

# Drug utilization study of mood stabilizers and antipsychotics drugs among bipolar disorder patients

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**Abstract.** A key component of SDG 3, which is about good health and wellbeing, is mental illness. The burden of disease and mental illness is a priority for global development. Bipolar is a mental illness that causes unusual changes in mood, energy, physical activity, and concentration. Combinations of mood stabilizers and antipsychotic drugs have significantly altered the long-term prognosis for bipolar patients. This study aims to evaluate the drug utilization of mood stabilizers and antipsychotics in bipolar disorder patients. We conducted a retrospective, descriptive, hospital-based cross-sectional study among bipolar patients attending the psychiatric department at Hospital X, Yogyakarta, Indonesia, from January to May 2017. This study employed two methods to analyse the data: calculating the percentage of rational prescriptions and computing based on the defined daily dose (DDD) per 1000 patient days. In this study, there were 28 respondents between the ages of 26 and 46, with 98 total bipolar cases. 53.6% of participants were female, while 46.4% were male. The rational use of the concurrent administration of mood stabilizers and antipsychotics to patients with bipolar disorder was as follows: 69.39% precise use, 90.82% precise dose, 98.98% precise indication, 76.53% precise patient, and 76.53% precise drug. The result showed that mood stabilizer lithium had the lowest total annual consumption of 2.15 DDD/1000 outpatient visits, and sodium divalproex had the highest total annual consumption of 26.66 DDD/1000 outpatient visits. Risperidone was the antipsychotic with the highest quantity, at 25.92% DDD/1000 outpatient visits, while trifluoperazine had the lowest, at 0.17% DDD/1000 outpatient visits.

## 1 Introduction

Bipolar disorder is distinguished by profound fluctuations in mood, manifesting as manic and depressive episodes [1]. In episodes of mania, individuals feel extreme euphoria from every activity or become unusually active (hyperactive), which is associated with emotional disturbances [2]. While depressive episodes are characterized by the main symptoms, namely: depression, loss of interest and excitement, lack of energy, fatigue and decreased activity, and thoughts of death or suicide [3]. Bipolar disorder patients employ both

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antipsychotics and mood stabilizers therapeutically to modify their affective states. Globally, mood stabilizers like lithium carbonate, valproic acid, and carbamazepine serve as the primary treatment agents during the manic phase of bipolar disorder. Additionally, pharmacological treatment of the bipolar mania phase may involve antipsychotics. Antipsychotics have an important role in diminishing manic symptoms, agitation, and aggression in acute mania [4][5]. The concurrent use of antipsychotics and mood stabilizers may increase the incidence of severe adverse drug reactions and significant drug interactions, as well as reduce medication adherence [6]. Therefore, it is critical to assess the use of these medications in light of their rationality and quantity.

Rational drug use refers to the systematic practice of prescribing, dispensing, and administering medications to patients in a manner consistent with their clinical needs [7]. Appropriate indication, patient, drug, information, and evaluation are several criteria for rational drug use. Irrational drug use has numerous kinds of negative consequences, including changes in treatment quality and services, treatment costs, and the possibility of unexpected side effects [8][9]. Because it can classify and measure drug use, the ATC/DDD (Anatomical Therapeutic Chemical/Defined Daily Dose) method, which measures drug amount, has become a popular way to advance drug use research. The defined daily dose (DDD) is a technical unit of measurement that is described as "the assumed average maintenance dose per day for a drug intended for its primary indication in adults" [10]. As a method of drug use evaluation research, the ATC/DDD approach aims to enhance the quality of drug use. One of its components is to compare drug consumption at the international level or between health care systems [11]. Most middle-income nations, particularly Indonesia, currently have limited data on drug consumption for treating bipolar disorder. As a result, it is necessary to conduct research on the rationality and quantity of using combined mood stabilizers and antipsychotic drugs in bipolar patients. With a great commitment to prioritize "prevention and treatment of non-communicable disease by 2030, our study, in accordance with Sustainable Development Goal 3, seeks to ensure the health and well-being of all individuals.

