is found in only 47.5% ($n=87$) of all included DDIs with clozapine ($n=183$). This finding is in line with recent literature on the reliability of DDI databases and underlines the poor agreement between these sources.[25] More specifically, our study shows poor agreement between sources on the assignment of contraindicated combinations. About 56.7% ($n=55$) of all included DDIs are considered contraindicated by the APB Delphicare interaction database as opposed to 3.7% ($n=4$)

Table 3. Determination of the level of severity of each DDI based on information from five sources on DDI.

Level of severity	Concluded when. . .
Contraindicated	⩾50% sources mentioned contraindication
Caution needed	At least one source mentioned a possible harmful interaction
Safe	All sources reported interaction as safe/no action needed

DDI, drug–drug interaction.

Table 4. The number of sources (of the five included sources on DDI) that reported on a potential DDI (of the 183 DDI included).

Number of sources	Number of DDI mentioned (% of total DDI included)
1	17 (9.3)
2	33 (18.0)
3	37 (20.2)
4	46 (25.2)
5	50 (27.3)

For instance, in 17 DDI there was information from only one source.
DDI, drug–drug interaction.

Table 5. Prevalence of consensus on the level of severity of an interaction between the included sources on DDI.

Level of consensus	Proportion of DDI on a total of $n = 183$, n (%)
No determination of consensus	17 (9.3)
Consensus	87 (47.5)
Based on 2 sources	29 (15.8)
Based on 3 sources	22 (12.0)
Based on 4 sources	23 (12.6)
Based on 5 sources	13 (7.1)
No consensus	79 (43.2)

Information of at least two sources was needed in order to determine consensus.
DDI, drug–drug interaction.

by the database of Clinical Pharmacology. Although mechanisms of interaction with clozapine are complex and can involve pharmacokinetic interactions, pharmacodynamics interactions, and individual pharmacogenetics and require an individual expert risk assessment, these discrepancies between specific DDI sources could result in excessive caution or on the other hand ignorance when it comes to prescribing clozapine. Especially, the significant differences in the allocation of contraindicated combinations are alarming. It is hypothesized that the existence of major discrepancies between DDI sources could contribute to the reluctant prescribing behavior regarding clozapine.

Evaluation of the severity of the DDI

In recent literature, clinicians are advised to consult more than one source or database on DDI when assessing the risk of a drug–drug combination.[25] In our study, two researchers separately evaluate each unique potential DDI with clozapine based on the assigned categories from the five included sources. A conclusion on the risk of each potential DDI is made and labeled as 'contraindicated', 'caution needed' or 'safe' (see Appendix of Supplemental Materials). In conclusion, 11.5% ($n = 21$) of all included DDIs are evaluated as 'contraindicated' and 88.0% ($n = 161$) as 'caution needed'. It can be hypothesized that this combined information of different sources could help clinicians to safely prescribe drug combinations with clozapine although further knowledge on the potential interaction mechanisms and clinical expertise is needed to monitor the potential ADR. In order to increase the clinical relevance of the concluded label, a short clinical advice on clinical monitoring is added based on information retrieved from the sources.[26]

Our findings underline the impact of the choice of a DDI database on the evaluation of a drug combination with clozapine or on the hospital CPOE alert system. It is clear that the SmPC and the APB Delphicare interaction database are more conservative in the categorization of a potential DDI with clozapine. This contributes to a poor degree of consensus between sources. The lacking consistency of DDI databases and poor agreement among DDI databases on DDI with clozapine is in line with recent findings on the matter.[25,27]

It is hypothesized that reasons for these discrepancies lie in the lack of solid evidence on DDI with clozapine. Most literature on DDIs with clozapine addresses pharmacokinetic interactions through the CYP enzyme metabolism. Some drugs, such as fluoroquinolones,[15,28] fluvoxamine,[29] and omeprazole,[30] have extensive literature on their CYP inducing/inhibiting properties. Some DDI result in conflicting findings, such as mirtazapine[31] and valproate[32] or in mere case

Table 6. Prevalence of the combination of different levels of severity assigned to a DDI where no consensus was concluded.

Lowest level of severity	Highest level of severity	Prevalence n (%)
No interaction (green)	Contra-indication (red)	4 (5.1%)
No interaction (green)	Moderate–major (orange)	16 (20.2%)
Moderate–major (orange)	Contra-indication (red)	59 (74.7%)

DDI, drug–drug interaction.

reports such as olanzapine[33] and flupentixol.[34] Interestingly, literature on potential pharmacodynamical interactions of clozapine with drugs such as benzodiazepines is scarce. Moreover, recent research shows none of the potential psychotropic DDIs with clozapine are supported by primary studies containing a combined sample size of more than 100 patients.[35] Although these combinations are common in psychiatric care, supporting evidence is lacking and is predominantly based on case reports.

Strengths and limitations

This study is the first to compare five different sources on DDIs with clozapine. The inclusion of five international sources can be considered as a strength. A total of 183 DDIs are included; however, this list may not be exhaustive. Furthermore, some databases render no detailed information on certain interactions. This affects the assessment of some DDIs and may lead to an overestimation of the risk of certain DDI with clozapine.

Conclusion

Clozapine is important in the management of treatment resistant schizophrenia though it is known to be under prescribed due to its potential harmful ADR. DDIs can have an important impact on the efficacy as well as the ADR of clozapine. Physicians across specialties and pharmacists can rely on DDI databases for information on a potential DDI with clozapine. Moreover, these databases are often implemented in the CPOE software in hospitals to warn clinicians when potentially harmful combinations are prescribed.

Our study shows major discrepancies between five different sources on DDI with clozapine. There are large differences in the number of reported interactions by DDI sources. Furthermore, researchers find a poor agreement between sources, with a consensus in less than half of all included DDIs. The impact of relying one specific database in the risk assessment of DDIs with clozapine proves to be potentially problematic.

Furthermore, substantial evidence on potential DDIs with clozapine is lacking. Although primary literature on DDIs with clozapine is much needed, our comparison of different sources on DDI may help clinicians in evaluating the safety of specific drug combinations and managing further monitoring of a potential DDI with clozapine.

Declarations

Ethics approval and consent to participate

Ethical approval was not sought for the present study because the study does not contain or refer to patient data and does not contain any studies with human or animal subjects.

Consent for publication

No personal details were used for this manuscript, so no declaration of consent is needed.

Author contributions

Jeroen Govaerts: Conceptualization; Investigation; Methodology; Writing – original draft; Writing – review & editing.

Annelies Verluyten: Data curation; Formal analysis; Writing – original draft.

Filip Bouckaert: Supervision; Validation.

Marc A. F. De Hert: Formal analysis; Supervision; Validation.

Franciska A. M. Desplenter: Data curation; Supervision; Validation.

Acknowledgements

None.

Funding

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

Competing interests

The authors declare that there is no conflict of interest.

Availability of data and materials

Not applicable.

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Supplemental material

Supplemental material for this article is available online.

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