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Unraveling the relationship between the DRPs with PANNS and extrapyramidal symptoms in schizophrenia: Implications for antipsychotic therapy

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ABSTRACT

Schizophrenia is a severe and chronic mental disorder that requires long-term antipsychotic therapy. However, the use of these medications is often accompanied by drug-related problems (DRPs), which affect the effectiveness of treatment and increase the risk of health complications. Objective: This study aims to evaluate the relationship between DRPs and therapy outcomes in schizophrenia patients at Syamrabu Bangkalan Hospital. Methods: A cross-sectional design with a retrospective method was used in this study. The sample was selected through purposive sampling from patients diagnosed with mental disorders who were using antipsychotic drugs. The PANSS scores and the frequency of extrapyramidal events were assessed to evaluate therapy outcomes. The data analysis was conducted using statistical correlation tests. Results: Among the 110 patients studied, 200 cases of DRPs were found, with drug interactions being the most common (42.5%). Correlation analysis showed a significant relationship between the number of drugs consumed and the number of DRPs (p=0.000, r=0.352). However, no significant association was found between the number of DRPs and patient therapeutic outcomes (p=0.340, r=-0.076). Combining atypical and typical antipsychotics proved more effective in reducing PANSS scores and demonstrating a lower risk of extrapyramidal side effects compared to monotherapy. Conclusion: An increase in the number of medications taken by a schizophrenia patient correlates with a higher incidence of DRPs. Therefore, close monitoring and pharmaceutical interventions are needed to optimize therapy and reduce the risk of side effects and complications.

Keywords: schizophrenia, drug-related problems (DRPs), extrapyramidal syndrome, therapeutic outcome.

ABSTRAK

Skizofrenia merupakan gangguan jiwa berat dan kronik yang memerlukan terapi antipsikotik jangka panjang. Namun, penggunaan obat-obatan tersebut sering kali disertai dengan drug related problems (DRPs) yang mempengaruhi efektivitas pengobatan dan meningkatkan risiko komplikasi kesehatan. Tujuan Penelitian ini bertujuan untuk mengevaluasi hubungan DRPs dengan luaran terapi pada pasien skizofrenia di RSUD Syamrabu Bangkalan. Metode: Penelitian ini menggunakan rancangan cross-sectional dengan metode retrospektif. Sampel dipilih secara purposive sampling dari pasien yang didiagnosis gangguan jiwa yang sedang menggunakan obat antipsikotik. Skor PANSS dan frekuensi kejadian ekstrapiramidal dinilai untuk mengevaluasi luaran terapi. Analisis data dilakukan dengan menggunakan uji korelasi statistik. Hasi Dari 110 pasien yang diteliti, ditemukan 200 kasus DRPs, dengan interaksi obat menjadi kasus terbanyak (42,5%). Analisis korelasi menunjukkan adanya hubungan yang signifikan antara jumlah obat yang dikonsumsi dengan jumlah DRPs (p=0,000, r=0,352). Namun, tidak ditemukan hubungan signifikan antara jumlah DRP dan hasil terapi pasien (p=0,340, r=-0,076). Menggabungkan antipsikotik atipikal dan tipikal terbukti lebih efektif dalam mengurangi skor PANSS dan menunjukkan risiko efek samping ekstrapiramidal yang lebih rendah dibandingkan dengan monoterapi. Kesimpulan: Peningkatan jumlah obat yang diminum oleh pasien skizofrenia berkorelasi dengan insiden DRP yang lebih tinggi. Oleh karena itu, pemantauan ketat dan intervensi farmasi diperlukan untuk mengoptimalkan terapi dan mengurangi risiko efek samping dan komplikasi.

Kata kunci: skizofrenia, masalah terkait obat (DRP), sindrom ekstrapiramidal, hasil terapi.

INTRODUCTION

Schizophrenia is a complex mental disorder characterized by a range of symptoms, including disordered and bizarre thoughts, delusions, hallucinations, inappropriate affect, and disturbances in psychosocial functioning. These symptoms significantly disrupt an individual's ability to function in daily life and require a comprehensive treatment approach (Launders et al., 2022a). Moreover, the duration of illness and long-term treatment are associated with a significantly increased risk of developing physical illness (Wien et al., 2024). Antipsychotic medications serve as the cornerstone of management for schizophrenia, aimed at alleviating symptoms and enhancing the quality of life for affected individuals (Cahaya et al., 2024). However, there are risk factors that potentially reduce compliance and continued use of these drugs (Tharanon et al., 2022). One of these risk factors is the occurrence of unwanted reactions or side effects, such as extrapyramidal syndrome (EPS), one of which is akathisia, a movement disorder triggered by the use of antipsychotics (Tadesse et al., 2023).