## **2 Material and Methods**

This study was a descriptive cross-sectional design that involves collecting data retrospectively. We derived data for this study from electronic medical records of outpatients with bipolar disorder who visited Hospital X from January through May 2017. The scope of drug use evaluation includes the right indication, the right patient, the right drug, the right dose, and the total amount of mood stabilizer and antipsychotic drug. The inclusion criteria in this study were: outpatients diagnosed with bipolar disorder according to the International Classification of Diseases (ICD) codes F31.1, F31.2, F31.4, F31.5, and F31.6; received a combination regimen of both mood stabilizers and antipsychotic drugs; and had complete medical records. We excluded pregnant and breastfeeding women from this study.

### **2.1 Research and procedure**

We carried out the study in three phases: the initial preparation stage, the data gathering stage, and the data processing stage. During the initial stage, we collected literature studies and reviews, prepared a thesis proposal, and obtained ethical clearance and research permits. During this stage, researchers retrospectively collected research data from the medical records of bipolar disorder patients undergoing outpatient care at Hospital X Yogyakarta between January and May 2017. During the data collection stage, researchers gathered data from the medical records of bipolar disorder outpatients receiving mood stabilizers and antipsychotic drugs at the Hospital X in Yogyakarta between January and May 2017. We then categorized the extracted data from the medical records based on the following factors:

age, gender, complications, educational degree, occupation and health insurance. We additionally employed the ATC/DDD method to determine the frequency of antipsychotic and mood stabilizer use among patients diagnosed with bipolar disorder.

## **2.2 Data analysis**

We evaluated the data using descriptive analysis to determine the rationality of drug use. This included calculating the percentage of the four key factors, known as the 4Rs (right indication, right patient, right drug, and right dose). The right indication is the accuracy of the indication, which ensures that the patient obtained the right medication to achieve the main goal of therapy. The right patient ensures that the medication reaches the intended patient. The right drug guarantees that the administered medication matches the prescribed drug in the correct form for the prescribed route. By administering medications at the correct dosage, the right dose prevents errors related to incorrect dosages, unit conversions, and substance concentrations. ATC/DDD method was used to analyze data for drug use quantity. The study evaluated mood stabilizers and antipsychotic drugs used by outpatients with bipolar disorders from January to May 2017.

## **3 Results and Discussion**

Patients diagnosed with bipolar disorder and currently receiving combination therapy involving mood stabilizers and antipsychotic drugs met the eligibility criteria for this study. Among the 40 patients, only 28 patients (or 98 cases) fulfilled the specified criteria. The study excluded twelve patients due to incomplete data and pregnancy.

### **3.1 Patient Characteristics**

#### *3.1.1 Patient characteristic according to gender*

The data was obtained from the medical records of patients, which included 13 male patients (46.4%) and 15 female patients (53.6%). Table 1 indicated a higher prevalence of female patients compared to male patients. According to the previous study reported women in middle age experience a significant prevalence of mental disorders [12]. Furthermore, it is crucial to take into account the distinct mental health consequences for women, in addition to the larger proportion of female participants in this research. A research highlights the significant prevalence of mental disorders among women, particularly during middle age [13]. This emphasizes the crucial need for mental health awareness and support for female patients. The higher incidence of bipolar disorder in women underscores the necessity for focused interventions and resources to tackle the distinct mental health difficulties encountered by women.

