

Identification of Off-Label Drugs for Patients with Neurological Disorders at the Psychiatric Hospital “Ghrasia” Yogyakarta

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Abstract: Off-label drug use is the prescription of drugs outside the indications approved by the authorized agency. The reasons for off-label drug use include a lack of clinical response to previous treatments, intolerance, or contraindications to drug therapy. The scientific evidence of off-label prescribing was lacking, and the risk of adverse events increased. This study aims to identify the off-label drug use for patients with neurological disorders at the Psychiatric Hospital “Ghrasia” Yogyakarta. This study used a descriptive observational design with a cross-sectional method. Data collection was conducted retrospectively. Sampling was carried out by using the purposive sampling technique. The sample was patients who received a psychotropic prescription at the Psychiatric Hospital “Ghrasia” Yogyakarta in January-December 2019. The data were analyzed by scrutinizing the therapeutic goals according to the diagnosis on the medical record. Prescriptions not matching the indications registered by NADFC are included in the off-label category. We used descriptive analytics for demographic data, disease diagnosis, and frequency of the off-label use of drug in neurological disorders. The research obtained a total sample of 662 patients that met the inclusion criteria, with 2,823 psychiatric drugs used. The off-label use of drug in neurological disorders at the Psychiatric Hospital “Ghrasia” Yogyakarta was 884 (31%). The most frequent off-label use was lorazepam (17.53%). This study concludes that there is an off-label prescription at the Psychiatric Hospital “Ghrasia” Yogyakarta. Some of the off-label use has no solid scientific evidence. These results require further research regarding the reasons for off-label prescribing and the patient's safety.

Keywords: NADFC; neurological disorders; off-label; The Psychiatric Hospital “Ghrasia” Yogyakarta

1. Introduction

An off-label drug is the use of drugs outside the indication approved by the authorized agency. It includes off-label dose, off-label age, off-label administration procedure, and off-label indications (Le Jeune *et al.*, 2013; Wittich *et al.*, 2012). According to the Ministry of Health of the Republic of Indonesia 2018, off-label drugs define as using drugs outside the indications approved by the authorized agency, for instance, the Food and Drug Administration (FDA), the official agency in the United States. Meanwhile, Indonesia has the National Agency for Drug and Food Control of the Republic of Indonesia (NADFC) (Rusli, 2018).

Research in Brazil stated that, out of 1,054 prescriptions given to 73 patients, 23.4% of the off-label drug, 12.6% of the non-licensed drug, and 1.4% of both (off-label and non-licensed) were found (Ferreira *et al.*, 2012). In addition, research conducted by Rahajeng *et al.* in 2018 regarding using off-label anticonvulsants in a private hospital in Indonesia revealed 35.11%. The highest frequency was in the treatment of neurological and psyche disorders. As many as 97.19% of the off-label use of anticonvulsants has no clinical evidence (Rahajeng *et al.*, 2018).

Using off-label drugs has a higher adverse drug event (ADE) than on-label drugs. It is in line with research conducted by Egualé *et al.*, (2016), stating that 3,484 ADE was found in 46,021 patients, with a 13.2% incidence per 10,000 people per month. ADE level for off-label use (19.7% per 10,000 people per month) is higher than of on-label use (12.5% per 10,000 people per month) (Egualé *et al.*, 2016). However, many physicians still prescribe off-label drugs to the patient. Psychotropic is one of the off-label drugs most frequently prescribed. A study from Canada has found that 36.2% of prescriptions for psychotropic medication are off-label. Anxiolytic or hypnotic drugs are the most commonly used psychotropic drugs for off-label purposes (Brown *et al.*, 2018).