A study conducted in Indonesia revealed concerning patterns in the treatment of schizophrenia patients with antipsychotic medications (Solmi et al., 2017). It identified a high risk of clinically

relevant drug interactions associated with combination antipsychotic treatments. More than 40% of antipsychotics were prescribed without appropriate indications, and over 50% of patients received two or more antipsychotic medications simultaneously (Nasim et al., 2025). Additionally, long-term exposure to antipsychotic treatment, particularly second-generation antipsychotics, is a known risk factor for developing diabetes mellitus (DM), hypertension, and coronary artery disease (CAD) (Sampogna et al., 2023). A study investigating the occurrence of drug-related problems (DRPs) in patients with depression showed that out of 120 cases, there were 33 cases of DRPs (15.83%) (Ng et al., 2022).

Pharmacists are crucial in optimizing patient therapeutic outcomes by conducting thorough medication reviews and ensuring that treatments are effective, safe, and tailored to individual needs (Rubio et al., 2021). DRPs encompass a range of issues related to actual or potential complications arising from drug therapy, such as side effects and drug-drug interactions. The burden of DRPs is particularly pronounced in psychiatric patients, where the interplay between medication regimens and underlying mental health conditions can exacerbate health complications (Mosolov & Yaltonskaya, 2022). All of the above studies have highlighted poor patterns in antipsychotic prescribing practices, revealing that a substantial percentage of patients receive polypharmacy regimens without clear clinical indications, heightening the risk of drug-related problems (DRPs) and poor health outcomes. As the complexities of managing schizophrenia continue to evolve, it is essential to address the prevalence and impact of DRPs in this population.

Understanding the correlation between DRPs, therapeutic outcomes as measured by the Positive and Negative Syndrome Scale (PANSS), and the incidence of EPS will provide valuable insights for clinicians and pharmacists alike (Mateti et al., 2015). This study seeks to investigate the relationship between DRPs and therapy outcomes in schizophrenia patients at Syamrabu Bangkalan Hospital to identify potential strategies to minimize these problems and optimize patient care.

METHOD

Research design

This study uses a cross-sectional design, emphasizing the simultaneous measurement/observation time collected and the retrospective data collection at Syamrabu Hospital, Bangkalan, Madura, East Java Province, Indonesia. Data collection was carried out by observation method and looking at medical record data on patients with mental disorders at Syamrabu Hospital, Bangkalan, Madura, East Java Province, Indonesia, including demographic data, patient lifestyle, disease history, drugs used (including other drugs used other than mental disorder drugs) and lab results of mental disorder patients. The data about PANSS scoring and the frequency of extrapyramidal events for evaluating therapy outcomes were also assessed. The Health Research Ethics Committee approved this study, Noor Huda Mustofa University, Bangkalan, Madura, East Java Province, Indonesia (Number: 2591/KEPK/UNIV-NHM/EC/VII/2024).

Population and sample

The subject population in this study was obtained from the last 3 months of medical record data of mental disorder patients at Syamrabu Bangkalan Hospital, East Java, from August 2024 to October 2024. Sampling was carried out using purposive sampling, which is a sampling method that has been selected by researchers based on special characteristics, such as patients suffering from mental disorders at Syamrabu Bangkalan Hospital, East Java, who meet the criteria for using mental disorder drugs. The number of samples used was 110 patients. The inclusion criteria for this study were mental disorder patients at Syamrabu Bangkalan Hospital, East Java, who used mental disorder drugs. Patients with complete and transparent medical record data containing patient name, gender, age,

complaints, treatment date, medications used, and others. Meanwhile, patients with incomplete medical record data, severe comorbidities, and pregnant or breastfeeding women were omitted.