#### *3.1.2 Patient characteristic according to age*

Table 1 presented the age distribution of bipolar patients who received outpatient care at Hospital X in Yogyakarta. The results for the age group 17–25 years indicated that there were 10 patients, representing 35.71% of the total. Among individuals aged 26–45 years, there were a total of 17 patients, accounting for 60.71% of the overall respondents. Out of the total number of patients, only one individual, which accounts for 3.6% of the total, is classified into the age category of 46–65 years. There is a significant difference from previous study, which states that most of all bipolar cases occur at the age of 25 [14]. Bipolar disorder usually

develops during the later stages of adolescence or the early stages of adulthood [15]. The typical age at which bipolar disorder first appears is 20 years, although it may develop in individuals ranging from early childhood to their mid-40s. Individuals with the bipolar disorder who are over the typical age of 60 are more likely to develop other illnesses as a result of it [16].

### ***3.1.3 Patient characteristic according to comorbidities***

Table 1 reported patients who had comorbidities of diabetes mellitus. Patients with bipolar disorder consume mood stabilizers, antipsychotics, or antidepressants as part of their therapeutic regimen. Certain literature suggests that these medications have the potential to induce metabolic disorders in individuals with bipolar disorder. These metabolic disorders encompass dysfunctions in glucose metabolism, leading to elevated levels of glucose in the bloodstream [17]. Metformin, an antidiabetic medication, is prescribed for bipolar patients [18].

### ***3.1.4 Patient characteristic according to education degree***

This study classified the level of education into three groups: basic school, senior high school, and bachelor's degree. The results indicated that during the period of January to May 2017, 53.57% of bipolar disorder patients at Hospital X Yogyakarta had completed their education at either senior high school. Currently, there is a lack of data regarding the correlation between education level and bipolar disorder. However, a study stated that there is a connection between education level and issues related to poverty. Individuals who are unmarried and have a lower level of education exhibit a higher prevalence of bipolar disorder [19].

### ***3.1.5 Patient characteristic according to occupation***

Table 1 indicated that the largest proportion of the 42.86% respondents are jobless, followed by students, accounting for 28.57%, private employees, accounting for 14.29%, civil servants, accounting for 7.14%, self-employed and retired individuals, each accounting for 3.57%. While the majority of individuals with bipolar disorder are capable of to regain their initial level of working, approximately 20-30% of patients keep demonstrating emotional instability and have difficulties in their work and interpersonal relationships [20]. Approximately 30% of individuals diagnosed with bipolar I disorder experience unemployment, leading to a decrease in their socio-economic status [21]. Bipolar disorder is a chronic condition that frequently relapses, even when individuals are using medication. The relapse rates are significant, with approximately 40% occurring within one year, 60% within two years, and 73-88.7% within four to five years. Recurring relapses can disrupt family, social, and occupational activities [22].

### ***3.1.6 Patient characteristic according to health insurance method***

Table 1 indicated that the majority of payments provide by bipolar patients at Hospital X Yogyakarta during the January-May 2017 period were individual coverage (67.86%), while 9 patients (32.14%) utilized the National Health Insurance. This demonstrates the utilization of mental health services; however, the demand for such services as covered by national health insurance remains unfulfilled, resulting in bipolar patients resorting to more conventional payment methods.

### 3.2 Patient characteristic according to bipolar diagnosis

Between January and May 2017, medical records indicated that there were a total of 98 cases of bipolar disorder among 28 patients. Out of the total, 80 cases (81.6%) presented manic episodes with psychotic symptoms, 5 cases (5.1%) had manic episodes without psychotic symptoms, 4 cases (4.08%) experienced severe depression episodes with psychotic symptoms, and 8 cases (8.16%) were diagnosed with bipolar mixed episodes. Table 2 presented the proportion of individuals diagnosed with bipolar disorder among the outpatients.

**Table 1.** Patient characteristics according to gender, age, comorbidities, education, occupation, and health insurance coverage.

