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A Cross-Sectional Pharmacovigilance Study of Adverse Drug Reactions in Patients with Mental Health Disorders at the Social Rehabilitation Yogyakarta

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Abstract

Background: *Chronic mental health disorders require long-term psychopharmacotherapy, frequently necessitating complex psychotropic combination regimens that significantly elevate the risk of experiencing adverse drug reactions (ADRs).* ***Objective:*** *This study aimed to systematically identify specific ADR types, rigorously evaluate their clinical causality using the standardized Naranjo algorithm, and analyze the correlation between medication regimen complexity and the resulting causality scores.* ***Methods:*** *A descriptive, cross-sectional, observational study was conducted in July 2025 at the Social Rehabilitation Yogyakarta. A total sampling technique was successfully employed to recruit participants (N=27).* ***Results:*** *A total of 11 ADR types were identified, with drowsiness and tremors being the most prevalent clinical manifestations, affecting 85.2% of patients. Standardized causality analysis categorized 23 cases (85.2%) as possible, 3 (11.1%) as doubtful, and 1 (3.7%) as probable. Notably, the highest causality score was observed exclusively under clozapine monotherapy, whereas highly complex five-drug combination therapies were associated with doubtful classifications. Spearman's rank correlation analysis revealed a moderate negative trend between the number of combined drugs within a regimen and Naranjo causality scores ($\rho = -0.42$), although this relationship was not statistically significant ($p = 0.08$). This negative correlation clinically highlights how overlapping side-effect profiles in combination therapies confound definitive drug-ADR attribution.* ***Conclusion:*** *ADRs are highly prevalent in psychiatric rehabilitation settings. While combination therapy remains a standard clinical necessity for complex cases, increasing regimen complexity significantly obscures causality assessments due to cumulative neuroreceptor blockades. These findings underscore the critical need for intensive pharmacovigilance and individualized medication monitoring to enhance patient safety and optimize therapeutic outcomes.*

Keywords: *Drug-Related Side Effects and Adverse Reactions; Mental Disorders; Psychotropic Drugs*

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INTRODUCTION

Mental health disorders are a global health issue, with more than 970 million people worldwide experiencing these conditions, particularly anxiety and depression, which impact productivity, social relationships, and quality of life [1]. In 2022, the results of the I-NAMHS survey showed that 15.5 million adolescents (34.9%) experienced mental health problems, and 2.45 million adolescents (5.5%) experienced mental disorders. The 2023 Indonesian Health Survey (SKI) stated that the national prevalence of depression in 2023 was 1.4%, with the 15-24 age group having the highest rate of depression at 2%, but they had the least access to treatment at 10.4%. In Yogyakarta Province, there has been a 9.3% increase in cases of severe mental illness, such as psychosis or schizophrenia, based on symptoms: 1% for depression, 3.7% for anxiety disorders, 0.9% for Secondary Post-Traumatic Stress Disorder (SPTSD), and 0.5% for Attention Deficit Hyperactivity Disorder (ADHD) [2].

Common types of mental disorders in society include depression, bipolar disorder, anxiety disorders, schizophrenia, eating disorders, obsessive-compulsive disorder (OCD), and post-traumatic stress disorder (PTSD) [3]. Management of this condition uses psychopharmaceutical drugs such as antipsychotics, antidepressants, antianxiety drugs, and mood stabilizers. However, long-term use of medication often causes adverse drug reactions that can interfere with patient compliance with treatment [4].

Drugs that have anticholinergic properties, such as antipsychotics and antidepressants, can cause adverse drug reactions, both peripheral and central. Peripheral or systemic effects include dry mouth (associated with dental caries), anhidrosis, tachycardia, constipation or decreased intestinal motility, vomiting, urinary retention, blurred vision, and narrow-angle glaucoma [5,6]. Central effects include cognitive impairment and memory loss [5]. These central effects of anticholinergics are particularly concerning in elderly individuals, given decreased cholinergic reserve in the aging brain [7]. Studies suggest that centrally acting anticholinergics may worsen cognitive dysfunction associated with schizophrenia, with negative impacts on cognitive and psychosocial rehabilitation and activities of daily living [8,9]. There is a risk of medication abuse and suicide with the use of Alprazolam. For the first time, adverse drug reactions related to the cardiovascular system and platelet function have been revealed. Reports of serious adverse events resulting in “hospitalization” and “death” reached 30.96% and 21.86%, respectively. This study highlights the risks of suicide and abuse from Alprazolam use [10]. Mood stabilizers and second-generation antipsychotics have been associated with insomnia and suicide. In addition to clozapine as a second-generation antipsychotic, it is associated with a significantly increased chance of developing insomnia. For mood stabilizers other than lithium, there have been reports of significant side effects, including suicide deaths [11].

