

Original Research Article

Drug-drug interactions in patients with schizophrenia and depression in outpatients at PKU Muhammadiyah Gamping Hospital, Yogyakarta, Indonesia

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Abstract

Purpose: To identify possible drug-drug interactions in patients with schizophrenia and depression in the Outpatient Department at PKU Muhammadiyah Gamping Hospital. Additionally, the relationships between patient characteristics and drug interactions were investigated.

Methods: A descriptive observational design and a longitudinal approach were used. The study which was conducted at PKU Muhammadiyah Gamping Hospital for one year, was based on medical records of patients and interviews. Consecutive sampling was utilized to generate a sample size of 81 patients with schizophrenia and depression who met the inclusion criteria. The data were evaluated by examining the occurrence of drug-drug interactions and by performing a bivariate chi-square statistical test to determine the relationship between patient characteristics and actual drug-drug interactions.

Results: This study identified 93 cases of drug interactions, 63.44 % of which occurred pharmacodynamically, while 36.56 % occurred pharmacokinetically. The intensity of drug interactions was categorized as major (31.18 %), moderate (63.44 %), and minor (5.38 %). The 93 drug interactions encompassed precisely seven actual types of interaction. Bivariate chi-square analysis revealed that gender was a major factor associated with actual drug interactions.

Conclusion: There were 93 drug-drug interactions, with gender being an influencing factor.

Keywords: Drug-drug interactions, Schizophrenia, Depression, Drug combination

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INTRODUCTION

The 2023 data from *Survei Kesehatan Indonesia* (SKI), i.e., Indonesia Health Survey, highlight the relatively high prevalence of mental disorders in Indonesia. The national average indicates that in Indonesia, 4 out of 1,000 households have mental disorders. This implies that out of every 1,000 households, approximately 4 households have at least one family member experiencing a

mental disorder. In Indonesia, Yogyakarta has the most significant prevalence of mental disorders, with a rate of 9.3 ‰ (per mille). In contrast, the province of South Papua has the lowest incidence at 1.0 ‰ [1].

There are various forms of mental disorders, including schizophrenia and depression. Typically, people suffering from schizophrenia and depression are treated with

antipsychotics and antidepressants, either alone or in combination. The antipsychotics frequently used in Indonesia are typical first-generation antipsychotics such as haloperidol, chlorpromazine, and fluphenazine, and atypical second-generation antipsychotics such as risperidone, olanzapine, and quetiapine. The commonly used antidepressants are SSRIs/SNRIs such as fluoxetine, sertraline, escitalopram, and tricyclics/tetracyclics, e.g., amitriptyline.

Empirical studies have demonstrated that when people with schizophrenia do not respond to a single antipsychotic medication, combined administration of antipsychotics and additional antidepressants effectively ameliorates the negative symptoms and affective disorders associated with schizophrenia without exacerbating extra-pyramidal side effects [2]. Therapy is usually achieved by the administration of not just a single drug but rather a combination of two or more drugs. This prescription practice which involves combinations of numerous drugs is referred to as polypharmacy or multiple-drug therapy. The simultaneous use of five or more drugs daily also constitutes polypharmacy. Adverse drug reactions (ADRs) and drug-drug interactions (DDIs) occur more frequently as a result of combination of prescription drugs and over-the-counter (OTC) drugs, and it may increase the risk of hospitalization and death [3].

Drug interactions influence the pharmacological effects associated with taking one medication alongside another. Drug interactions produce detrimental effects through various mechanisms such as diminishing the effectiveness of drugs, intensifying the effects of drugs to potentially dangerous levels, and causing severe reactions. Antipsychotics and antidepressants which are usually prescribed for mental disorders such as depression, schizophrenia and anxiety, have been reported to exert hepatotoxic effects [4]. Several studies have established that antidepressants have the potential to exacerbate extra-pyramidal motor disorders. For instance, selective serotonin reuptake inhibitors (SSRIs) and tricyclic anti-depressants (TCAs) are linked to the risk of extra-pyramidal symptoms (EPS). One of these drugs, i.e., Amitriptyline, has been associated with the risk of bradykinesia. The exact mechanism underlying SSRI-induced EPS is not fully understood, although it is thought to be related to the interaction between serotonin and dopamine pathways in the brain. It has been demonstrated that anti-depressants induce bradykinesia and catalepsy in a dose-dependent manner [5].