No.	Patient Distribution	Number of Patients	Percentage
a.	Gender		
	Male	13	46.4%
	Female	15	53.6%
b.	Age		
	17-25 years old	10	35.71 %
	26-45 years old	17	60.71 %
	46-65 years old	1	3.6 %
c.	Complication		
	Diabetes Mellitus Type 2	1	3.57 %
	Uric Acid and Anemia	1	3.57 %
	No Complication	26	92.86 %
d.	<b>Education</b>		
	Elementary School	3	10.71 %
	Senior High School	15	53.57 %
	Bachelor	10	35.71 %
e.	Occupation		
	Jobless	12	42.86 %
	Student	8	28.57 %
	Private Laborer	4	14.29 %
	Civil Servant	2	7.14 %
	Self-Employed	1	3.57 %
	Retired	1	3.57 %
f.	Health insurance		
	Individual	19	67.86 %
	National Health Insurance	9	32.14 %

All of these diagnoses in DSM-V TR are classified as subtypes of bipolar I. Bipolar I is diagnosed when the patient experiences at least one episode of mania. Approximately 30% of individuals diagnosed with bipolar I disorder are facing unemployment, leading to a decline in their socio-economic status [22]. Mania episodes are more prevalent among patients with bipolar disorder at Hospital X in Yogyakarta. According to literature, mania is more prevalent because it occurs earlier in patients compared to depression [23].

**Table 2.** The percentage of patients classified as bipolar at Grhasia Mental Hospital in Yogyakarta from January to May 2017.

Bipolar Type	Number of Cases	Percentage (n=98)
Manic episodes with psychotic symptoms	80	81.63 %
Manic episodes without psychotic symptoms	5	5.10 %
Major depressive episode with psychotic symptoms	4	4.08 %
Mixed episode	8	8.16 %
Hypomanic episode	1	1.02 %
Total	98	100 %

### 3.2.1 Mood stabilizer and antipsychotic drug use by product category

Table 3 showed the utilization of mood stabilizers and antipsychotic drugs for outpatient treatment at Hospital X Yogyakarta from January to May 2017.

**Table 3.** The utilization of various drug categories among bipolar patients at Hospital X in Yogyakarta from January to May 2017.

Drug Categories	Name	Frequency of Use	Percentage
Mood Stabilizer	Lithium	5	1.99 %
	Divalproex sodium	93	37.05 %
First Generation Antipsychotics (Typical)	Chlorpromazine	8	3.19 %
	Trifluoperazine	1	0.4 %
	Haloperidol	36	14.34 %
Second Generation Antipsychotics (Atypical)	Clozapin	58	23.11 %
	Risperidone	44	17.53 %
	Quetiapin	3	1.20 %
	Aripiprazole	3	1.20 %
Total		251	100 %

According to Table 3, bipolar disorder patients at Hospital X Yogyakarta are prescribed lithium and divalproex sodium as mood stabilizers. Lithium is used only in five cases, accounting for 1.99%. Lithium is the recommended initial treatment for bipolar disorder when controlling it at home [24]. However, this medication has a narrow range of effective doses and can cause potentially harmful side effects. The side effects identified are polyuria (excessive urination), polydipsia (excessive thirst), hypothyroidism (underactive thyroid), gastrointestinal disorders (gastrointestinal disorders), and tremor (involuntary shaking)[25]. Furthermore, lithium has the potential to induce reduced kidney function and hypothyroidism [26]. Divalproex sodium was administered in 93 cases (37.05%), with the majority of patients undergoing these drug therapy. The selection of divalproex sodium was based on its superior efficacy as an antimanic agent, as well as the presence of evidence indicating its long-term prophylactic effect in preventing relapses of bipolar disorder [27].

Haloperidol was the predominant antipsychotic used in bipolar therapy at Hospital X Yogyakarta from January to May 2017. Haloperidol commonly exhibits a more rapid onset of action when compared to mood stabilizers [28]. There is limited but supportive data regarding the efficacy of typical antipsychotics in treating mania. Haloperidol is not included in the Indonesia formulary, however, it is readily available at Hospital X. As a result, a significant proportion of patients (14.34% in 36 cases) depend on oral haloperidol for treatment. In this study, patients demonstrated a higher use of atypical antipsychotics compared to typical antipsychotics. Atypical antipsychotics are recommended for the treatment of bipolar patients due to the evidence that their extrapyramidal side effects are less severe than those associated with typical antipsychotics. Hence, the majority of patients who

are prescribed atypical antipsychotics exhibit favorable responses and a low tolerance to their adverse effects. Antipsychotics are recommended for first-line maintenance therapy in order to prevent relapse [29].