Psychotropic drugs are the front line for the management of mental illness. According to research conducted by Lesli & Rosenheck (2012), it is stated that the use of off-label drugs is common, especially among the elderly and children or adolescents. In practice, the administration of off-label drugs in elderly patients is frequently used in off-label indications. One of them is the prescription of off-label psychotropics carried out by more than 50% of psychiatrists treating schizophrenia. On the other hand, scientific evidence of the off-label use of psychotropics was lacking. Despite that, the adverse effects of psychotropics were high, which can affect patient adherence. Noncompliance therapy can interfere treatment of mental illness. (Leslie & Rosenheck, 2012; Lucca *et al.*, 2019). Therefore, this research aims to identify the amount of off-label drug used in neurological disorders, especially in the Psychiatric Hospital “Grhasia” Yogyakarta. The results of this study are expected to be a database for off-label drug use in neurological disorders, allowing the prevention of adverse drug events can be carried out.

The difference between this research and similar research is the difference in the data analysis method (descriptive) and the research place. This research is still relevant to be carried out in Indonesia because there are still little data on the use of off-label drugs use in neurological disorders.

2. Material and Methods

2.1. Ethical approval

This study was approved by Health Research Ethics Committee of the Psychiatric Hospital “Grhasia” Yogyakarta with Ethical Approval number: .37/EC-KEPKRSJG/IV/2020

2.2. Data collection

This study is descriptive observational research using a cross-sectional design. The data collection of prescribed off-label drugs was carried out retrospectively. This research was conducted at the Psychiatric Hospital “Grhasia” Yogyakarta using one-year medical record data from January to December 2019. The medical record used in this study was the medical record of patients with neurological disorders who received drug prescriptions that act on the nervous system. The data collection was conducted from July to October 2020. The inclusion criteria included patients who received a prescription for drugs that act in the nervous system from January to December 2019. We collected data from the medical record about the patient's demographics (age, gender, occupation), disease diagnosis, drugs used (including past medical history), and symptoms.

The sample used was taken by the purposive sampling method. The minimal sample calculation formula (Slovin) used in Equality 1.

$$n = N / (1 + N.(e)^2)$$

$$n = \frac{1632}{1+(1632 \times (0,05)^2)} = 321,259$$

Equality 1. The minimal sample calculation formula (Slovin) at the Psychiatric Hospital “Grhasia” Yogyakarta using one-year medical record data from January to December 2019. Description: n = number of samples, N = total population, E = limit error.

Sampling using a purposive sampling method. The samples obtained were 662 patients who met the inclusion criteria. This number of samples exceeds the minimum number of samples required according to the calculation.

2.3. Data analysis

Identifying off-label prescribing patterns refers to the National Drug Information Center (PIO Nas). Prescriptions not matching the indications registered by NADFC are included in the off-label category. We used descriptive analytics for demographic data, disease diagnosis, and frequency of the off-label use of drug in neurological disorders. We present the result in percentage form.

3. Results and Discussion

This study was carried out by 662 patients who met the inclusion criteria. Patient characteristics data can be seen in Table 1. Patients' age in this study was grouped based on the

Republic of Indonesia government law number 36 (2009) on health (Pemerintah Pusat, 2009). The highest age category is dominated by productive age (26-35 years old) with an average of 38.74 ± 15.55 . Based on table 1, male patients are higher than female patients. Most of the patients in this study were unemployed (49.09%).

Table 1. Characteristics of patients who received prescription drugs that act on the neurological system at the Psychiatric Hospital “Grhasia” Yogyakarta.

No	Characteristic	Total (n)	Percentage (%)
1	Gender		
	Male	366	55,29
	Female	296	44,71
2	Age (years)		
	0 – 5	2	0,30
	5 – 11	3	0,45
	12 – 16	10	1,51
	17 – 25	146	22,05
	26 – 35	168	25,38
	36 – 45	106	16,01
	46 – 55	114	17,22
	56 – 65	73	11,03
	>65	40	6,04
3	Occupation		
	Unemployed	325	49,09
	Private employee	93	14,05
	Students	87	13,14
	Entrepreneur	45	6,80
	Labor	44	6,65
	Farmer	42	6,34
	Retired	11	1,66
	Civil Servant	9	1,36
	Police / pensioner	3	0,45
	Teacher	2	0,30
	Housewife	1	0,15
	Total	662	100

In January-December 2019, this study revealed that patients receiving medication for neurological disorders were dominated by male patients (55.29%). It occurred since the patients at the Psychiatric Hospital “Grhasia” Yogyakarta was treated with a diagnosis of schizophrenia. Schizophrenia occurred 1.4 times more frequently in men than women and, in particular, appears earlier in men (Picchioni & Murray, 2007).