The large number of reports and incidents of dangerous side effects from psychopharmaceutical drugs makes it important for patients and all medical personnel to pay attention. Pharmacovigilance activities are related to the prevention of adverse drug reactions or the collection, detection, assessment, understanding, and prevention of adverse drug reactions or problems related to the use of drugs [12].

An adverse drug reaction is an undesirable and noxious response to a drug that occurs at doses normally used in humans for the prevention, diagnosis, or therapy of disease or for the modification of physiological function [13]. Although adverse drug reaction monitoring is now a mandatory procedure to observe negative reactions to medication, reporting of adverse drug reactions for psychiatry in Indonesia, including in Yogyakarta, is still low, with a reporting rate of only 2.4% [14]. Therefore, pharmacovigilance aims to improve patient safety by assessing treatment safety and the potential for individual ADRs [15].

The Social Rehabilitation Yogyakarta, as a technical implementing unit under the Independent Social Services of Yogyakarta Province, provides social rehabilitation services to psychotic patients who have received medical treatment. Patients at SRCBKL are people with mental disabilities with a diagnosis of a mental disorder that a psychiatrist has confirmed. The novelty in this study is to examine pharmacovigilance regarding adverse drug reactions in patients with mental disorders at the Social Rehabilitation Yogyakarta, especially the use of psychopharmaceuticals, which until now has been carried out only to a limited extent.

MATERIALS AND METHODS

Materials

The research sample used the total sample method, with data obtained from 27 respondents who met the inclusion and exclusion criteria. Sampling was conducted in July 2025. Inclusion criteria included being over 18 years of age, being diagnosed by a psychiatrist with a mental disorder, using psychopharmaceutical drugs, and being willing to participate by signing a consent form. The exclusion criteria for this study included patients with chronic kidney disease, as this condition can mimic adverse drug reactions.

Tools

The adverse drug reaction form is used to identify the drug type, duration of use, and the adverse drug reaction. To assess whether the drug itself causes an adverse drug reaction, the Naranjo instrument was used, with scores of 0 (doubtful), 1-4 (possible), 5-8 (Probable), and 9+ (Highly Probable).

Method

The research design was a cross-sectional observational study to explore the types of adverse drug reactions and to assess causality scores. Ethical Considerations: The research titled A Cross-Sectional Pharmacovigilance Study of Adverse Drug Reactions in Patients with Mental Disorders at the Social Rehabilitation Yogyakarta obtained ethical approval from the Ethics Commission of Achmad Yani University, Yogyakarta, under number Skep/261/KEP/VI/2025. Data collection was conducted through direct interviews with patients or their families and with the health workers who treated the patients, using the adverse drug reaction form and the Naranjo instrument. Data Analysis: Data were analyzed using descriptive statistics in Microsoft Excel to calculate the frequency distribution and percentage of adverse drug reaction types.

RESULTS AND DISCUSSION

This study was conducted for 1 month in July 2025 and included all 27 patients who met the research criteria. The distribution of patients' characteristics is shown in Table 1. In men, masculine traits are associated with strength, dominance, and privilege over women. These traits make it difficult for men to express emotions, and they tend to keep their sadness and fear to themselves. Men also exhibit aggressive and violent tendencies, so adherence to these rigid masculine norms can lead to worse mental health outcomes than for women[18]. The education level of most patients in this study was secondary education, with 33% completing high school and 30% junior high school, followed by elementary education (22%) and a diploma or bachelor's degree (15%). These results indicate that, in formal education at the junior and secondary school levels, the incidence of mental disorders is higher than in diploma/bachelor's degrees.

