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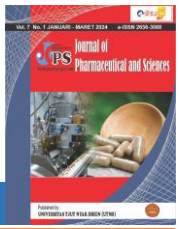

Drug-Related Problems in Hospitalized Patients with Schizophrenia: A Systematic Review of Prevalence and Intervention

Permasalahan Terkait Obat pada Pasien Skizofrenia Rawat Inap: Tinjauan Sistematik Mengenai Prevalensi dan Intervensi

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Abstract

Schizophrenia is a severe mental disorder with increasing prevalence. Treatment for schizophrenia is chronic and often leads to Drug-Related Problems (DRPs), especially in hospitalized schizophrenia patients. This systematic review aims to map the prevalence and most common types of DRPs and evaluate the impact of clinical pharmacist involvement in addressing DRPs. A literature search was conducted across six electronic databases (Scopus, PubMed, ScienceDirect, Web of Science, ProQuest, and Springer Nature) for publications published between January 2009 and December 2024. Eleven studies met the inclusion criteria, consisting of nine cross-sectional studies and two quasi-experimental studies, with a total of over 61,000 hospitalized schizophrenia patients. The prevalence of DRPs has been reported to range from 52.8% to 100%, depending on the study design and the DRP identification method. Studies using structured medication reviews reported a higher DRP burden, at 0.75–2.5 DRPs per patient. The most frequently identified types of DRPs include polypharmacy, drug interactions, inappropriate medication selection, and dosing problems (overdose and underdose). QTc prolongation was reported in 2.5–8.26% of patients. Clinical pharmacist involvement was reported in three studies, with physician acceptance of recommendations ranging from 49 to 50%. DRPs are a common problem in hospitalized patients with schizophrenia, and clinical pharmacist involvement has the potential to improve the rationality and safety of drug therapy.

***Keywords*: Schizophrenia, Drug-Related Problems, Hospitalized Patients, Clinical Pharmacist.**

Abstrak

Skizofrenia merupakan gangguan mental berat yang memiliki prevalensi yang terus meningkat. Terapi skizofrenia bersifat kronis dan sering menimbulkan Drug-Related Problems (DRP), terutama pada pasien skizofrenia rawat inap. Tinjauan sistematis ini bertujuan untuk memetakan prevalensi dan jenis DRP yang paling sering terjadi serta mengevaluasi dampak keterlibatan apoteker klinik dalam mengatasi DRP. Pencarian literatur dilakukan menggunakan enam basis data elektronik (Scopus, PubMed, ScienceDirect, Web of Science, Proquest, dan Springer Nature) yang diterbitkan antara Januari 2009 dan Desember 2024. 11 studi memenuhi kriteria inklusi, terdiri dari sembilan studi cross-sectional dan dua studi quasi-experimental, dengan total lebih dari 61.000 pasien skizofrenia rawat inap. Prevalensi DRP dilaporkan bervariasi antara 52,8% dan 100%, tergantung pada desain studi dan metode identifikasi DRP. Studi yang menggunakan telaah pengobatan terstruktur melaporkan beban DRP yang lebih tinggi, yaitu 0.75-2,5 DRP per pasien. Jenis DRP yang paling sering diidentifikasi meliputi polifarmasi, interaksi obat, pemilihan obat yang tidak tepat, dan masalah dosis. Efek samping QTc prolongation dilaporkan pada 2,5-8,26% pasien. Keterlibatan apoteker klinis dilaporkan pada tiga studi, dengan tingkat penerimaan rekomendasi oleh dokter sebesar 49-50%. DRP merupakan masalah yang sering terjadi pada pasien skizofrenia rawat inap, dan keterlibatan apoteker klinik berpotensi meningkatkan rasionalitas serta keselamatan terapi obat.

***Kata Kunci*: Schizophrenia, Drug-Related Problems, Hospitalized Patients, Clinical Pharmacist.**

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Introduction

Schizophrenia is one of the severe mental disorders that is a serious challenge in the health system, both at the global and national levels. In Indonesia, the prevalence of severe mental disorders, including schizophrenia, increased from 1.7 per 1,000 households in 2013 to 7 per 1,000 households in 2018, which means that there are 7 households per 1,000 households with schizophrenia [1]. Globally, this disorder is estimated to affect about 1% of the world's population [2]. The latest figures from the WHO state that around 24 million people, or 1 in 300 people (0.32%), have schizophrenia, and in the adult population, the figure increases to 1 in 222 people (0.45%) [3,4]. Individuals with schizophrenia also have a 2-3 times higher risk of premature death than the general population [5].