This study showed that patients receiving medication for neurological disorders were mainly 26-35 years old (25.38%). As this age range is categorized as productive age with much-precipitating stress and a considerable burden of responsibility. These factors included problems with family and colleagues, heavy workload, and economic issues that could later affect emotional development (Yulianty et al., 2017).

Furthermore, the data showed that most of the patients were unemployed. Unemployment can lead to several adverse effects such as stress, depression, and mental weaknesses; thus, they are likely to feel unempowered and pessimistic about the future. It becomes the risk factor for people to experience a mental disorder such as schizophrenia. The results of this study are also in line with the research of Darsana and Suariyani at the Psychiatric Hospital in Bali, which found that most of the patients were men of productive age (26-46 years) and unemployed (Darsana & Suariyani, 2020; Semiun, 2006).

As many as 2.823 psychiatric drugs were given to 662 patients at the Psychiatric Hospital “Grhasia” Yogyakarta with various diagnoses. The diagnosis for patients who received psychiatric drug prescriptions is presented in Table 2. Table 2 shows 16 diagnoses experienced by patients who receive a psychiatric drug. The most common disease diagnosis was schizophrenia (35.5%).

Table 2. The diagnosis of patients who received psychotropics prescriptions at the Psychiatric Hospital “Grhasia” Yogyakarta

No	Patient's Diagnosis	Total	Percentage (%)
1	Schizophrenia	235	35,50
2	Depression	89	13,44
3	Bipolar	51	7,70
4	Acute psychotic disorder	49	7,40
5	Schizo affective	47	7,10
6	Mental illness due to psychoactive	44	6,65
7	Anxiety	40	6,04
8	Other mental disorders due to brain dysfunction and physical illness	26	3,93
9	Mental retardation	21	3,17
10	Dementia	18	2,72
11	Mental disorder due to sedative-hypnotic	15	2,27
12	Obsessive Compulsive Disorder	7	1,06
13	Insomnia	7	1,06
14	Alzheimer	6	0,91
15	Mental disorders due to other stimulants, including caffeine	5	0,76
16	Stress	2	0,30
Total		662	100

The drugs prescribed for patients at the Psychiatric Hospital “Grhasia” Yogyakarta included 30 types of psychiatric medication. The category of drugs can be seen in Figure 1. Classification of drug category is intended to identify the prescription that was most frequently off-label drug used from January to December 2019 at the Psychiatric Hospital “Grhasia” Yogyakarta.

Based on Figure 1, the use of atypical antipsychotics is 28.52 %. Based on the research results, drugs included in the atypical antipsychotic category were most often prescribed by

physicians in the Psychiatric Hospital “Grhasia” Yogyakarta Yogyakarta. The drugs included clozapine, olanzapine, risperidone, aripiprazole, and quetiapine. This data follows the data on the diagnosis of most patients, namely schizophrenia. The first choice of therapy for schizophrenia is antipsychotics (Hariyanto *et al.*, 2016; McDonagh *et al.*, 2017).