Data analysis

The determination of DRPs is based on the Pharmaceutical Care Network Europe (PCNE) standards. Untreated indications may occur if the patient has a medical problem that requires drug therapy (an indication for the use of the drug) but does not receive medication for the indication. Incorrect drug selection occurs if the patient has indications but is using the wrong medication. Subtherapeutic doses may occur if the patient has a medical problem with too few correct medications. Failure to receive medication is a problem that occurs if the patient has a medical problem resulting from not receiving medication (Abouzaid et al., 2014a). An overdose potentially occurs if the patient has a medical problem, namely, getting treatment by receiving too many doses of the drug (toxicity). Adverse drug reactions potentially occur if the patient has a medical problem that is the result of an adverse drug reaction. Drug interactions occur if a patient has a medical problem that is the result of an interaction of drugs or drug-laboratory test interactions. DRPs are assessed based on patient observations and the examination of patient medical record data. The research findings are presented in a table, including descriptive data, and correlation tests are statistically analyzed by Spearman correlation coefficient analysis using SPSS 22.0 software.

RESULTS AND DISCUSSION

Demographic data of 110 participants are presented in Table I. The sample consisted of 73% of patients aged between 21 and 50 years; 98.2% of the subjects were students, and 41.8% were undergraduate students. According to the World Health Organization, 8% of children and 15% of adolescents have a mental disorder. However, the majority of them do not seek help or receive treatment. Suicide is the third leading cause of death in the 15-29 age group. This finding aligns with data at Syamrabu Hospital, Bangkalan City, East Java Province, which occurred in many students' lives.

Table 1. Demographic data of subjects.

Characteristics of respondents	N (%)
Sex	
Man	50 (45.0)
Woman	60 (55.0)
Age (years)	
15-20	17 (15.0)
21-50	80 (73.0)
51-70	13 (12.0)
Education	
Without formal education	2 (1.8)
Elementary school	8 (7.3)
Junior high school	10 (9.1)
High school	44 (40.0)

Undergraduate school	46 (41.8)
Occupation	
Not working	1 (1.0)
Student	108 (98.2)
Employee	1 (1.0)

The results showed that most of the subjects were 73% aged 21-50 years because, according to data from the Basic Health Research (Riskesdas) of the Ministry of Health of the Republic of Indonesia, the prevalence of emotional disorders in people aged 15 years and above increased, from 6% in 2013 to 9.8% in 2018. The prevalence of depression in 2018 is also still relatively high, which is 6.1% (Ministry of Health of the Republic of Indonesia, 2018). For information, cardiovascular disease (36.4%) is the leading cause of illness and death in Indonesia nowadays, followed by neoplasms, maternal-neonatal disorders, respiratory tract infections, and tuberculosis. However, in terms of causes of severity and disability, mental illness had a more significant impact compared to other diseases (Aryastami & Mubasyiroh, 2023). This is based on the research, which is the data in the table, primarily for students aged 15 years and above, and the average.

Table 2. Number of medications used per patient.

Number of drug items per patient	N (%)
1 drug	8 (72)
2 drugs	10 (9.0)
3 drugs	34 (31.0)
4 drugs	36 (33.0)
5 drugs	15 (13.6)
≥6 drugs	7 (6.2)
Total	110 (100.0)

Based on Table II, it is known that the most drug items obtained by each patient are a combination of 4 drugs (33.0%). The combination of the four drugs is an antipsychotic drug. However, there are different classes of drugs, and there are also several drugs given for other diseases or comorbidities, such as antihypertensives and antidiabetics, to overcome symptoms that appear simultaneously with the patient's complaints. This aligns with the previous research, which states that the three highest diseases that become comorbidities are diabetes mellitus with 52 cases, hypertension with 43 cases, and epilepsy with 40 cases (Launders et al., 2022b). In Table III, it is shown that out of 110 respondents, there were many cases of drug-related problems (DRP). DRP analysis was performed based on the drugs used, complaints reported by respondents, and patient behavior during treatment. As many as 200 cases of DRP were identified by 110 patients, with the highest number of DRPs (85 cases, 42.5%) related to the interaction between one drug and another drug or comorbidities.

Table 3. Types of DRP experienced by patients.