Schizophrenia is chronic and requires long-term treatment, usually with antipsychotics. Although effective in controlling symptoms of psychosis, the use of antipsychotics often presents clinical challenges such as drug interactions, side effects, and non-adherence to medication. In addition, schizophrenia patients generally have comorbidities that require the use of several medications at the same time (polypharmacy), thus increasing the risk of Drug-Related Problems (DRPs). These DRPs not only reduce the effectiveness of therapy but can also lead to extended hospitalizations, readmissions, and increased health service costs [6,7,8].

To overcome these challenges, pharmaceutical care approaches have been introduced and developed. Pharmaceutical care is defined as the professional responsibility for the patient's drug therapy to achieve optimal therapeutic outcomes and improve quality of life. This approach has been widely applied in clinical practice, including in the field of psychiatry, with the main goal of identifying and managing various forms of DRPs, such as the use of drugs that are not as indicated, non-adherence, drug interactions, irrational use, and drug side effects. One of the mini reviews by Bereda[9] highlights the importance of this issue, where it was found that 38.5% of schizophrenic patients experienced DRPs, with the highest proportion being unnecessary drug therapy (24.4%) and non-compliance (20%).

Drug-Related Problems have long been recognized as a serious challenge in health services. Since 1990, DRPs have been systematically classified based on the dimensions of indication, effectiveness, safety, and compliance. This approach aims to optimize drug use, minimize risk, and improve patient clinical outcomes [10,11]. DRPs contribute significantly to the increase in morbidity, mortality, and economic burden of health services. Therefore, the identification and intervention of DRPs are one of the important pillars in ensuring treatment safety and patient safety, especially in the management of severe mental disorders such as schizophrenia.

However, to date, comprehensive studies that specifically examine Drug-Related Problems in inpatients with a diagnosis of schizophrenia are limited. A systematic review by Wien et al.[12] It has indeed evaluated the prevalence and management strategies of DRPs in the adult psychiatric population in hospitals. Still, its focus includes a wide range of diagnoses of psychiatric disorders and does not specifically highlight schizophrenic patients. The characteristics of schizophrenia patients – both in terms of pharmacotherapy profile, polypharmacy risks, and compliance challenges – have the potential to give rise to DRP patterns that are distinctive and different from other psychiatric disorders.

Based on this, this systematic review aims to present an updated mapping of the prevalence and types of DRPs that most frequently occur in patients with schizophrenia and to evaluate the impact of clinical pharmacist involvement in addressing DRPs. This study is expected to contribute to clinical practice, particularly by improving the quality of pharmaceutical services and patient safety in the psychiatric field. The research questions to be answered through this review are: What are the types of DRP that are most

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commonly identified in inpatient schizophrenia patients based on the PCNE classification? and What are the forms of clinical pharmacist intervention in dealing with DRPs, also what is the level of acceptance of clinical pharmacist recommendations by doctors?

Method

This research is a systematic review prepared in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) 2020 guidelines. The definitions used in this review are in Table 1.

Table 1. Definitions used in the review

Term	Definition
Drug-Related Problems (DRP)	DRP refers to a condition or event related to the use of a drug, which can potentially disrupt the expected therapeutic outcome. The DRP category in PCNE V9.00 covers a variety of things, such as side effects, adverse reactions, medication administration errors, unsafe drug interactions, inappropriate drug use, and patient non-compliance with the recommended regimen.
Polypharmacy antipsychotics	It is defined as two or more combinations of antipsychotics prescribed at the same time.
Unnecessary drug therapy	Too many different drugs are prescribed for the same indication.
Non-compliant with medication	Patients intentionally use/take less medication than prescribed or do not take medication at all for any reason.
Drug interactions	Drug interactions occur when two or more active substances negatively affect each other, both in terms of effectiveness and safety of therapy. These interactions are pharmacokinetic, pharmacodynamic, or involve specific medical conditions and foods.

Search Methods

Literature searches will be conducted in electronic databases, including PubMed, Scopus, and ScienceDirect. The search strategy uses a combination of relevant keywords to describe the population and topic, namely "Schizophrenia" OR Psychotic Disorder" AND "Inpatient" OR "Hospitalized" AND "Drug-related Problems" OR "Medication Errors" OR "Adverse Drug Event" OR "Inappropriate Prescribing" OR "Polypharmacy". These keywords will be applied to the title and abstract fields without subject restrictions, but with an adult age filter (≥18 years old).

Eligibility Criteria

Inclusion Criteria

All types of primary research will be included in this review, including observational studies, quasi-experimental studies, and randomized controlled trials related to DRPs in adult patients with an inpatient diagnosis of schizophrenia. To provide a comprehensive overview, studies that report on the prevalence of DRPs, types of DRPs (such as medication errors, adverse drug events, inappropriate prescribing, polypharmacy, or drug interactions), or describe interventions aimed at detecting, preventing, or managing DRPs, either as primary or secondary outcomes, will be included. Studies reporting potential DRPs, including potentially inappropriate medication (PIM) based on criteria such as Beers or STOPP/START, will also be considered as part of DRP type mapping.