### **3.2.2 *The use of combination antipsychotics and mood stabilizers***

Supplementary Table 1 reported the number of patients who received a combination of mood stabilizers and antipsychotic drugs. The study findings indicated that the most frequently used combination of mood stabilizers and antipsychotic drugs consists of mood stabilizers (in particular, lithium and divalproex sodium) along with atypical antipsychotics, with a prevalence of 55 cases (56.12%). The selection of drugs for bipolar maintenance therapy is based on a thorough assessment of the symptoms typically experienced by patients, as well as the efficacy and possible side effects of the drugs. This combination is used for treating the mild-to-moderate symptoms of mania episodes [30]. In first-line treatment, it is advised to administer mood stabilizers and atypical antipsychotics. The specific mechanism by which mood stabilizers and antipsychotics resolve mania is still unclear. However, several studies have demonstrated that both agents trigger a favorable response in patients with bipolar mania compared to bipolar depression. The concurrent administration of mood stabilizers and antipsychotics provides greater efficacy compared to their individual use as monotherapy [31].

### **3.2.3 *Utilization of Supplementary Pharmacological Agents in Individuals with Bipolar Disorder***

During the period of January-May 2017, studies were conducted regarding supplementary therapies administered with the combination of mood stabilizers and antipsychotic medications. The quantity of supplementary therapies used in patients with bipolar disorder is shown in Supplementary Table 2. The study's findings indicated that trihexyphenidil (THP) is the most commonly prescribed adjunctive therapy drug for bipolar patients at Hospital X Yogyakarta, with a utilization rate of 92.86%. Antipsychotics frequently result to the onset of extrapyramidal symptoms as drug side effects in patients. Extrapyramidal symptoms include dystonia, akathisia, and dyskinesia [32]. The patient was administered THP in order to alleviate the extrapyramidal symptoms [33]. The administration of THP requires the patient's family's involvement. Whenever the family demonstrates a high level of concern in monitoring the onset of extrapyramidal symptoms, the physician will prescribe THP once these symptoms become prominent.

## **3.3 Evaluation of the Rational Use of Combination *Mood Stabiizer* and Antipsychotic**

A study was conducted at the Hospital X Yogyakarta to evaluate the rationality of using a combination of mood stabilizers and antipsychotic drugs in bipolar patients during the period of January-May 2017. The study focused on determining whether the drugs were being used for the appropriate indication, in the right patients, with the correct drug selection, and at the appropriate dosage, based on relevant literature. The literature resources mentioned are Pharmacotherapy Handbook, Drug Information Handbook, and The Michigan Implementation of Medication Algorithms (MIMA). The results of the evaluation of the rational use of a combination of mood stabilizer and antipsychotic drugs in bipolar patients at Hospital X Yogyakarta in the period January-May 2017 could be seen at Supplementary Table 3.

### 3.3.1 Right Indication

Supplementary Table 3 indicated that out of 98 cases, 94 cases (95.92%) were considered rational, while 4 cases (4.08%) were categorized as irrational. Patients suffering from bipolar disorder, particularly severe depressive episodes associated with psychotic symptoms, are not being provided with the right drug and a comprehensive bipolar therapy algorithm. This study reported that four patients were not administered antidepressants to alleviate the depressive episodes they were experiencing. As the principal therapeutic approach for bipolar disorder, selective serotonin reuptake inhibitor (SSRI) antidepressant medications ought to be prescribed to patients. As a result of the patient's ongoing state of depression [34].