Formal education at the junior and secondary school levels produces proficient, creative, and environmentally conscious users of today's technology. This generation has experienced significant social, administrative, and technological changes compared with prior generations. They tend to prioritize efficiency and convenience, driven by social media platforms that emphasize speed and instant gratification [19]. In addition, the COVID-19 pandemic has affected mental health, especially among this generation, who are constantly exposed to pandemic-related information, thereby increasing their stress levels [20]. The majority weighed 40-60 kg (67%), an important factor in pharmacotherapy because it affects drug distribution and metabolism [21]. All respondents were of Javanese ethnicity (100%), consistent with Yogyakarta's demographics. The most common diagnosis was schizophrenia (89%), followed by bipolar disorder (7%) and depression (4%), indicating a predominance of severe mental disorders requiring complex, long-term treatment.

Table 1 describes the characteristics of the patients in this study. The age categories in this study are based on the Ministry of Health criteria: adults (18–59 years) and older adults (60+ years). Among patients with mental disorders, most were adults (24, 89%). The growing use of electronic communication and digital media has likely changed how social interactions are conducted, thereby influencing mood disorders in adults compared with older adults [16]. In this study, the proportion of male patients with mental disorders (59%) was higher than that of females (41%). These results may be due to men being less likely than women to accept their life situations. A prior study indicates that men are at a greater risk of developing mental disorders (by 2.48%), which may be attributed to their lower capacity to accept life circumstances compared to women [17].

Table 1. Characteristics of patients with mental disorders in the Social Rehabilitation Yogyakarta

Characteristics	Category	Number (n)	Percentage (%)
Age	Adults (18-59 years old)	24	89%
	elderly (> 60 years old)	3	11%
Gender	Male	16	59%
	Female	11	41%
Highest Level of Education	Elementary school	6	22%
	Junior high school	8	30%
	High school	9	33%
	Diploma/bachelor's degree	4	15%
Occupation	Employed	0	0%
	Unemployed	27	100%
Duration of Illness	0-5 years	21	78%
	6-10 years	4	15%
	11-15 years	2	7%
Duration of Treatment	<1 year	6	22%
	1-3 years	11	41%
	>3 years	10	37%
Weight	40-60 kg	18	67%
	41-70 kg	5	18%
	71-80 kg	4	15%
Ethnicity	Javanese	27	100%
Diagnosis	Bipolar	2	7%
	Depression	1	4%
	Schizophrenia	24	89%

Table 2 describes the use of antipsychotic drugs and their types among patients with mental health disorders at the Social Rehabilitation Yogyakarta. In this study, medication use among patients with mental health disorders included typical and atypical antipsychotics, anticholinergics, selective serotonin reuptake inhibitors (SSRIs), and benzodiazepines. These classes of drugs are standard therapy for patients with bipolar disorder, depression, and schizophrenia [22,23]. Psychiatrists at the Social Rehabilitation Yogyakarta identified diagnoses in this study, including bipolar disorder, depression, and schizophrenia. Patients with mental health disorders, including schizophrenia, typically receive antipsychotic therapy, both typical and atypical. Both typical and atypical antipsychotic drugs can cause extrapyramidal effects such as tremors, rigidity, akathisia, and dystonia [24]. In addition to extrapyramidal effects, other adverse drug reactions with antipsychotics can include dizziness, drowsiness, weakness, constipation, and blurred vision [24].

Table 2. Clinical distribution of psychopharmacotherapy regimens, classifications, and Naranjo causality scores

Drug Regimen	Therapeutic Classification	Number of Patients (n)	Number of Combined Drugs	Naranjo Score (Causality)
Clozapine	Atypical antipsychotic	1	1	5 (Probable)
Clozapine + Risperidone	Atypical antipsychotics	3	2	2 (Possible)
Clozapine + Haloperidol	Atypical and typical antipsychotics	1	2	2 (Possible)
Clozapine + THP	Atypical antipsychotic and anticholinergic	2	2	2 (Possible)
Clozapine + Fluoxetine	Atypical antipsychotic and SSRI	1	2	2 (Possible)
Haloperidol + Aripiprazole	Typical and atypical antipsychotics	1	2	2 (Possible)
THP + Risperidone + Fluoxetine	Anticholinergic, atypical antipsychotic, and SSRI	2	3	0 (Doubtful)