Various DRP classification systems, such as the Pharmaceutical Care Network Europe (PCNE) Classification, Cipolle, and others, will be accepted according to the one used by each study. Articles written in English can be included with the Publication year limit from January 2009 to December 2024.

Exclusion Criteria

Research will be excluded if the manuscript is not open or accessible. Studies that only examine outpatients or community-based mental health services will not be included. Studies conducted on outpatient schizophrenia patients will be excluded. In addition, articles that do not adequately explain the methodology for identifying or classifying DRPs will also be excluded.

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In addition, narrative reviews, comments, editorials, opinion articles, letters to the editor, unfinished research protocols, phase I or II clinical trials, posters, and conference abstracts without a complete manuscript will be excluded.

Selection Process

The title and abstract of the article retrieved from the database will be screened first to assess initial eligibility against the inclusion and exclusion criteria. The screening process will be carried out carefully by examining the title and abstract, and continues at the stage of reviewing the full text. At this stage, the reviewer will read the article in full to ensure all inclusion and exclusion criteria are met.

If there is disagreement about including an article, the reviewer will discuss the points of disagreement until a consensus is reached. If there are still doubts, then the final review will be determined together with the involvement of a third reviewer. The selection results will be recorded in the PRISMA flowchart and reported transparently.

Data Collection Process and Data Items

The data extraction form will be developed specifically to collect information from primary studies that meet the inclusion criteria. The DRPs will be classified according to the relevant classification system, i.e., PCNE V9.1 or the treatment management guidelines used in each study. Additional categories can be added as needed, based on the findings in each article.

The data to be collected from each study includes: article title, author's name, country of origin, year of publication, demographic characteristics of the subject, research objectives, study location and setting, study design, duration of implementation, sample size, inclusion and exclusion criteria, data collection method, who collected the data, type of prescribing system (manual/electronic), method of identification of DRPs, types and subtypes of DRPs, prevalence figures of DRPs, total DRPs detected, severity of DRPs, and if available blood drug level test results associated with DRPs (especially ADRs).

In addition, if the study reported an intervention to complete the DRPs, the description of the intervention, the DRPs remaining after the intervention, the statistical analysis methods, and the source of research funding will also be recorded. All collected data will be summarized in a results table and used as the basis for descriptive analysis in this systematic review.

Quality and Bias Assessment

Methodological quality assessments and potential bias in selected studies will be conducted by one lead reviewer (SAF), and, when necessary, verified by a second reviewer to ensure consistency.

DRPs Reporting Quality Assessment

The reporting quality of the DRPs in each study will be evaluated using criteria adapted from Allan and Barker (1990), which have previously been used in several systematic reviews of medication errors. The maximum score for the assessment is 12 points, reflecting the high quality of the reporting.

Given the variation in DRP identification methods and the absence of a standard validation tool (gold standard) to detect DRPs, direct observation by pharmacists or clinical pharmacologists will be scored lower (1 point) than the use of standardized validation instruments or causality scales (2 points). Examples of these instruments include the WHO UMC-Causality Assessment or the Naranjo Algorithm to assess the probability of ADR.

To minimize subjectivity in the assessment of DRPs, a study is considered high-quality if it also assesses inter-observer reliability by calculating a reliability coefficient or inter-rater agreement.

Specific Quality Assessment Based on Study Type

Each selected study will be evaluated for risk of bias using the JBI Critical Appraisal Checklist tailored to its design. The University of Adelaide developed this research tool, which is available online at https://jbi.global/critical-appraisal-tools. The total score will be calculated based on the number of criteria met across all checklist items.

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Overall Bias and Risk Assessment

In addition to the risk of bias in each study, potential bias will also be analyzed, including publication bias between studies and selective reporting bias within each study. To maintain the quality of reporting, this review will follow the latest PRISMA 2020 guidelines.

Assessment of the Certainty of the Evidence

The overall certainty of the evidence will be summarized in the summary table of findings, especially for studies reporting the prevalence of DRPs or mistreatment. The assessor will use the GRADE (Grading of Recommendations, Assessment, Development and Evaluation) approach to assess the quality of the available evidence.

If the interventions reported in the study cannot be quantitatively compared due to high heterogeneity, they will not be included in the summary table of results.

Synthesis and Analysis Data

The main outcomes to be synthesized include the prevalence of DRPs, the different types of DRPs reported, and the forms of interventions tested to treat DRPs in inpatient schizophrenia patients. Because the methods for detecting, classifying, and reporting DRPs varied across studies, meta-quantitative analysis was unlikely. Instead, the results will be summarized descriptively by DRP and ADE categories.