Type of DRP	N (%)
Untreated indications	3 (1.5)
Improper selection of drugs	7 (3.5)
Subtherapeutic dosage	1 (0.5)
Failing to receive medication	15 (7.5)
Overdose	2 (1.0)

Adverse drug reactions	75 (37.5)
Drug interactions	85 (42.5)
Use of the drug without indications	12 (6.0)
Total	200 (100.0)

Untreated indications may occur if the patient has a medical problem that requires drug therapy (indications for drug use) but does not receive medication for those indications. A recent study showed 3 cases (1.5%) of untreated indications. In this case, patients complain of various symptoms, including hypertension, cholesterol, restlessness/sleep, and eating disorders (Abouzaid et al., 2014b). However, the doctor only prescribes hypertension and cholesterol medications, not complaints of restlessness, sleep, and eating disorders. Incorrect drug selection potentially occurs if the patient has indications but is using the wrong medication. In this study, there were 7 cases (3.5%) of inappropriate drug selection. A patient who suffers from general anxiety disorders such as difficulty sleeping, difficulty breathing, and irritability are prescribed risperidone medication by the doctor who diagnoses it; anxiety disorders are more effective with the administration of benzodiazepine drugs, namely alprazolam, extrapyramidal side effects of risperidone make patients more anxious and uncomfortable (Marvin et al., 2018).

Table 4. Number of DRPs per patient.

Number of DTP Per Patient	N (%)
0 DRP	15 (13.7)
1 DRP	32 (29.0)
2 DRPs	34 (31.0)
3 DRPs	25 (22.7)
4 DRPs	3 (2.7)
5 DRPs	1 (0.9)
Total	110 (100.0)

Subtherapeutic dosing may occur if the patient has a medical problem with too few doses of the drug being administered. There was 1 case (0.5%) of patients who underwent a dose of subtherapy. The patient gets one of the drugs, namely risperidone, where he only gets a dose of 0.5mg/day, while according to the practical guideline, the dose of risperidone is 2-8mg/day. Patients still hear disturbing noises every day, too low doses are not enough to suppress psychosis symptoms such as hallucinations and delusions, and even patients experience acute psychoses (Kluzek et al., 2022). Failure to receive medication is a problem that occurs when the patient has a medical problem resulting from not receiving medication. Fifteen cases (7.5%) of patients failed to receive medication because the patients had some medical issues, such as diabetes. The patients should have taken olanzapine to treat their mental disorders. However, the patients failed to receive medication because they complained that since taking the drug, their blood sugar had been getting more and more under control. The doctor said that the patients needed insulin even though they could control their blood sugar levels with medication previously. Olanzapine causes increased weight and insulin resistance, thereby worsening the patient's diabetes, so the patient needs safer drugs such as aripiprazole that may be considered (Indriani et al., 2020).

An overdose occurs if the patient has a medical problem, namely, getting treatment by receiving too many doses of the drug (toxicity). There were two patients (1%) who overdosed. The patient took a high dose of diazepam after experiencing very severe stress. The patient complained of drowsiness and could not get up, had difficulty breathing, and felt lightheaded. It is suggested that an overdose of antipsychotic drugs can lead to severe complications. Thus, medical doctors should evaluate the patient's symptoms and awareness and provide the necessary therapy (Arozal et al., 2019). Adverse drug reactions may occur if the patient has a medical problem that is the result of an adverse drug reaction in 75 cases (37.5%) who experience adverse reactions due to drugs. Patients complain of restlessness, unable to sit still, the neck feels stiff, and hands continue to tremble, which is an extrapyramidal side effect caused by antipsychotic drugs such as risperidone and haloperidol, especially antipsychotic drug combinations. The reaction of these drugs is very detrimental and often occurs in patients with mental disorders to antipsychotic drugs. Therefore, medical doctors must monitor closely, and open communication with patients is essential to adjust the dosage and prevent further complications (Alshaikhmubarak et al., 2023).

Drug interactions occur if a patient has a medical problem that is the result of an interaction of drugs or drug-laboratory test interactions. 85 cases (42.5%) experienced drug interactions. Like risperidone and haloperidol, and not only fellow antipsychotic drugs, but sometimes patients get polypharmaceutical therapy, which consists of several comorbidities such as hypertension and diabetes. Most patients complained that they were very sleepy and had difficulty getting out of bed; they often felt dizzy as if they wanted to faint, and they felt weak and had difficulty concentrating. The interaction of these drugs must be considered; if the combination of drugs is not needed, then use other drugs or give the lowest possible dose because it will cause severe complications in the patient. Unindicated use of the drug occurs if the patient takes the drug without a valid medical indication. There were 12 cases (6%) of patients using the drug without indications. Patients complain of not getting therapy, but instead experience adverse side effects. Patients get alprazolam, which is taken primarily for patients with severe anxiety disorders; patients should get the appropriate medications, such as risperidone or haloperidol.