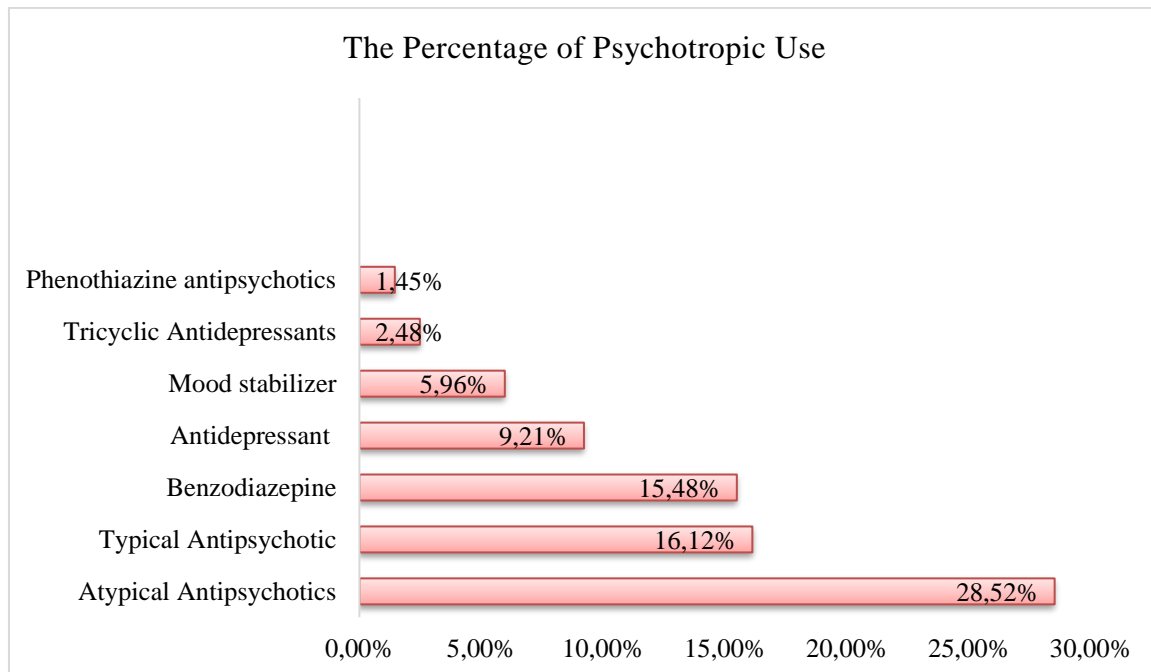


Figure 1. The psychiatric medication use is based on drug category at the Psychiatric Hospital “Grhasia” Yogyakarta.

3.1. The off-label drug use in patients with the neurological disorder

Based on the 662 patients’ medical records data at the Psychiatric Hospital “Grhasia” Yogyakarta, there were 2.823 drug prescribed to patients with neurological disorders. In addition, 884 medications were used off-label (31 %), and 1.939 (69 %) were used the on-label. One prescription may consist of more than one off-label use of the drug. The off-label psychiatric drug used is present in Table 3.

There were 884 off-label psychiatric drug of which the prescription was for 18 diagnoses, as shown in Table 4. The off-label drug used in the Psychiatric Hospital “Grhasia” Yogyakarta for neurological disorders is primarily used for schizophrenia, followed by depression and bipolar. The most frequently used off-label psychiatric is lorazepam. The following is a description of 4 types of off-label drug use that are most frequently used at the Psychiatric Hospital “Grhasia” Yogyakarta:

3.1.1. Lorazepam

Lorazepam is the drug most prescribed off-label in the Psychiatric Hospital “Grhasia” Yogyakarta. It is a drug categorized into benzodiazepines. According to NADFC (2015), known as BPOM in Indonesia, Lorazepam is indicated for the short-term treatment of anxiety and

insomnia. The off-label lorazepam at the Psychiatric Hospital “Grhasia” Yogyakarta was used to treat depression (30,97%), schizophrenia (30,32 %), a mental disorder due to psychoactive substances (9,68 %), dementia (8,39 %), psychotic disorders (8,39 %), bipolar (5,81 %), schizoaffective disorder (3,22 %), severe stress (1,29 %), mental retardation (1,29 %), and OCD (0,64 %).