Results and Discussion

A total of 2,933 articles were successfully identified through systematic searches across five major scientific databases: Scopus, PubMed, ScienceDirect, Web of Science, ProQuest, and Springer Nature. After deduplication, 314 studies were removed, leaving 2,619 articles for further selection based on their titles and abstracts. At this stage, 317 articles were excluded because their titles and abstracts were irrelevant to the study's focus, mainly because they did not address Drug-Related Problems (DRPs) or did not explicitly mention the population or clinical conditions targeted by this study.

Furthermore, as many as 2,302 articles were selected for full-text retrieval. However, 212 articles are not accessible in full text. A total of 2,029 articles were successfully accessed in full text and thoroughly evaluated against previously set inclusion and exclusion criteria. Of these, 2,079 articles were excluded from the final analysis for various reasons, namely: (1) articles were published outside the predetermined time span (n=302), (2) inappropriate study design or research methods were not adequately explained (n=1,354), (3) did not report DRP prevalence data (n=358), and (4) articles were not relevant to the Kadian topic because they discussed inappropriate aspects, such as community, non-clinical, or outpatient population contexts (n=65).

Thus, only 11 studies met the inclusion criteria and were included in this systematic analysis. This number reflects the rigorous selection of literature conducted and shows the limited number of studies that are methodologically robust, thematically relevant, and explicitly report data on the prevalence of DRPs in a given clinical context. These findings highlight gaps in the available literature and underscore the importance of further, focused, structured, and methodologically rigorous research to strengthen the scientific evidence on DRP issues, especially in real clinical practice settings. Details of the search and selection process are presented in the PRISMA flowchart (Figure 1).

Quality assessment and risk of bias in the included studies were conducted using two methods, depending on the study type. For all studies that reported the quality of DRP reporting, the Allan and Barker (1990) criteria were used, with a maximum of 12 points. Meanwhile, for specific assessments based on the study type (e.g., prevalence studies, cohort studies), the JBI Critical Appraisal checklist is used according to the research design. The results of this assessment are presented as the median score, IQR, and range of scores, and are described in the following discussion. Based on the quality assessment of all incoming studies using the Allan and Barker (1990) criteria (maximum score of 12), the median score was 9 (IQR: 5-10). All studies clearly define DRP, operationalize it, discuss research limitations, and link methods to research outcomes. However, only a few studies describe in detail the categories of errors, explanations of error-detection methods, observation techniques that conform to standards, data validation, the validity of the analysis of research results, and the calculation of error incidence rates. Meanwhile, only 4 studies used the official DRP classification system, only 3 controlled for observer bias, and only 1 conducted reliability tests between assessors. The assessment results are shown in Table 2.

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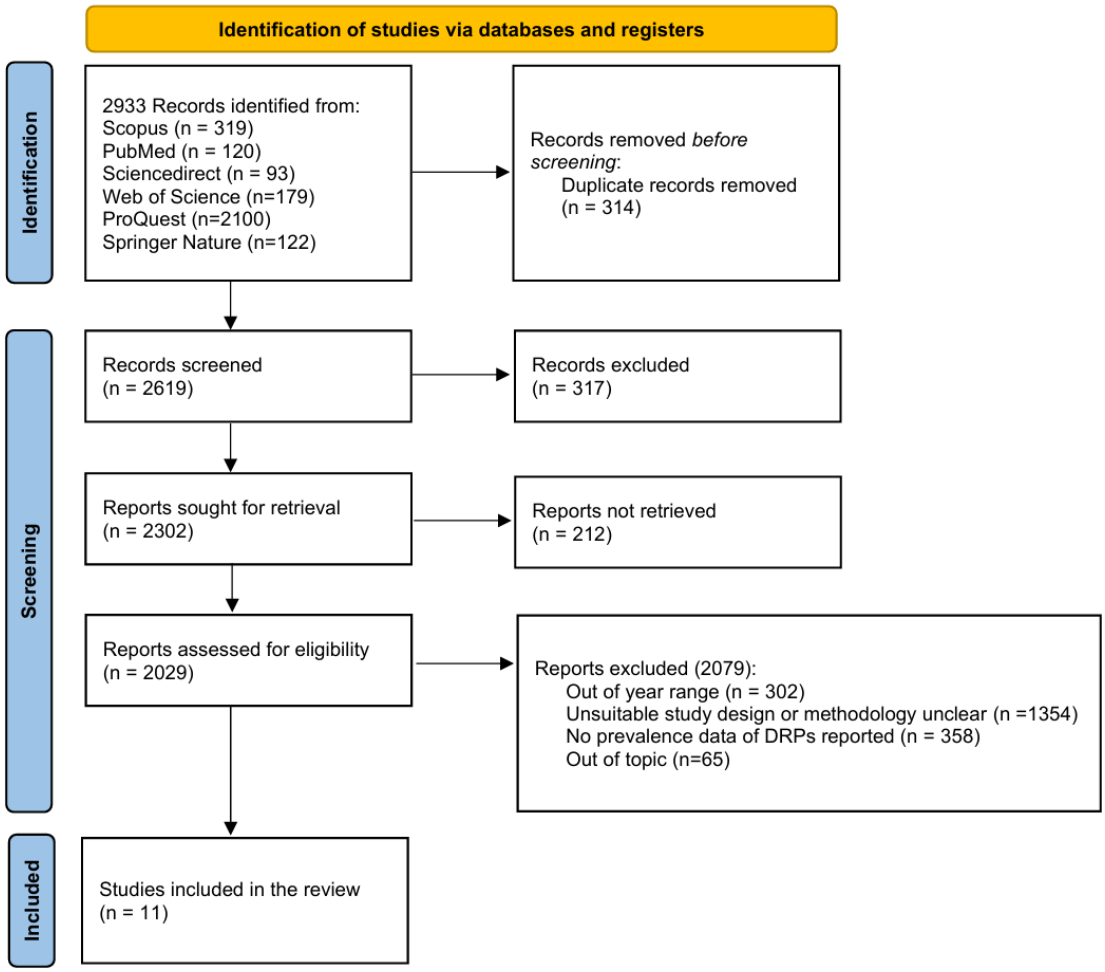