The present study on drug interactions in outpatients with schizophrenia and depression was undertaken at PKU Muhammadiyah Gamping Hospital, from January to December 2023, in view of the detrimental effect of the drug combination on treatment outcomes.

METHODS

Research design

This study employed a descriptive observational design utilizing consecutive sampling and a longitudinal approach. The study was undertaken in 2023 by collecting data from medical records of patients diagnosed with schizophrenia and depression in the Outpatient Department of PKU Muhammadiyah Gamping Hospital, Yogyakarta, Indonesia. Furthermore, patients were interviewed in order to obtain information regarding any side effects or adverse reactions experienced following medication use.

Assessment of subjects

Inclusion criteria

Patients in the following categories were included in the study: (a) patients diagnosed with schizophrenia and depression, (b) subjects who underwent outpatient care for one year, and (c) patients who received two or more types of medications.

Exclusion criteria

Patients with incomplete medical record data and patients who did not receive pharmacological treatment were excluded from the study. Moreover, patients who received only one type of medication were not included.

Following the application of these criteria, 81 patients were found eligible and were included in the final analyses. Qualitative data consisted of findings from investigations on drug interaction mechanism using a literature-based search. The keywords used in the literature search were: potential drug-drug interactions, antipsychotics, antidepressants, schizophrenic patients, and depression patients. In contrast, quantitative data were presented as percentages of drug-drug interaction results among several study subjects. A bivariate chi-square analysis was performed to determine the relationship between patient characteristics and the occurrence of drug-drug interactions. The assessment/identification of the intensity of drug-drug interactions was based on *Drug Interaction*

Facts, Stockley's Drug Interactions, and Drugs.com.

Ethical approval

This study was approved by the Ethics Committee of PKU Muhammadiyah Gamping Hospital (approval no. 026/KEP-PKU/II/2023).

Data analysis

Data presented were primarily processed as percentages representing the frequency of each characteristic analyzed. The pharmacodynamic analysis was based on the mechanism of action (synergistic or antagonistic). Pharmacokinetic analysis was focused on the stage of interaction (absorption, distribution, metabolism, or excretion). All data presented in this study are intended to identify the most dominant variables.

RESULTS

The study conducted in the Outpatient Department of PKU Muhammadiyah Gamping Hospital, Yogyakarta, Indonesia, utilized patient medical record data to identify 81 eligible patients. Among these, 54 patients were diagnosed with schizophrenia, while 27 subjects were diagnosed with depression, as indicated in Table 1.

Figure 1 shows that potential drug-drug interactions occurred in 60 (74.07 %) out of the 81 patients who satisfied the inclusion criteria. In contrast, actual drug-drug interactions were determined based on adverse drug effects that

occurred in the patients. Potential drug interactions refer to adverse effects identified through literature review; these drug interactions were not observed in the patients, but there was a possibility of their occurring/taking place in 21 (25.93 %) of them. The actual drug-drug interactions in patients were determined based on interview data.

The investigation identified 93 drug-drug interactions which were subsequently examined in terms of severity and mechanism. These drug-drug interactions were evaluated in terms of pharmacodynamic and pharmacokinetic mechanisms of action. As shown in Figure 2, the predominant mechanism of interaction was pharmacodynamic which accounted for 63.44 %, while pharmacokinetic interaction accounted for 36.56 %.

With respect to the mechanism of action, pharmacodynamic interactions may occur synergistically, antagonistically, or additively. In this study, synergistic interactions (81.36 %) were the most common pharmacodynamic interactions, while antagonistic interactions and additive interactions accounted for 8.33 and 14.58 %, respectively. These data are shown in Figure 3.

The same pattern was observed in pharmacokinetic interactions where the interactive effects usually occur during the stage of absorption, distribution, metabolism or excretion. In this study, it was found that the most common pharmacokinetic interactions occurred at the metabolism stage (88.24 %).