Table 3. The Use of Off-Label Psychiatric drug at the Psychiatric Hospital “Grhasia” Yogyakarta.

No	Drug Name	Total (N)	Percentage (%)
1	Lorazepam	155	17,53
2	Fluoxetine	106	11,99
3	Clozapine	90	10,18
4	Risperidone	74	8,37
5	Diazepam	72	8,14
6	Na-valproate	56	6,33
7	Clobazam	54	6,11
8	Diazepam Injection	40	4,52
9	Haloperidol Injection	35	3,96
10	Haloperidol	27	3,05
11	Alprazolam	23	2,60
12	Escitalopram	21	2,38
13	Amitriptyline	19	2,15
14	Maprotiline	19	2,15
15	Aripiprazole	13	1,47
16	Quetiapine	13	1,47
17	Fluphenazine Injection	12	1,36
18	Sertraline	11	1,24
19	Trihexyphenidyl (THP)	9	1,02
20	Zolpidem	6	0,68
21	Trifluoperazine (TFP)	5	0,57
22	Methylphenidate hydrochloride	5	0,57
23	Sulpiride	4	0,45
24	Phenytoin	3	0,34
25	Donepezil	3	0,34
26	Buspirone	3	0,34
27	Olanzapine	2	0,23
28	Phenobarbital	2	0,23
29	Chlorpromazine	1	0,11
30	Diazepam + Metamizole	1	0,11
Total		884	100

The mechanism of lorazepam has been identified for the past years. Lorazepam has a mechanism that inhibits Gamma-Aminobutyric Acid (GABA) in the central nerve and specifically binds to the post-synapse receptor. As a result, it produces sedation, sleep, and muscle relaxation. A study conducted by Brand *et al.*, (2016) showed that although the effect

is still far below the combination therapy between lorazepam and a sleep hygiene program, the use of lorazepam is proven to reduce sleep disturbances and depression. However, clinicians should consider the drug dependence on lorazepam (Brand *et al.*, 2016).

In schizophrenia, lorazepam is commonly used both as a single-use and in combination with antipsychotics, especially to treat symptoms of catatonia. Chin-Chuen Lin and Tiao-Lai Huang found that the lorazepam-diazepam combination can reduce the symptoms of catatonia. Another study stated that there was no significant difference between haloperidol-lorazepam and olanzapine (Huang *et al.*, 2015; Lin & Huang, 2013). Due to its ability to reduce symptoms of catatonia, lorazepam is frequently prescribed to patients with depression (Hung & Huang, 2006). Meanwhile, for dementia, lorazepam has been used for a long time, especially for dementia associated with agitation. Mario Amore *et al.* have conducted a systematic review on using lorazepam for agitation. It has been included in the algorithm treatment of agitation in Alzheimer's disease and dementia (Amore *et al.*, 2021; Davies *et al.*, 2018; Defrancesco *et al.*, 2015).

3.1.2. Fluoxetine

The physicians prescribed fluoxetine for off-label use at the Psychiatric Hospital “Grhasia” Yogyakarta to 106 patients (8.60%). Fluoxetine is an antidepressant drug categorized as SSRI. The official registration of fluoxetine is to treat moderate to severe depression. Fluoxetine works by inhibiting 5-HT from pre-sympathetic neurons. It leads to stable serotonin concentration, later improving mood and re-cultivating one's interest in the regular activity (Santarsieri & Schwartz, 2015).

The off-label use of fluoxetine at the Psychiatric Hospital “Grhasia” Yogyakarta was used to treat schizophrenia (42.5%), anxiety (18.9%), mental disorders due to psychoactive substances (9.4%), insomnia (8.5%), bipolar (7.5%), mental disorders due to other stimulants, including caffeine (3.8%), schizoaffective disorder (3.8%), other mental disorders due to brain dysfunction or physical illness (2.8%), dementia (1.9%) and mental retardation (0.9%). Due to the mechanism of the antidepressant SSRI, it can maintain serotonin levels by preventing its absorption, thus giving a sense of happiness and psychological relaxation.