Table 5. Distribution of antipsychotics in schizophrenia patients.

Types of Antipsychotics	N (%)
Typical:	
Haloperidol	21 (19.1)
Chlorpromazin-haloperidol	10 (9.1)
Trifluoperazin-chlorpromazine	5 (4.5)
Flufenazin-trifluoperazine	0 (0)
Subtotal	36 (32.7)

Atypical	
Risperidone	58
Risperidone-olanzapin	6
Risperidone klozapin	0
Subtotal	64
Typical-Atypical Combinations	
Haloperidol-klozapin	6
Resperidone-haloperidol	4
Subtotal	10
Total	110

Based on Table 4, most patients experienced two drug-related problems in 34 cases (31%), while 15 patients (13.7%) did not experience drug-related problems. Furthermore, most patients experienced interactions between the prescribed drug combinations. In Table 5, the findings showed that the most common therapy using antipsychotic drugs is atypical antipsychotics, with a total of 64 (58.2%), consisting of risperidone and risperidone-olanzapine (Table 5). This study also found that the atypical-typical combination antipsychotic drug group was more effective in lowering the PANSS score compared to the treatment of the atypical and typical groups. Based on the study results, the antipsychotic group combined with the atypical-typical group was more effective in lowering the PANSS score than the atypical and typical or other antipsychotic groups (Table 6). The combination of atypical and typical antipsychotics is more effective in treatment, as it has a lower risk of side effects in causing EPS compared to the use of atypical or typical antipsychotics separately (Table 7).

Table 6. Assessment of PANSS scoring for schizophrenic patients.

Measurement	Domain	Antipsychotic Group		
		Atypical	Typical	Atypical-Typical
PANSS Scoring before the initiation of treatment	Positive	31.02±1.26	28.88 ±1.26	32.42±1.23
	Negative	28.54±9.54	28.66±8.49	32.28±9.01
	Psychopathology	53.93±1.88	64.55±2.72	66.14±2.17
PANSS Scoring after antipsychotic treatment	Positive	15.88±6.53	15.77 ±7.53	14.28±2.71
	Negative	14.75±3.19	15.42±5.13	15.42±5.13
	Psychopathology	34,13±1,41	45.55±1.61	46.14±3.12
Final Scoring PANSS	Positive	15.14±1.86	14.11 ±3.79	18.14±8.76
	Negative	13.79±1.99	14.88±6.12	17.85±6.75
	Psychopathology	19.80±1.21	14.11±3.79	18.14±8.76
Total		43.34±31.2	41.66±24.5	55.00±12.1

Based on correlation analysis with the Spearman test, this study found that the number of drugs

consumed and DRPs in schizophrenia patients were positively and significantly correlated, as represented by p = 0.000 and correlation coefficient = 0.352 (Table 8). Thus, this study found a phenomenon that the more patients consumed medication, the higher the DRPs they experienced. Meanwhile, the relationship between the number of DRPs and treatment outcomes of schizophrenia patients did not show a significant correlation (p = 0.340 and correlation coefficient = -0.076), indicating the possibility of involvement of other factors that affect therapeutic outcomes in this phenomenon, and is interesting for further exploration.

Table 7. Number of DRPs per patient.

Antipsychotics	N (%)	EPS Frequency
Atypical	64 (58.2)	7
Typical	36 (32.7)	8
Atypical-Typical	10 (9.1)	3

Table 8. Correlation analysis between the number of DRPs and the number of drugs and the therapeutic outcome.

Variables	Number of DRPs
Number of drugs	p value = 0.000[a] Spearman correlation coefficient = 0.352
Therapeutic outcomes	p value = 0.340[b] Spearman correlation coefficient = -0.076

[a] There is a significant correlation between the number of drugs and the number of DRPs ($p < 0.05$).

[b] There is no significant correlation between the number of DRPs and therapeutic outcomes ($p > 0.05$).

CONCLUSIONS

The findings of this study showed a significant relationship between the number of drugs used by patients and the number of DRPs per patient. This study displayed clear evidence that the collaboration of pharmacists and medical doctors to improve and monitor the drugs used for schizophrenic patients is crucial to prevent various DRPs such as untreated indications, improper drug selection, subtherapeutic doses, failure to receive medication, overdose, drug interactions, and unindicated drug use.

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