Table 1: Characteristics of the patients

Characteristic	Total; n (%)	Patients with schizophrenia; n (%)	Patients with depression; n (%)
Total number of patients	81(100)	54 (66.67)	27 (33.33)
Gender			
Male	41 (50.62)	31 (57.41)	10 (37.04)
Female	40 (49.38)	23 (42.59)	17 (62.96)
Age (years)			
18-25	23 (28.40)	7 (12.96)	16 (59.26)
26-35	18 (22.22)	15 (27.78)	3 (11.11)
35-45	14 (17.28)	9 (16.67)	5 (18.52)
>45	26 (32.10)	23 (42.59)	3 (11.11)
Treatment duration (years)			
0 – 3	59 (72.84)	41 (75.93)	18 (66.67)
3.1 – 6	22 (27.16)	13 (24.07)	9 (33.33)
Comorbidity			
Present	4 (4.94)	3 (5.56)	1 (3.70)
Absent	77 (95.06)	51 (94.44)	26 (96.30)
Number of drugs received			
2-3	32 (39.51)	22 (40.74)	10 (37.04)
>3	49 (60.49)	32 (59.26)	17 (62.96)

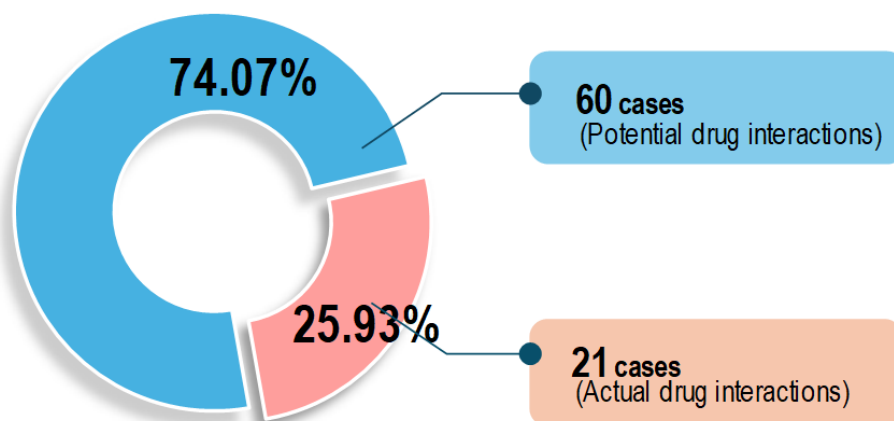


Figure 1: Percentages of drug-drug interactions in patients with schizophrenia and depression

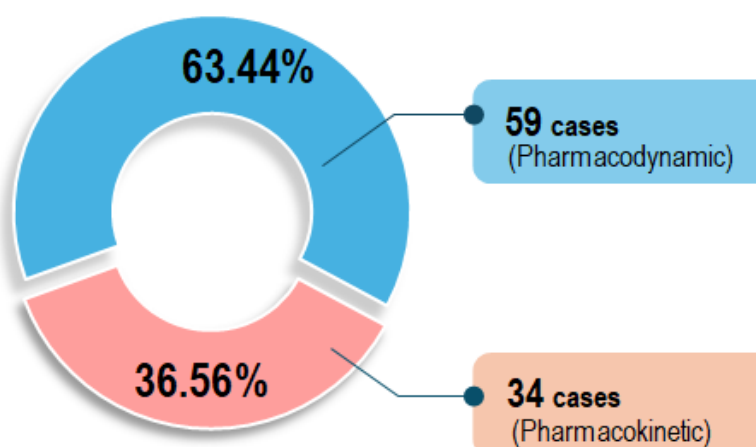


Figure 1: Percentage occurrence of drug-drug interactions based on the mechanism of action

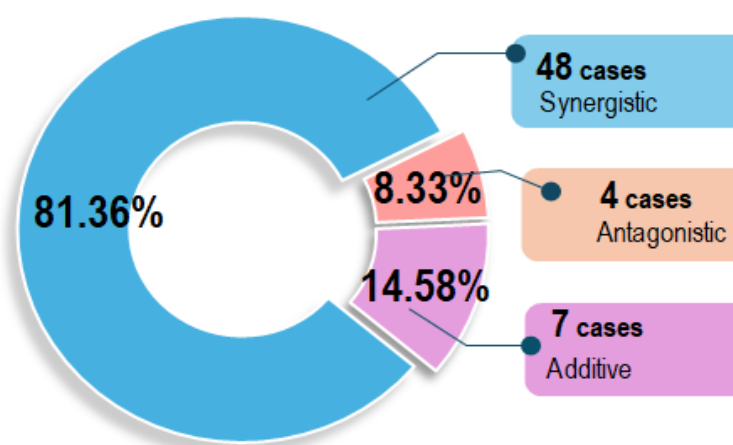


Figure 2: Percentages of types of pharmacodynamic mechanisms of action

Drug-drug interactions were categorized into three degrees, based on their severity: major, moderate, and minor. Findings from this research revealed that most drug interactions were moderate (63.44 %). Major drug-drug interactions accounted for 31.18 % of cases, while minor interactions accounted for only 5.38 %, as presented in Figure 5.