Drug Regimen	Therapeutic Classification	Number of Patients (n)	Number of Combined Drugs	Naranjo Score (Causality)
THP + Risperidone + Clozapine	Anticholinergic and atypical antipsychotics	5	3	2 (Possible)
THP + Risperidone + Lorazepam	Anticholinergic, atypical antipsychotic, and benzodiazepine	1	3	2 (Possible)
THP + Risperidone + Haloperidol	Anticholinergic, atypical, and typical antipsychotics	1	3	2 (Possible)
Risperidone + Clozapine + Stelazine	Atypical and typical antipsychotics	1	3	2 (Possible)
THP + Clozapine + Stelazine + Sodium valproate	Anticholinergic, atypical/typical antipsychotics, and anticonvulsant	1	4	2 (Possible)
THP + Lorazepam + Olanzapine + Sodium valproate	Anticholinergic, benzodiazepine, atypical antipsychotic, and anticonvulsant	1	4	2 (Possible)
THP + Risperidone + Clozapine + Sodium valproate	Anticholinergic, atypical antipsychotics, and anticonvulsant	2	4	2 (Possible)
THP + Risperidone + Clozapine + Soroquin	Anticholinergic and atypical antipsychotics	1	4	2 (Possible)
THP + Risperidone + Clozapine + Soroquin + Sodium valproate	Anticholinergic, atypical antipsychotics, and anticonvulsant	1	5	0 (Doubtful)
THP + Stelazine + Risperidone + Clozapine + Sodium valproate	Anticholinergic, typical/atypical antipsychotics, and anticonvulsant	1	5	2 (Possible)
THP + Risperidone + Aripiprazole + Lorazepam + Sodium valproate	Anticholinergic, atypical antipsychotics, benzodiazepine, and anticonvulsant	1	5	2 (Possible)
Total		**27**		

*Note.*THP: Trihexyphenidyl; Stelazine: Trifluoperazine HCl 5 mg; Soroquin: Quetiapine Fumarate; SSRI: Selective Serotonin Reuptake Inhibitor

Combining risperidone and clozapine can cause mild adverse drug reactions, including bradykinesia, muscle stiffness, tremor, dystonia, akathisia, and dyskinesia [24,25]. In this study, the relationship between the number of drug combinations and the Naranjo score yielded a p-value of 0.08 (>0.05) and a Spearman's rho (ρ) of −0.42 (Table 3). Spearman correlation analysis revealed a negative correlation between the number of drugs in the combination therapy and the Naranjo score (ρ = −0.42). This indicates a trend in which the Naranjo score tends to be lower as the number of drugs in a regimen increases. However, this relationship was not statistically significant (p = 0.08); thus, there is insufficient evidence to conclude that regimen complexity, as measured by the number of drugs, is associated with adverse drug reaction causality scores according to the Naranjo scale.

Spearman correlation analysis was performed to assess the relationship between the number of prescribed drugs and the Naranjo causality scores (Table 3). The analysis revealed a moderate negative correlation (ρ = -0.42), indicating a trend where the certainty of ADR causality (Naranjo score) tends to decrease as the number of drugs in a regimen increases. However, this relationship was not statistically significant ($p = 0.08$). Consequently, there is insufficient statistical evidence to conclude that regimen complexity intrinsically dictates the causality score.

Table 3. Correlation analysis between the number of prescribed drugs and causality categories

Variables	Spearman's ρ	p-value
Number of combined drugs vs Naranjo score	-0.42	0.08

Despite the non-significant correlation, the negative trend in causality scores underscores a common clinical challenge in psychiatric polypharmacy: as the number of concurrent medications increases, identifying the single causative agent for an adverse event becomes increasingly difficult because of overlapping side-effect profiles. The specific occurrences and types of ADRs observed in this study are shown in Figure 1.