Figure 1. Flow Chart of Selection of Studies for Review

Methodological quality assessment using the JBI Critical Appraisal Checklist indicated that most included studies had good to very good methodological quality. Of the 11 studies, JBI scores ranged from 75% to 100%, with a median of 100% (IQR 87.4-100%), reflecting the dominance of high-quality studies. The majority of cross-sectional studies demonstrate high compliance with the JBI checklist criteria, particularly regarding the clarity of inclusion criteria, the validity of outcome measurements, and the suitability of statistical analyses.

Studies with quasi-experimental designs showed slightly lower scores (78-89%), mainly due to limitations in controlling confounding factors and the lack of reporting bias mitigation strategies. Nonetheless, all studies met most JBI criteria, so the overall risk of bias was assessed as low to moderate, and the study findings could be considered to have adequate internal validity.

This systematic review synthesizes 11 observational studies that examined the prevalence, types, and interventions of DRPs in schizophrenic patients. Although there were variations in the study design, detection methods, and types of DRP studied, all studies reported a significant DRP burden in this population. Nine studies were retrospective observational studies with a cross-sectional design, while two studies were quasi-experimental pre-post with retrospective and prospective analyses. These studies were published between 2010 and 2023 and came from countries such as Slovenia, China, Spain, Japan, Germany, Ethiopia, Denmark, and Mexico. This shows that attention to Drug-Related Problems (DRPs) in schizophrenia patients is global, although the number is still limited. The sample size varied between 52 and 56861 participants, all of whom were adult patients (≥18 years) who were hospitalized with a diagnosis of schizophrenia. All studies were conducted in mental health service facilities, including both mental hospitals and general hospital psychiatric units. A summary of the studies included in this systematic review is presented in Table 3.

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Table 2. Allan-Barker Rating

Author	(Bačar Bole et al., 2023)	(Cao et al., 2021)	(Ramos-Ríos et al., 2010)	(Hashimoto & Tensho, 2016)	(Grohmann et al., 2014)	(Yang et al., 2011)	(Ilickovic et al., 2016)	(Temtem et al., 2023)	(Kibsdal et al., 2020)	(Ocaña-Zurita et al., 2016)	(Ozeki et al., 2010)
Clear and operational definition of DRPs	1	1	1	1	1	1	1	1	1	1	1
Detailed description of error categories	1	1	1	1	1	0	1	1	1	0	0
Description of error detection methods	1	1	1	1	1	0	1	1	1	1	0
Observation techniques according to the standard	0	1	1	0	1	1	1	1	1	0	0
Data validation	0	1	1	0	1	1	1	1	1	0	1
Inter-rater reliability described	0	1	0	0	0	0	0	0	0	0	0
Validity of results analysis	1	1	1	0	1	1	1	1	1	0	1
Explanation of error rate calculation	0	0	1	0	1	0	0	1	1	1	0
Control of observer bias	0	1	1	0	0	1	0	0	0	0	0
Discussion of study limitations	1	1	1	1	1	1	1	1	1	1	1
Use of an official DRP classification system	0	0	0	0	1	0	1	1	1	0	0
Link between methods and results	1	1	1	1	1	1	1	1	1	1	1
Score	6	10	10	5	10	7	9	10	10	5	5

Based on the eleven studies included in this systematic review, drug-related problems (DRPs) are a very common problem in inpatient schizophrenia patients. The prevalence of reported DRP varies widely, ranging from 52.8% to 100%, depending on the definition of DRP, the identification methods used, and population characteristics and treatment settings. This variation reflects methodological heterogeneity between studies, but consistently confirms that inpatient schizophrenia patients are a group at high risk of developing DRP. This is in accordance with research conducted by Utami et al. [13], where the prevalence of DRP in schizophrenia patients is quite high, which is 89.5% with a total of 117 incidents. Based on the PCNE classification, the types of DRPs in this review can be grouped into three main domains: indication, effectiveness, and safety of therapy. The most commonly reported types of DRP in the reviewed studies included polypharmacy, drug interactions, improper dosage, and adverse drug reactions (ADRs).