In this study, the off-label use of fluoxetine was most widely used to cope with schizophrenia (42.5%). A systematic review by Kylie J. Thaler *et al.*, (2012) showed that the second generation of antipsychotics, such as fluoxetine for anxiety, insomnia, and pain, still had moderate to low evidence (Thaler *et al.*, 2012).

Table 4. The diagnosis of *off-label* Psychotropics at the Psychiatric Hospital “Grhasia” Yogyakarta was given to more than five patients.

Drug	A total patient	Bipolar	OCD	Schizophrenia	Acute psychotic disorder	Dementia	Depression	Anxiety	Mental illness due to psychoactive	Insomnia due to stimulant	Other mental disorders due to brain dysfunction and physical illness	Schizoaffective	Severe Stress	Mental Retardation	Mental disorders due to other stimulants, including caffeine	Mental illness due to sedative-hypnotic	Alzheimer	Insomnia	Disorders due to multiple drugs
Lorazepam	155	9	1	47	13	13	48	0	15	0	0	5	2	2	0	0	0	0	0
Fluoxetine	106	8	0	45	0	2	0	20	10	9	3	4	0	1	4	0	0	0	0
Clozapine	90	21	0	0	0	3	22	17	6	0	7	0	0	10	0	4	0	0	0
Risperidone	74	22	1	0	0	0	9	15	4	0	7	0	0	10	0	0	5	1	0
Diazepam	72	4	0	28	6	1	13	2	0	0	3	6	0	9	0	0	0	0	0
Haloperidol	62	17	0	0	2	12	12	0	0	0	18	0	0	0	0	0	0	1	0
Valproic Er Acid	56	3	0	21	6	0	6	2	0	0	3	2	2	3	1	3	0	0	4
Clobazam	54	13	0	2	3	2	22	0	0	0	1	1	2	1	0	2	0	1	4
inj. Diazepam	40	16	0	2	10	0	8	0	0	0	0	0	0	3	0	1	0	0	0
Alprazolam	23	4	1	0	0	0	1	2	0	0	1	2	0	0	0	8	0	0	4
Escitalopram	21	2	0	3	1	0	0	4	0	0	1	1	0	0	1	8	0	0	0
Amitriptyline	19	1	0	7	0	0	0	4	0	0	0	3	0	0	0	1	0	0	3
Maprotiline	19	1	0	9	3	0	0	1	0	0	0	2	0	0	0	0	0	0	3
Aripiprazole	13	4	0	0	3	0	3	0	0	0	1	1	0	1	0	0	0	0	0
Quetiapine	13	1	0	6	3	0	1	1	0	0	0	0	0	1	0	0	0	0	0
inj. Fluphenazine	12	0	0	12	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
sertraline	11	5	0	2	0	0	0	1	0	0	0	0	0	0	0	2	0	0	1
THP	9	2	1	0	0	1	3	0	0	0	0	0	0	0	0	1	0	0	1
zolpidem	6	0	0	0	0	0	1	3	0	0	0	0	0	0	1	0	0	0	1
Total of	855	133	4	184	50	34	149	72	35	9	45	27	6	41	7	30	5	3	21
Percentage (%)	100	15,56	0,47	21,52	5,85	3,98	17,43	8,42	4,09	1,05	5,26	3,16	0,70	4,80	0,82	3,51	0,58	0,35	2,46

3.1.3. Clozapine

Clozapine is a drug often prescribed by physicians in the Psychiatric Hospital “Grhasia” Yogyakarta. The percentage of the use of off-label clozapine is 7,31 %. It is categorized as an atypical antipsychotic, indicating the treatment of schizophrenia. Clozapine has a mechanism to affects neurotransmitters in the brain, especially dopamine. It can reduce dopamine levels; thus, it affects the levels of neurotransmitters such as serotonin, noradrenaline, and acetylcholine, which balance the levels of each substance. In addition, it can prevent a change in behavior, emotions, and feelings and influence brain control. The circulation permit of the clozapine issued by NADFC is for schizophrenia (including psychosis in Parkinson's) in patients who do not respond or are intolerant to conventional antipsychotic drugs (Aronson, 2015; PIO Nas, 2021).