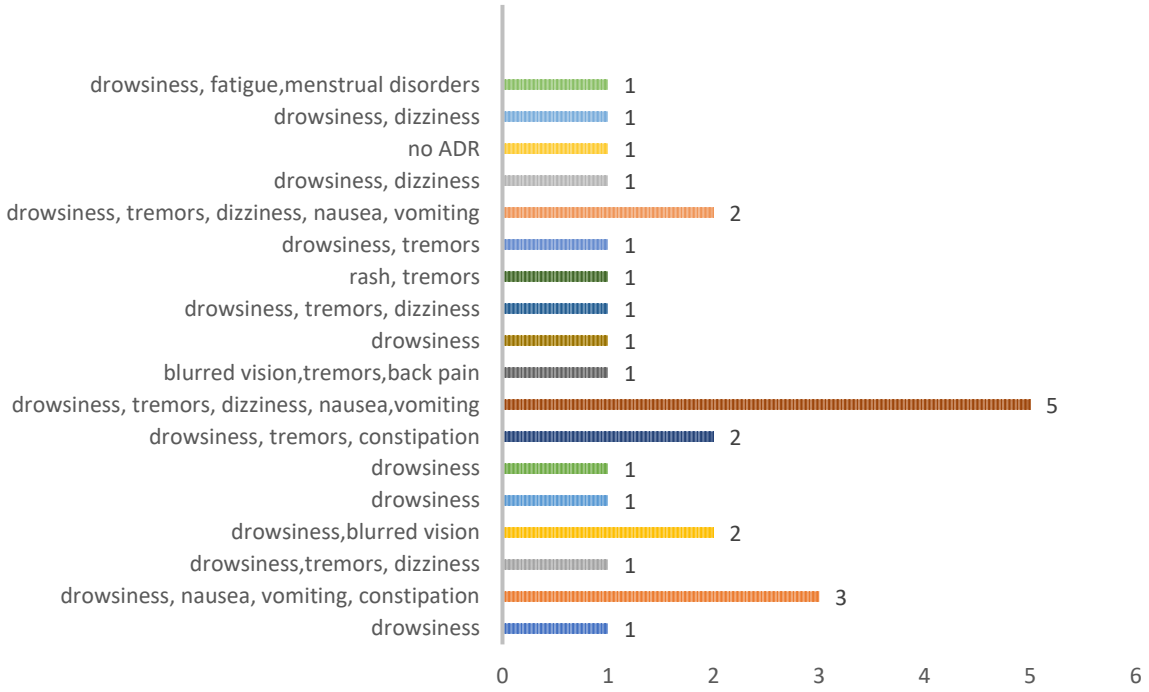

Figure 1. The occurrence of adverse drug reactions from the use of antipsychotic drugs, either singly or in combination (n=27)

Figure 1 shows the incidence of adverse drug reactions associated with antipsychotic use, either alone or in combination, among patients at SRCBKL. The five SRCBKL patients who received a combination of clozapine, risperidone, and THP experienced adverse drug reactions, including drowsiness, tremors, dizziness, nausea, and vomiting. Trihexyphenidyl (THP) is an anticholinergic agent used to treat symptoms such as tremors, seizures, stiffness, and poor muscle control [26]. In the five patients who received the combination of risperidone and clozapine, additional drugs, such as the anticholinergic THP, were given to mitigate adverse drug reactions, even though adverse drug reactions still occurred despite THP. In addition to the combination of these three drugs, this study also identified two combinations of atypical antipsychotic drugs (clozapine-risperidone) in 3 patients. Adverse drug reactions associated with this combination include drowsiness, nausea, vomiting, and constipation. In theory, adverse drug reactions in the form of drowsiness and constipation can occur when administering the antipsychotic clozapine [27]. Meanwhile, according to the theory, the most common adverse drug reactions of risperidone are drowsiness, headache, and fatigue [22].