Based on medical records and interviews, drug-drug interactions occurred in 25.93 % of the patients, with 21 of them experiencing direct effects (Table 2). A bivariate chi-square statistical test was performed to identify the relationship among

factors such as age, gender, number of drugs, comorbidities, and duration of treatment, and their impact on drug-drug interactions in the outpatients with schizophrenia and depression. The results of the statistical test are summarized in Table 3. Lower degrees of drug-drug interactions occurred during the distribution and metabolism phases (5.88 % each), in addition to interactions that occurred via unknown mechanisms (5.88 %). These results are shown in Figure 4.

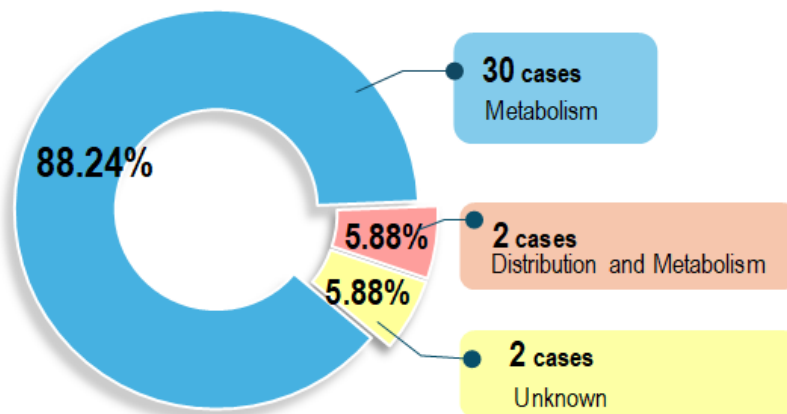


Figure 3: Percentages of pharmacokinetic mechanism of action

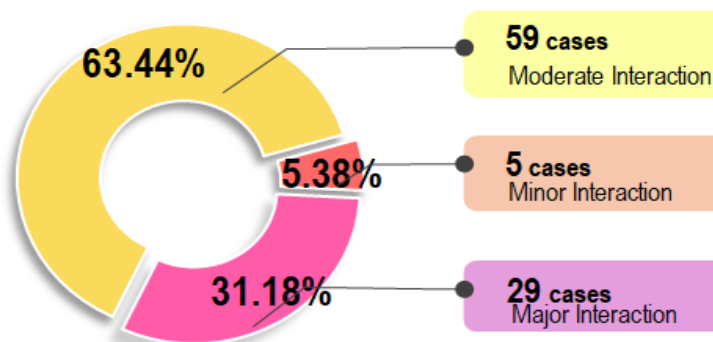


Figure 5: Drug-drug interactions based on degree of severity

Table 2: Actual drug-drug interactions experienced by patients

Drug-drug interaction		Effects	Frequency of occurrence	Percentage (%)	Recommendation
Risperidone	Trihexyphenidyl	1. Xerostomia (bitter tongue) 2. Hot sting on the tongue 3. Blurred vision	2	9.52	Possible drug substitution
Risperidone	Haloperidol	1. Neuroleptic Malignant Syndrome (NMS) 2. Drowsiness	3	14.29	Medication time management
Risperidone	Clozapine	1. Oculogyric Crisis (OGC) 2. Disorientation 3. Drowsiness	5	23.81	Dose reduction and medication time management
Haloperidol	Clozapine	Drowsiness	2	9.52	Medication time management
Clozapine	Divalproate sodium	Weight gain	3	14.29	Possible drug substitution and/or addition of metformin to the therapy regimen
Trihexyphenidyl	Haloperidol	1. Tachycardia 2. Paralytic ileus	5	23.81	Possible drug substitution and/or medication time management
Trihexyphenidyl	Chlorpromazine	1. Blurred vision	1	4.76	Dose adjustment of one or both interacting drugs
Total			21	100	

Table 3: Results of bivariate Chi-square analysis

Characteristic	Description	OR	CI	P-value
Age	18–30	0.356	0.036–3.536	0.363
	31–65			
Gender	Female	0.113	0.011–1.119	0.036
	Male			
Number of drugs	0–3	0.425	0.042–4.263	0.457
	>3			
Comorbidity	Present	0	0	0.474
	Absent			
Duration of treatment (years)	0–3	4.25	0.639–28.245	0.117
	3.1–6			