### 3.3.2 Right Patient

According to Supplementary Table 3, a combination of mood stabilizers and antipsychotic drugs was considered rational in 97 cases (98.98%). The conclusion was made because there were no clinical reasons to avoid using these drugs in the patients. However, in one case (1.02%), the drugs that the patients were using were considered irrational due to contraindications. The patient demonstrated contraindications to the use of atypical antipsychotics risperidone. The administration of risperidone could exacerbate the patient's condition with diabetes mellitus [35].

### 3.3.3 Right Drug

In this study, the evaluation of right drug was based on the diagnosis for the use of *mood stabilizers*, antidepressants, atypical antipsychotics, and typical antipsychotics, according to the bipolar disorder therapy algorithm. Supplementary Table 3 showed that the right use of a combination of *mood stabilizer* and antipsychotic drugs in bipolar patients was defined rational as many as 75 cases (76.53%). The cause of irrational drugs are patients using typical antipsychotic drugs who are not recommended based on the therapy algorithm. Atypical antipsychotics are more consequential than typical antipsychotics due to their reduced incidence of extrapyramidal side effects [36]. In addition, atypical antipsychotics have the ability to manage negative symptoms such as alogia, consciousness, depression, and impaired concentration [37]. Nevertheless, in fact, numerous typical antipsychotics remain in use, primarily due to their lower cost. The American Psychiatric Association (APA) recommends against the use of antidepressants in the absence of a mood stabilizer for individuals with bipolar disorder [38]. Bipolar disorder patients require a mood stabilizer or anticonvulsant to prevent severe fluctuations in mood [39]. Nevertheless, the simultaneous administration of antipsychotic medications, particularly atypical antipsychotics, could effectively regulate mood [37].

### 3.3.4 Right Dosage

Ensuring the right dose involves administering the drug within its therapeutic range, thereby considering the dose as a crucial factor in assessing accuracy. Inadequate dose will not be sufficient to achieve the intended therapeutic effect, whereas an excessive dose may lead to potential drug toxicity. Supplementary Table 3 reported that the combination of mood stabilizer and antipsychotic drugs administered to bipolar patients was considered to be the rational dosage in 89 cases (91.84%), while an irrational dosage was detected in 8 cases (8.16%). In one case, a dose of 200 mg of lithium was used once a day (under dose). The initial dose of lithium should be given 300 mg 1-2 times a day, increased weekly, gradually monitored levels, not to exceed 900–1200 mg/day [40]. In 8 cases, the dose of clozapine was



6.25 mg (underdose). The initial dose of clozapine is 12.5 mg 1-2 times a day, dose can be increased to 25–50 mg once or twice daily, with a maximum dose of 300–900mg/day [41].

### ***3.3.5 The rationality of using a combination of mood stabilizers and antipsychotics***

Drug utilization is considered rational when it follows to the criteria for the right indication, right patient, right drugs, and the right dosage. Supplementary Table 3 indicated that the utilization of a combination of mood stabilizers and antipsychotic medications in bipolar patients at Hospital X Yogyakarta during the period of January–May 2017 was classified as rational in 68 cases (69.39%) and irrational in 30 cases (30.61%). This is caused by the inaccuracy in administering drugs based on indications of patients' illnesses, a number of contraindications in drug administration, the inaccuracy in selecting drugs, and the inappropriate administration of drugs by giving doses of antipsychotic drugs below the recommended therapeutic dose or underdose.