Then, another combination involving the atypical antipsychotic (clozapine) and the anticholinergic (THP) was administered to two patients. In this study, this drug combination caused adverse drug reactions such as drowsiness and blurred vision. The occurrence of adverse drug reactions from both drugs is in accordance

with existing theory, which states that they can cause sedation, constipation, tachycardia, and arrhythmia [27]. The combination of an anticholinergic (THP), an atypical antipsychotic (risperidone), and an SSRI (fluoxetine) was studied in two patients. This combination resulted in adverse drug reactions such as drowsiness, tremors, and constipation. These symptoms are similar to those of SSRI-class drugs, such as fluoxetine, which are usually prescribed for patients with depression and generally cause adverse drug reactions such as nausea, vomiting, insomnia, drowsiness, headache, decreased sex drive, and agitation [28]. The average group of patients who received the combination of typical and atypical antipsychotics experienced adverse drug reactions (Table 4), such as drowsiness. This finding is also in accordance with the existing theory that general use of antipsychotics can cause several adverse drug reactions, such as weight gain, metabolic dysregulation, drowsiness, and anticholinergic adverse drug reactions [27].

Table 4. Distribution of Naranjo causality categories in the Social Rehabilitation Yogyakarta

Naranjo Score Range	Causality Category	Frequency (n)	Percentage (%)
≥ 9	Highly probable	0	0.0
5–8	Probable	1	3.7
1–4	Possible	23	85.2
≤ 0	Doubtful	3	11.1
Total		**27**	**100.0**

Table 4 shows the distribution of Naranjo causality categories in 27 patients at SRCBKL who received a combination of typical and atypical antipsychotics. These categories include ‘Highly Probable’ (the drug is highly likely to cause the adverse drug reactions), ‘Probable’ (likely caused by the drug), ‘Possible’ (potentially caused by the drug), and ‘Doubtful’ (unlikely to be related to the drug). In this study, the adverse drug reactions experienced by 23 (85%) patients receiving antipsychotic drugs were classified as possible. The treatment regimen consisted of a combination of two to five medications, including risperidone, clozapine, sodium valproate, trihexyphenidyl, aripiprazole, haloperidol, lorazepam, olanzapine, trifluoperazine, fluoxetine, and quetiapine. Adverse drug reactions categorized as 'possible' included drowsiness, nausea, vomiting, constipation, tremors, dizziness, blurred vision, back pain, rash, fatigue, and menstrual disorder. In this study, one patient receiving clozapine experienced an adverse drug reaction that fell into the 'Probable' category. Three patients treated with either the THP-risperidone-fluoxetine or the THP-risperidone-clozapine-quetiapine-sodium valproate combination experienced adverse drug reactions that fell into the 'Doubtful' category, including drowsiness, tremors, and constipation.

The variations in adverse drug reactions observed in patients at the Social Rehabilitation Yogyakarta could be attributed to drug interactions with various receptors in the brain. Typical antipsychotics have a very high affinity for dopamine receptors. If dopamine receptor blockade in the nigrostriatal pathway exceeds 80%, the patient will almost certainly experience extrapyramidal symptoms (EPS), such as tremors and dystonia. Atypical antipsychotics have a lower affinity for dopamine receptors but bind strongly to serotonin, histamine, and muscarinic receptors; consequently, they rarely cause EPS, but instead trigger metabolic adverse drug reactions (such as weight gain) and severe sedation [28].

CONCLUSION AND SUGGESTIONS

This study identified eleven types of adverse drug reactions (ADRs) among patients at the Social Rehabilitation Yogyakarta, with drowsiness, nausea, and tremors the most common. Causality assessment using the Naranjo algorithm classified 85.2% of these reactions as "possible," and a "probable" relationship was observed only in a patient on clozapine monotherapy. Notably, complex multidrug regimens, including a five-drug combination, were associated with "doubtful" causality scores. Statistical analysis showed a moderate negative correlation between the number of medications and Naranjo scores ($r = -0.42$; $p = 0.08$), indicating that increasing regimen complexity is necessary to identify a single causative agent.

Given these findings, intensive pharmacovigilance monitoring is crucial in social rehabilitation settings to improve patient safety during combination therapy. Healthcare providers should prioritize personalized medication reviews to effectively differentiate ADRs from underlying psychiatric symptoms. Additionally, future research with larger cohorts is needed to further confirm the clinical impact of treatment complexity on adverse outcomes in chronic mental health care.

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CONFLICT OF INTEREST

The authors declare that they have no conflicts of interest.

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