DISCUSSION

Studies have shown lower incidence of schizophrenia in women than in men, due to the neuroprotective effects of estrogen, while depression is more common in women due to social stress. Patients with schizophrenia and depression are generally of working age, and they undergo relatively shorter periods of therapy (about 3 years). In contrast, schizophrenic patients tend to require long-term treatment. Discontinuation of antipsychotics increases the risk of relapse. Majority of the patients have no comorbidities, but many of them receive more than three types of medication comprising antipsychotics, antidepressants, and

These results are consistent with those obtained in 2022 in a prospective 8-month study on 112 psychiatric inpatients by Sunny *et al* [7]. A total of 201 potential interactions were found, with majority of them (52.73 %) being of significant severity, while 37.31 % of the interactions were of moderate severity. The drug most commonly involved in the interactions was Olanzapine when used in combination with sodium Valproate or Lorazepam. In addition, data from the study revealed that delayed onset (34.82 %) and unknown onset (50.24 %) interactions were predominant, thereby indicating the importance of long-term monitoring of interaction effects [7].

A study conducted by Bačar Bole *et al* on 311 inpatients with schizophrenia spectrum disorders showed that 88.7 % of the patients experienced potential drug-drug interactions (pDDIs), with 54.6 % of them affected by type X interactions which should be avoided. In the present study, 74.07 % of the patients had potential drug interactions, while 25.93 % had actual drug interactions which were confirmed through medical record data and clinical interviews. The most dominant mechanism of drug interaction in both studies was pharmacodynamic interaction. In the current study, 63.44 % of interactions were classified as pharmacodynamic, while 36.56 % of interactions were pharmacokinetic. Most of the pharmacodynamic interactions (81.36 %) were synergistic, while antagonistic and additive interactions accounted for 8.33 and 14.58 %, respectively. Moreover, a study conducted in Slovenia also showed significant pharmacodynamic interactions, especially from combinations of antipsychotics such as Haloperidol and Quetiapine or benzodiazepines such as Diazepam and Olanzapine which are associated with risk of cardiorespiratory depression and severe sedation. A total of 59 patients (19.0 %) received a combination of Diazepam and Olanzapine, while 26 patients (8.4

tranquilizers. Single therapy is preferred for schizophrenia, but drug combinations are used if initial therapy is ineffective [6].

In this study, 93 drug interactions were found among 81 outpatients diagnosed with schizophrenia and depression. Most of these interactions were pharmacodynamic (63.44 %), with moderate-level interactions (63.44 %), while major and minor interactions accounted for 31.18 and 5.38 %, respectively. In 21 patients (25.93 %), there were actual clinically impactful interactions, with effects such as xerostomia, oculogyric crisis, drowsiness, tachycardia, and weight gain.

%) received a combination of Lorazepam and Olanzapine, both of which are categorized as type X interactions with significant severity. In terms of severity, both studies showed that most interactions were moderate.

In the present study, 63.44 % of the interactions were categorized as mild, with major and minor interactions accounting for 31.18 and only 5.38 %, respectively. The Slovenian study reported that all 10 drug combinations with type X interactions were of significant severity, and were backed with sound clinical evidence (i.e., good reliability rating). The most common actual interactions in the Indonesian study involved Risperidone + Clozapine (23.81 %), which caused oculogyric crisis; Trihexyphenidyl + Haloperidol (23.81 %) which resulted in paralytic ileus and tachycardia, and Risperidone + Haloperidol (14.29 %) which induced drowsiness [8]. In this study, pharmacokinetic interactions were most common in the metabolism phase (88.24 %), while the rest happened either in the distribution and metabolism phases (5.88 %), or through an unknown mechanism (5.88 %). Drugs such as Fluoxetine and Valproate sodium were involved in these interactions, as both affect the liver enzyme cytochrome P450 (CYP450) and increase circulating levels of other drugs such as Haloperidol and Clozapine. For example, the interaction between Haloperidol and Fluoxetine may increase Haloperidol levels through the inhibition of CYP2D6 enzyme by Fluoxetine. This increases the risk of side effects, e.g., malignant neuroleptic syndrome (NMS).