The off-label clozapine at the Psychiatric Hospital “Grhasia” Yogyakarta aimed for the treatment of depression (24.4%), bipolar (23.3%), anxiety (18.9%), mental retardation (10.0 %), mental disorders due to brain dysfunction or physical illness (7.8%), mental disorders due to psychoactive substances (6.7%), dementia (3.3%), mental disorders due to the sedative-hypnotics (4.4%), and dissociative amnesia (1.1%). The off-label use of clozapine is due to the ability of clozapine to affect neurotransmitters in the brain, particularly dopamine. Can lower dopamine levels to prevent changes in behavior, emotions, and feelings, create a psychologically relaxing effect, and affect brain control.

A study by Camelia, (2016) showed that the use of clozapine as a therapy in bipolar patients was 60% higher than other drugs. It indicates that clozapine is one of the effective drugs in treating bipolar with low extrapyramidal side effects. A pharmacoepidemiologic study database conducted by Nielsen *et al.*, (2012) revealed that the use of clozapine for bipolar provides a significant result and a relevant reduction clinically to the patients' hospitality, psychiatrist visit, and psychotropics treatment without an increase in medical treatment (Camelia, 2016; Nielsen *et al.*, 2012).

3.1.4. Risperidone

Risperidone is an anticholinergic drug. Based on NADFC 2015, risperidone treats acute and chronic psychosis and mania. Based on this study's result, the use of off-label risperidone at Ghrasia Mental Hospital Yogyakarta reached 6.01%. Risperidone was used to treat bipolar (29.7%), anxiety (20.3%), mental retardation (13.5%), depression (12.2%), other mental disorders due to brain dysfunction or physical illness (9.5%), Alzheimer's (6.8%), mental disorders due to psychoactive substances (5.4%) and OCD (1.4%). It was used due to its working mechanism for the dopamine of two receptors that caused the patient a sense of

pleasure and tranquility. The highest off-label use of risperidone is to treat bipolar (29,7) since risperidone is the first line in treating acute mania of bipolar disorder (Menteri Kesehatan RI, 2015).

A systematic review by Pascal Sienaert *et al.*, (2013) revealed that level I evidence for the treatment strategy for resistant depression is still rare. Although the incidence rate is highly reported, the treatment strategies majorly remain based on an experiment. Therefore, the guidelines for clinical practice for bipolar are still primarily based on an extrapolation of evidence about augmentation strategies and unipolar major depression. A summary written by Effective Health Care (2007) using the systematic review method on more than 100 research publications denoted that risperidone effectively treats OCD and dementia in Alzheimer's with moderate evidence. Meanwhile, using off-label risperidone to treat mental retardation, anxiety, personality disorders, and depression does not show significant evidence (Shekelle *et al.*, 2007; Sienaert *et al.*, 2013).

4. Conclusion

Based on the study results, the conclusion was that the use of off-label drug use for neurological disorders at the Psychiatric Hospital “Grhasia” Yogyakarta was 31% of 2.823 medications. Furthermore, the drug category most widely used included the atypical psychotic, with a percentage of 28.52 %. In addition, the highest percentage of the use of off-label psychotropics was Lorazepam (17, 53%). Some of the off-label use of psychotropics has no strong scientific evidence. Because this study is retrospective, these results require further research regarding the reasons for off-label prescribing and the patient's safety.

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Conflict of Interest

No conflict of interest

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