## **3.4 Evaluation of Quantity Use of Combination Mood Stabilizer and Antipsychotic Drugs**

The total quantity of combined mood stabilizers and antipsychotic drugs administered to bipolar patients receiving outpatient care at Hospital X Yogyakarta between January and May 2017 was evaluated using the ATC/DDD method. Supplementary Table 4 presented the ATC code and DDD value associated with drug use. The data regarding the number of outpatient visits was obtained from the medical records from January to May 2017, totaling 21,749 records. A total of 98 cases of bipolar disorder were diagnosed at the Hospital X Yogyakarta between January and May 2017. According to the data, mood stabilizers administered to bipolar patients as therapy between January and May 2017 included two different drug types such lithium and divalproex sodium. Antipsychotics, on the other hand, comprised seven distinct drug types such as chlorpromazine, trifluoperazin, haloperidol, clozapine, risperidone, quetiapine, aripiprazol. These drugs were categorized into two groups: typical antipsychotics, also known as first-generation antipsychotics, and atypical antipsychotics, also referred to as second-generation antipsychotics. The substance content of each preparation must be determined using the drug's strength in the preparation. In order to determine the cumulative strength of mood stabilizers and antipsychotics administered over a period of five months (in units of micrograms, milligrams, grams, and mmol), the total amount of use was necessary. Subsequently, the administration of antipsychotics and mood stabilizers is categorized using the ATC code established by the WHO Collaborating Centre [11].

After calculating the total DDD/1000 outpatient visits, it was determined that divalproex sodium had the highest usage of mood stabilizers during the five-month period, with a rate of 26.66/1000 outpatient visits. This means that out of 1000 outpatient visits, approximately 26-27 patients received 1 DDD of divalproex sodium. However, lithium had the lowest usage of mood stabilizers at a rate of 2.15 DDD/1000 outpatient visits. This indicates that out of 1000 outpatient visits, around 2-3 patients received 1 DDD of lithium. The selection of divalproex sodium was based on its superior efficacy as an antimania agent, as well as its documented long-term prophylactic effect in preventing relapses of bipolar disorder [42]. The preparation is administered in the form of extended release (ER) or controlled release, allowing for once-daily use to enhance patient adherence [43]. Furthermore, the utilization of ER divalproex sodium did not demonstrate an elevation in drug side effects in comparison to conventional sodium valproate formulations [44]. Among the antipsychotic medications, risperidone had the highest usage rate at 25.93 DDD/1000 outpatient visits. This means that every 1000 outpatient visits, approximately 25-26 patients were prescribed 1 DDD of

risperidone. However, trifluoperazine had the lowest usage rate at 0.17 DDD/1000 outpatient visits. This means that out of every 1000 outpatient visits, only 1 patient was prescribed 1 DDD of trifluoperazine.

There is a gap between the DDD utilized in hospitals and the DDD guidelines established by the WHO. DDD of divalproex sodium, chlorpromazine, haloperidol, clozapine, risperidone, and quetiapine administered in hospitals exceeded the standard DDD recommended by the World Health Organization (WHO), while the DDD of lithium, trifluoperazine, and aripiprazole under below the WHO standard DDD. Close monitoring of lithium levels in the blood is required due to the narrow therapeutic index. Lithium should not be used in patients with renal impairment due to its inhibitory effect on the excretion process, which can subsequently lead to toxicity. Long-term use of lithium has been associated with renal damage [45]. Due to these contraindications, the utilization of lithium is not extensively employed. Therefore, the utilization of lithium in Hospital X Yogyakarta is lower compared to divalproex sodium. Price, currency, or dosage form fluctuations have no impact on the fixed unit of the ATC/DDD system. Additionally, comparing institutions on a national, regional, or international scale is straightforward. The ATC/DD system has several limitations, including its inability to evaluate all drugs (e.g., topicals, vaccines, local or general anesthesia) and its specific inapplicability to pediatric patients [10].

## 4 Conclusion

The concurrent administration of mood stabilizers and antipsychotics to patients with bipolar disorder was rationally utilized as follows: 95.92% right indication, 98.98% right patient, 76.53% right drug; 90.82% right dosage. Divalproex sodium had the highest total annual consumption of 26.66 DDD per 1000 outpatient visits, while mood stabilizer lithium had the lowest total annual consumption of 2.15 DDD per 1000 outpatient visits. Risperidone had the highest quantity of antipsychotics at 25.92% DDD/1000 outpatient visits, while trifluoperazine had the lowest at 0.17% DDD/1000 outpatient visits.