Trihexyphenidyl is a class of anticholinergic drugs used as therapy for side effects such as extra-pyramidal symptoms caused by antipsychotic drugs. In this study, the interaction of Trihexyphenidyl with the drugs used was not very significant. Indeed, the potential for interaction between Trihexyphenidyl and other drugs was relatively minimal, except for certain

drugs. The administration of Trihexyphenidyl was aimed at overcoming the side effects of extra-pyramidal symptoms that might arise due to antipsychotic drugs. Unfortunately, pharmacological studies have shown that Trihexyphenidyl synergistically results in the potential effects of dry mouth, blurred vision, constipation, urinary retention, and cognitive dysfunction [6].

The study identified a wide range of interactions between Haloperidol and other drugs prescribed by the doctor. Pharmacodynamically, Haloperidol interacts with Clozapine, Diazepam, and Carbamazepine. The combination of Haloperidol and Clozapine may lead to elevated levels of Haloperidol in the bloodstream, which in turn raises the likelihood of experiencing negative effects. Furthermore, it should be noted that Haloperidol and Clozapine have the potential to lengthen the QTc interval and enhance the effects of anti-dopaminergic agents. This may manifest as symptoms of neuroleptic malignant syndrome. The interaction between Haloperidol and Carbamazepine reduces the therapeutic effect of Haloperidol. However, this interaction increases the effect of Carbamazepine. Incidents of neurotoxicity and Steven-Johnson syndrome have been experienced by patients using Haloperidol and Carbamazepine [9].

The Drug Interaction Checker Database indicates that concurrent use of Amitriptyline and benzodiazepines, e.g., Diazepam, results in a heightened sedative effect when compared to a situation where either of the drugs is used alone. Moreover, the co-administration of Chlorpromazine and Amitriptyline might lead to an interaction that potentially elevates the concentration of one or both drugs in the bloodstream, along with supplementary adverse effects. It has been demonstrated that most phenothiazines and TCAs undergo metabolism through the CYP450 2D6 enzyme. Consequently, co-administration of both drugs might lead to competitive inhibition of this enzyme [10]. The study identified potential significant drug interactions that may affect various aspects of the body, including the cardiovascular system, and may also result in neuroleptic malignant syndrome, serotonin syndrome, extra-pyramidal symptoms, bone marrow suppression, neurotoxicity, Steven-Johnson syndrome, Tardive kinesia, blood dyscrasias, nose bleeds, galactorrhea, and breast tenderness. There was a report of a case of xerostomia and a burning sensation on the tongue when Risperidone was combined with Trihexyphenidyl. Xerostomia is a medical term that describes the feeling of dryness in the

mouth, typically caused by a decrease in saliva production (hyposalivation). Polypharmacy is a frequent cause of xerostomia, particularly among the older population. This is so due to high incidence of dry mouth in geriatric patients who take many drugs due to chronic conditions and multiple morbidities [11].

Co-administration of Risperidone and Clozapine leads to the occurrence of oculogyric crisis (OGC), an effect which has been observed in patients due to interaction of the two drugs. Oculogyric crisis is a specific form of dystonic movement condition characterized by paroxysmal, conjugate, and usually upward deviation of the eyeball which occurs within a period ranging from seconds to hours. Most dopamine-inhibiting drugs such as anti-psychotics, anti-emetics, anti-epileptics, and anti-depressants, cause OGC. Oculogyric crisis (OGC) has been linked to the use of typical and atypical antipsychotic drugs [12]. Co-administration of risperidone and haloperidol leads to neuroleptic malignant syndrome (NMS), a rare but potentially life-threatening condition that arises as an adverse reaction to neuroleptic agents. It is clinically characterized by hyperthermia, pronounced muscle rigidity, autonomic dysregulation, and alterations in mental status. This severe pharmacological complication has been reported in approximately 0.2 to 3.2 % of patients undergoing neuroleptic treatment [13].