Indication problems include antipsychotic polypharmacy. Antipsychotic polypharmacy was one of the most commonly identified types of DRP in inpatient schizophrenia patients in this review. Antipsychotic polypharmacy is often used in clinical practice to manage symptoms that are not responsive to monotherapy, especially in patients with severe symptoms or resistance to APA therapy [25]. Evidence from large-scale national cohort studies suggests that combination therapy of two antipsychotics may be associated with reduced numbers of emergency visits and rehospitalization compared to Tiihonen et al. monotherapy [27]. In addition, no evidence was found that drug combinations are more harmful than the use of one drug, beyond the common side effects of each drug.

However, polypharmacy is still categorized as DRP because it increases the complexity of therapy, the risk of side effects, drug interactions, dosage errors, and the severity of adverse drug reactions. Therefore,

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clinical benefits and side effects should be closely monitored, and dosage changes should be made to a single drug at a time to facilitate evaluation of the therapeutic response. Furthermore, if the patient experiences an exacerbation of symptoms despite receiving a stable dose of medication, a thorough re-evaluation of the treatment plan is more advisable than simply adding new medications to the existing therapy regimen. Although polypharmacy is clinically needed, it still requires the active involvement of clinical pharmacists to identify DRP and ensure the rational and safe use of drugs APA [25].

Several studies have consistently shown that the amount of medication prescribed is a major risk factor for DRP. The results of Bačar et al.'s study.[14] show that the amount of medication prescribed is the main risk factor for DRP. Bačar et al. [14] reported that an increase in the amount of the drug significantly increased the risk of drug interactions (OR 2.85). Temtem et al. [17] also found that the amount of medication taken was strongly related to the incidence of DRP (AOR 5,936). In addition, factors such as advanced age and long duration of treatment also contribute to an increased risk of DRP, as reported by Cao et al. and Yang et al. These findings suggest that inpatient schizophrenia patients, particularly chronic and elderly patients, are a highly susceptible population to DRP due to the complexity of the regimen and long-term drug exposure [18,19].

The most common safety issue in this review was drug interactions. Drug interactions, specifically potential interactions between two antipsychotics or between antipsychotics and benzodiazepines, as well as antiparkinsonian drugs, are one of the dominant problems found in several studies. Bačar et al.[14] reported that 71.1% of patients experienced ≥1 DRP, which is mainly related to polypharmacy and drug interactions. In this study, potential drug interactions were assessed using the Lexicomp database, and drug interactions were identified only in group 1. A total of 85.3% (35) of patients in the same group experienced category D drug interactions, which indicates the need for therapy modification to prevent potential side effects. In addition, as many as 90.2% (37) of patients in group 1 experienced category X drug interactions, which means that the therapy undergone has a risk of serious interactions and, in principle, is not recommended for concomitant use. Of the 10 most common drug pairs, all have a "major" severity classification, and 9 have a "good" reliability rating, meaning they are based on controlled clinical trials or strong empirical data.

Similar findings were reported by Ocaña et al.[15], who used the Drug Interaction Checker (Drugs.com) to analyze potential drug interactions. The results of the study by Ocaña et al.[15] showed that 68.2% of patients were at risk of potential drug interactions, with 13.8% of interactions classified as major and 83.2% classified as moderate. The high prevalence of drug interactions in inpatient schizophrenia patients can be attributed to the complexity of pharmacological therapies, including the use of antipsychotic polypharmacy, combinations with additional drugs such as benzodiazepines, and antiparkinsonian, as well as long duration of hospitalization. This combination of therapy often involves antipsychotics with other groups of drugs such as benzodiazepines, anticholinergics, and other groups according to the clinical needs of patients Jusuf et al [26]. Identification of these drug interactions suggests that many drug interactions have the potential to occur but still require clinical attention.

The most effective issue in this review was dose-related. Dosing problems are an important DRP reported by several studies Kibsdall et al. [16] reported that dosing problems were the most common DRP (19.9%), while Temtem et al. [17] reported overdose as a significant DRP (20.5%). Sub-therapy doses have the potential to lead to therapy failure and recurrence of psychotic symptoms. Overdosing increases the risk of side effects such as excessive sedation, extrapyramidal disorders, and cardiovascular toxicity. Hashimoto & Tensho's findings [24] suggest that clinical pharmacist interventions can significantly lower the use of overdoses of antipsychotics, confirming the importance of optimizing individual doses based on the patient's clinical symptoms. These results are in line with the research of Ilickovic et al., where pharmacist-proposed interventions, including overdose discontinuation, dose adjustment, and medication replacement, were accepted by physicians in 50% of cases and resulted in partial or complete resolution of 38 DRPs[22].