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### Data availability statement

Data will be made available on request.

### Declaration of competing interest

The authors certify that they do not have any affiliations with or involvement in any organization or entity with a financial interest, nor do they have any conflicts of interest.

### Author contribution statement

Lolita and Ika Meiliana Johan conceived and designed the study. Ika Meiliana Johan performed the computational analysis. Lolita and Ika Meiliana Johan wrote the manuscript. Lolita revised the manuscript. Lolita funded the research. All authors have approved the manuscript and have made significant contributions to this study.

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Supplementary **Table 1.** Use of Combination of Mood Stabilizer and Antipsychotic Drugs

Category	Name of drugs	Total	Number of Cases	Percentage
Mood stabilizers and atypical anti psychotic	Lithium + Risperidone	1	55	56.12 %
	Lithium + Clozapine + Risperidon	4		
	Divalproex sodium + Clozapine+ Risperidone	26		
	Divalproex sodium + Risperidone	15		
	Divalproex sodium + Clozapine	6		
	Divalproex sodium + Clozapine + Aripiprazole	2		
	Divalproex sodium+ Aripiprazole	1		
Mood stabilizers and typical antipsychotic	Divalproex sodium + Haloperidol	18	22	22.45 %
	Divalproex sodium + Chlorpromazine	3		
	Divalproex sodium + Haloperidol + Chlorpromazine	1		
Mood stabilizers, atypical anti psychotic and typical anti psychotic	Divalproex sodium + Clozapine + Chlorpromazine + Seroquel	3	21	21.43 %
	Divalproex sodium + Clozapine + Haloperidol	16		
	Divalproex sodium + Clozapine + Stelazine	2		
Total			98	100 %

Supplementary **Table 2.** The use of additional therapy in patients at Hospital X in January-May 2017

Category	Name of Drug	Frequency of Use	Percentage
Anticholinergics	Trihexylpenidil	52	92.86 %
Benzodiazepines	Lorazepam	1	1.8 %
Xantin Oxidase Inhibitor	Allupurinol	1	1.8 %
Vitamins	Neurodex	1	1.8 %
	Hemobion	1	1.8 %
Total		56	100 %

Supplementary **Table 3.** The rational use of a combination of mood stabilizer and antipsychotic drugs in bipolar patients

No.	Key Factors	Number of Cases	Percentage
a.	Right Indication		
	Rational	94	95.92 %
	Irrational	4	4.08 %
	Total	98	100 %
b.	Right Patient		
	Rational	97	98.98 %
	Irrational	1	1.02 %
	Total	98	100 %
c.	Right Drug		
	Rational	75	76.53 %
	Irrational	23	23.47 %
	Total	98	100 %
d.	Right Dosage		
	Rational	89	90.82 %
	Irrational	9	9.18 %

	Total	98	100 %
e.	Rationality Use		
	Rational	68	69.39 %
	Irrational	30	30.61 %
	Total	98	

Supplementary **Table 4.** ATC codes and quantity of combined use of mood stabilizer and antipsychotic drugs in DDD/1000 outpatient visits

No.	Category	ATC Code	Name of Drugs	DDD	DDD/1000 outpatient visits
1	<i>Mood Stabilizer</i>	N05AN01	Lithium	46.69	2.15
		N03AG01	Divalproex sodium	579.83	26.66
2	Typical Antipsychotics	N05AA01	Chlorpromazine	40.2	1.85
		N05AB06	Trifluoperazine	3.75	0.17
		N05AD01	Haloperidol	269.1	12.53
3	Atypical Antipsychotics	N05AH02	Clozapine	149.92	6.89
		N05AX08	Risperidone	564	25.93
		N05AH04	Quetiapine	45	2.07
		N05AX12	Aripipazole	60	2.76