Weight gain effect is seen in patients taking a combination of clozapine and divalproex sodium. It has been reported that atypical antipsychotic drugs, especially clozapine and olanzapine, have a weight gain effect [14]. This is related to changes in glucose metabolism through mechanism involving the inhibition of receptors for 5-HT_{2A} and 5-HT_{2C}, as well as decrease in insulin sensitivity through inhibition of dopamine D₂ receptors. Extant literature reveals that all antipsychotics produce metabolic side effects by activating the mother receptor against the decapentaplegic homolog (SMAD3) receptor. This results in neurological effects through activation of the TGF-beta pathway, a cellular mechanism that regulates various biological processes [14]. In the therapeutic management of drug interactions, it is known in principle that if adverse effects occur, the doctor should consider changing one of the therapeutic agents or using a single therapeutic agent (monotherapy). If anti-psychotic treatment needs to be changed, this is done by slowly reducing the dose of the previous anti-psychotic drug while simultaneously increasing the dose of the new anti-psychotic agent. This strategy is aimed at avoiding

psychotic relapse. Monitoring the patient's condition such as vital signs, is also recommended if there are adverse drug effects, e.g., an increase in the QTc interval or drug interactions that cause marrow suppression [9].

Results from chi-square bivariate analysis revealed that variables such as gender, age, number of drugs, comorbidities, and duration of treatment had *p-values* of 0.851, 0.338, 0.022, 0.004 and 0.08, respectively. Following bivariate analysis, multivariate analysis was used to determine which factors were most influential. The results of bivariate analysis with $p < 0.25$ were comorbid factors, number of drugs, and length of treatment, and the *p-values* for logistic regression were 0.256, 0.021, and 0.078, respectively. The conclusion that can be drawn from the results of the analyses is that the number of drugs is the factor with the most influence on the incidence of drug-drug interactions in patients with schizophrenia and depression. Therefore, these variables did not exhibit statistically significant relationships with the occurrence of drug-drug interactions. In contrast, the gender variable displayed a *p-value* of 0.036 ($p < 0.05$), indicating a significant correlation between gender and the occurrence of drug-drug interactions. This is in agreement with the results from a previous study in which it was shown that women up to the age of 79 years had a higher number of interaction events due to intake of more drugs than men in the same age bracket [15]. The study also revealed that women are more susceptible to adverse drug reactions due to various pharmacokinetic parameters such as drug absorption, body composition, kidney function, and liver metabolism, all of which may interfere with drug metabolism in the body and hinder the expected beneficial effects [15].

The common effects of taking a combination of antipsychotics with antipsychotics include xerostomia, oculogyric crisis (OGC), drowsiness, and weight gain. Xerostomia or dry mouth is usually caused by medications such as anticholinergics and antihypertensives. It is treated by increasing hydration, avoiding alcohol and tobacco, and reducing or stopping the offending medication. Oculogyric crisis (OGC) is an eye movement disorder due to the disruption of the dopamine pathway, and it is often triggered by conventional antipsychotics. The condition is treated with the administration of anticholinergics, reduction of the dose of the drug, or switching to a safer antipsychotic such as Clozapine. The sedative effects of dopamine and histamine receptor antagonism cause drowsiness. This is usually managed by scheduling drug administration at night, lowering

the drug dose, or switching to a less sedative drug. Weight gain is a significant side effect of anti-psychotics. This may lead to metabolic syndrome, diabetes, and heart disease. Weight gain may be treated via lifestyle changes, regular metabolic monitoring, change of medication, and the use of Metformin. Other weight-loss medications are still not widely recommended for this condition.

Pharmacists play a critical role in optimizing pharmacotherapy through the integration of their professional competencies (knowledge and clinical skills) with the utilization of computerized, evidence-based decision support systems. The implementation of such systems contributes significantly to the mitigation and prevention of adverse outcomes associated with drug-drug interactions (DDIs). The findings from this study indicate that the patient population investigated is at an elevated risk of experiencing detrimental effects due to the identified DDIs, thereby underscoring the necessity for rigorous and continuous clinical monitoring of their therapeutic regimens [16].

Limitations of the study

The study has some limitations: some medical records had incomplete information, particularly regarding patients' comorbidities. In addition, not all patients provided consent for the interview. These constraints may have limited the completeness of data collected through the qualitative method.

CONCLUSION

The 93 drug-drug interactions identified in this investigation involve anti-convulsants, anticholinergics, anti-depressants, and antipsychotics. There was a higher incidence of pharmacodynamic interactions (63.44 %) than pharmacokinetic interactions (36.56 %). Most of the interactions are of moderate severity (63.44 %), followed by interactions with major severity (31.18 %) and minor severity interactions (5.38 %). In a clinical setting, interactions occurred in six patients, with a total of nine incidents. Therefore, a deep understanding of drug-drug interactions is essential for optimizing therapy and minimizing the risk of side effects. Gender was identified as a variable factor that influences the incidence of drug-drug interactions.