Inappropriate drug selection was also reported as a relevant DRP. Influencing factors include prescriber preferences, limited access to medications, and insufficient consideration of patient comorbidities. The selection of antipsychotics with a risk of QTc prolongation in patients with cardiovascular disease may increase the risk of the occurrence of serious arrhythmias. Therefore, evaluation of individual risk-based therapies is essential in the management of inpatient schizophrenia patients.

Some studies in this review specifically highlight QTc prolongation as a clinically significant ADR. QTc prolongation is one of the adverse drug reactions (ADR) that have serious clinical implications because it can increase the risk of torsade de pointes and sudden death due to ventricular arrhythmias. Patients with schizophrenia, particularly those undergoing long-term hospital care, have a higher risk of QTc prolongation.

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Cao et al.[18] reported a prevalence of QTc prolongation of 8.26%, while Yang et al[19] and Ozeki et al. (2010) reported lower prevalences of 4.5% and 2.5%, respectively. Ramos et al.[20], reported that 6% of patients experienced QTc prolongation, with only a small fraction having QTc>500ms.

Differences in QTc cutoff definitions, patient characteristics (age and comorbidities), and antipsychotic type may account for differences in the prevalence of QTc prolongation across studies. The study of Ozeki et al.[21] showed that first-generation antipsychotics such as chlorpromazine, intravenous haloperidol, and sultopride had a higher risk of QTc prolongation than second-generation antipsychotics, most of which did not show a significant effect on QTc prolongation. These findings underscore the importance of ECG monitoring before and during therapy, especially in patients receiving drugs at high risk of prolonging QTc or a combination of drugs that are associated with these risks. Pharmaceutical interventions such as deprescribing high-dose antipsychotics or replacing drugs with a safer QTc profile can be a prevention strategy. In clinical practice, regular QTc screening, correction of electrolyte disorders, and periodic review of treatment regimens are essential steps to reduce the risk of serious arrhythmias in this population

Intervention studies show that clinical pharmacy has an important role in the detection and management of DRP. Hashimoto & Tensho[24] reported that a pharmacist-led, structured intervention was accepted by physicians in 50% of cases and led to DRP resolution. Kibsdal et al. [16] also reported a recommendation acceptance rate of 49% and implementation of 33%. This level of acceptance suggests that, although not all recommendations are accepted, interprofessional collaboration between pharmacists and clinicians has been underway and has made a significant contribution to therapeutic change in about half of the cases in which intervention has occurred. This figure is in line with findings from clinical pharmacy studies in other settings, where pharmacist recommendation acceptance rates generally range from 40-80%, depending on the clinical context, patient complexity, and collaborative culture of the healthcare team.

Several factors can affect the acceptance rate of pharmacist recommendations, including the complexity of psychiatric patients' clinical conditions, differences in perceptions of therapeutic risk-benefit, clinical experience, and interprofessional communication. In psychiatric settings, resistance to changes in therapy regimens may occur due to concerns of symptom recurrence, limited evidence in certain populations, and clinician preferences based on empirical experience. Therefore, an acceptance rate of around 50% can be considered an indication that the integrity of clinical pharmacy services can be improved through more systematic communication strategies, pharmacist involvement in ward rounds, and the implementation of evidence-based drug review protocols.

These findings confirm the need for structured clinical pharmacy services in psychiatric inpatient units, including routine medication reviews, drug interaction monitoring, dose optimization, laboratory outcome monitoring, and ECG. The implementation of integrated clinical pharmacist services has the potential to improve patient safety, therapeutic rationality, and treatment cost efficiency by preventing avoidable DRP.

Conclusions

This systematic review confirms that DRP is a very common problem in inpatient schizophrenia patients, especially polypharmacy, drug interactions, medication selection, and dosage errors, as well as adverse drug reactions such as QTc interval prolongation. This high burden of DRP highlights the urgency of implementing structured clinical pharmacy services, including routine drug reviews and drug therapy monitoring (laboratory test results, ECG, and others). Effective collaboration between clinical pharmacists and physicians, as reflected in the recommended acceptance rate of around 49-50%, has the potential to improve the safety and rationality of drug therapy in inpatient schizophrenia patients.