DECLARATIONS

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Ethical approval

This study was approved by the Ethics Committee of PKU Muhammadiyah Gamping Hospital (approval no. 026/KEP-PKU/II/2023).

Use of Artificial intelligence/Large language models

We also declare that we did not use Generative artificial intelligence (AI) and AI-assisted technologies in writing the manuscript.

Availability of data and materials

The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

Conflict of interest

No conflict of interest is associated with this work.

Contribution of authors

We declare that this work was done by the author(s) named in this article, and all liabilities pertaining to claims relating to the content of this article will be borne by the authors.

REFERENCES

1. BPS. Badan Pusat Statistik 2014. Available from: <https://www.bps.go.id/id/statistics-table/1/MTYxOSMx/persentase-penduduk-yang-mempunyai-keluhan-kesehatan-dan-penggunaan-obat-menurut-provinsi-dan-jenis-kelamin--2009-2014.html>. 2024
2. Cerveri G, Gesi C, Mencacci C. Pharmacological treatment of negative symptoms in schizophrenia: Update and proposal of a clinical algorithm. *Neuropsychiatr Dis Treat*. 2019; 15:1525–1535.
3. Herdaningsih S, Muhtadi A, Lestari K, Annisa N. Potential of drug-drug interaction in polypharmacy prescription: retrospective study on a drugstore in Bandung. *Indones J Clin Pharm* 2016; 5: 288–292.
4. Vukotić NT, Đorđević J, Pejić S, Đorđević N, Pajović SB. Antidepressants and antipsychotics induced hepatotoxicity. *Arch Toxicol Springer Science and Business Media Deutschland GmbH* 2021. p. 767–789.
5. Ohno Y, Kunisawa N, Shimizu S. Antipsychotic treatment of behavioral and psychological symptoms of dementia (BPSD): Management of extra-pyramidal side effects. *Front Pharmacol Frontiers Media SA* 2019.
6. Sheikh WA. Prophylactic use of trihexyphenidyl (Artane) in schizophrenia and psychosis: a critical review of literature to guide for evidence-based practice in Zambia. *Med J Zambia* 2019.
7. Sunny S, Prabhu S, Chand S, UP N, Chacko CS, Joel JJ. Assessment of drug-drug interactions among patients with psychiatric disorders: A clinical pharmacist-led study. *Clin Epidemiol Glob Heal* 2022; 13: 100930.
8. Bačar Bole C, Nagode K, Pišlar M, Mrhar A, Grabnar I, Vovk T. Potential drug-drug interactions among patients with schizophrenia spectrum disorders: prevalence, association with risk factors, and replicate analysis in 2021. *Med* 2023; 59.
9. Preston CL. *Stockley's Drug Interactions: A sourcebook of interactions, their mechanisms, clinical importance, and management*. 12th Editi. Pharmaceutical Press 2019.
10. Medscape. *Drug Interaction Checker*. 2024. Available from: https://www.drugs.com/drug_interactions.html
11. Kapourani A, Kontogiannopoulos KN, Manioudaki AE, Pouloupoulos AK, Tsalikis L, Assimopoulou AN, et al. A review on xerostomia and its various management strategies: the role of advanced polymeric materials in the treatment approaches. *Polymers (Basel)*. MDPI 2022.
12. Lv T, Wu L, Li L, Zhang M, Tan Q, Liu P. Oculogyric crisis symptoms related to risperidone treatment: a case report. *BMC Psychiatry* 2023; 23.
13. Ortiz JF, Wirth M, Eskander N, Cozar JC, Fatade O, Rathod B. The genetic foundations of serotonin syndrome, neuroleptic malignant syndrome, and malignant hyperthermia: Is there a genetic association between these disorders? *Cureus* 2020.
14. Sona A, Hasni D, Anissa M, Heppy F. Identification of subjective weight gain complaints in schizophrenia patients receiving antipsychotic therapy at HB Mental Hospital. Saanin Padang. *J Kedokt dan Kesehat* 2020; 16.
15. Zucker I, Prendergast BJ. Sex differences in pharmacokinetics predict adverse drug reactions in women. *Biol Sex Differ* 2020; 11.
16. Zafar R, Chishti KA, Zahoor M. Potential drug-drug interactions in the neurology ward of a tertiary care hospital in Peshawar, Pakistan. *Trop J Pharm Res* 2017; 16: 2521–256.