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Table 3. Summary of the Included Study

Author	Country	Study design	Number of participants	Mean age ± SD (years)	DRP identification method	Types of DRPs	Prevalence of DRPs	Prevalence of manifest DRPs per patient
(Bačar Bole et al., 2023)	Slovenia	Retrospective, Cross-sectional	76: I: 41 C: 35	Not assessed	Medication review from patient records by a Clinical Pharmacist	Polypharmacy and Drug Interaction	71,1% of patients with ≥1 DRPs	Not assessed
(Cao et al., 2021)	China	Retrospective, Cross-sectional	727: I: 436 C: 291	45.99 ± 12.52	ADR (QTc prolongation) was identified through ECG and statistical threshold	Polypharmacy and ADR (QTc prolongation)	54,81% of patients with ≥1 DRPs	8,26% of patients experienced at least one ADR; 15% of patients with DRP developed ADRs.
(Ramos-Ríos et al., 2010)	Spain	Retrospective, Cross-sectional	171	55.8 ± 15.4	QTc analysis via ECG & other clinical data	Polypharmacy and ADR (QTc prolongation)	86% of patients with ≥1 DRPs	6% of patients experience at least one ADR; 6,8% of all patients with DRP develop ADR.
(Hashimoto & Tensho, 2016)	Japan	Retrospective, Quasi-experimental	52 pre: 52 post: 52	51.6±16.8	Medication review from patient records by a Clinical Pharmacist	Polypharmacy and the dose is too high	**Polypharmacy:** Pre-intervention: 73,1% patients experienced antipsychotic polypharmacy. **Dose too high:** Pre-intervention: 46,2% patients received too high doses of CPZ antipsychotics. Post-intervention: 36,5% of patients received too high doses of CPZ antipsychotic	Not assessed
(Grohmann et al., 2014)	German	Analytical cross-sectional (observational pharmacovigilance study; AMSP database)	56.861: I: 3.640 C: 53.221	Not reported	AMSP (routine monitoring by trained psychiatrists, Heavy ADR reporting using standard questionnaires, layered reviews, and expert panel consensus)	ADR classified by organ system (EPMS, Neurologic, hepatic, cardiovascular, endocrine, weight gain, hematologic)	0,38-1,20% of exposed patients with ≥1 DRPs	Not assessed

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(Yang et al., 2011)	China	Cross-sectional naturalistic study	1.006: QTc Prolongation: 45 Non-QTc prolongation: 961	50.2±11.6	QTc measurement by medical personnel using ECG	ADR (QTc prolongation)	DRP/QTc prolongation was observed in 4.5% of patients.	Not assessed
(Ilickovic et al., 2016)	Montenegro, Eropa Selatan	Quasi- Experimental (prospective intervention)	49 patients	54,9±9,5	PCNE V6.2	Effectiveness-related DRPs (P1), ADR (P2), Treatment cost-related DRPs (P3)	100% of patients with ≥1 DRPs (Drug selection 64,1%, dose selection 23,4%, treatment duration 7,6%), 52,5% of patients with ≥1 DRPs (ADR 26,1%, dose too low 20,5%, ineffective drug therapy 20,5%, drug interaction 18,2%)	44.9% of patients experience manifest DRP.
(Temtem et al., 2023)	Ethiopia	Cross-sectional study	118 patients	34,04±11,5	Review of medical records and patient interviews; DRP classification with Cipolle	ADRs, dose too low, ineffective drug therapy, drug interaction, duplicate therapy	52,5% of patients with ≥1 DRPs (ADR 26,1%, dose too low 20,5%, ineffective drug therapy 20,5%, drug interaction 18,2%)	Average of 0.75 DRPs per patient (88 DRPs in 62 patients)
(Kibsdal et al., 2020)	Denmark	Retrospective descriptive study (chart review)	607 patients	Not assessed	Systematic medication review by a clinical pharmacist using an electronic patient chart and PCNE	Drug dosage, inappropriate drug, interaction, ADR, length of treatment, dosing time/interval, medication reconciliation, drug form/strength, non-adherence to guidelines, therapeutic duplication, EPC-related, drug allergies.	87% of patients with ≥1 DRPs Drug dosage (19.9%); Inappropriate drug (16.3%); Interactions (15.6%); Side effects (11.8%); Length of treatment (6.1%); Dosing time & interval (5.9%); Medication reconciliation (5.0%); Drug form & strength (4.8%); Non-adherence to guidelines (3.3%); Therapeutic duplication (2.1%); EPC-related (1.8%); Drug allergies (1.2%)	Average of 2,5 DRPs per medication review
(Ocaña-Zurita et al., 2016)	Mexico	Retrospective cross-sectional study	126 patient	32,8±9,10	Drug interaction checker software + ATC WHO Classification	Potential drug-drug interaction (DDIs)	68,2% of patients with ≥1 DRPs	Not assessed
(Ozeki et al., 2010)	Jepang	Cross-sectional study	1017 patient	42,6±18,2	QTc measurement by medical personnel using ECG	ADR (QTc prolongation)	2,5% of patients with 1 DRP	Not assessed

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