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Original Article

Pattern of Antipsychotics in Schizophrenia Outpatients at Lampung Province Mental Hospital

Pola Antipsikotik pada Pasien Rawat Jalan Skizofrenia di Rumah Sakit Jiwa Provinsi Lampung

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Abstract: Schizophrenia as a chronic mental disorder has increased in number in the last three decades DALYs (Disability Adjusted Life Years). Antipsychotics have been the mainstay of treatment. The use of combinations of typical/atipycal antipsychotic active substances is very often done. The purpose of this study was to look at patient characteristics and clinical characteristics including the number and type of antipsychotic combinations. This research is descriptive research with a quantitative and cross-sectional approach. Data age, gender, duration of illness, financing status, number of drugs, and the name of the antipsychotic used were taken from medical records and prescription sheets from 207 outpatients diagnosed with schizophrenia. The data was then processed and analyzed using univariate analysis. Outpatient schizophrenia patients were dominated by 62.8% male, aged 26-35 years 32.4%, duration of illness more than 12 months was 92.3%, 82.8% used health insurance, the average number of drugs prescribed was 3.5 drugs. The combination with two antipsychotics was 58%. The atypical-typical combinations (30.9%) were higher with the most risperidone-clozapine. Typical-typical combinations (19.3%) included chlorpromazine-haloperidol, trifluoperazine-chlorpromazine. Atypical-atypical combinations include risperidone-clozapine. The combination of three antipsychotics reached 7.7%. The conclusion of this study shows that the combination of antipsychotics is widely used in the treatment of schizophrenia, with two types of antipsychotics being the most widely used. The combination of risperidone-chlorpromazine was the most common at 21.7%.
Keywords: combination antipsychotics, outpatient, Schizophrenia.

Abstrak: Skizofrenia sebagai gangguan jiwa kronis mengalami peningkatan jumlah dalam tiga dekade terakhir DALYs (Disability Adjusted Life Years). Antipsikotik telah menjadi andalan pengobatan. Penggunaan kombinasi zat aktif antipsikotik tipikal/atipikal sangat sering dilakukan. Tujuan dari penelitian ini adalah untuk melihat karakteristik pasien dan karakteristik klinis termasuk jumlah dan jenis kombinasi antipsikotik. Penelitian ini merupakan penelitian deskriptif dengan pendekatan kuantitatif dan cross sectional. Data umur, jenis kelamin, lama sakit, status pembiayaan, jumlah obat, dan nama antipsikotik yang digunakan diambil dari rekam medis dan lembar resep dari 207 pasien rawat jalan yang didiagnosis skizofrenia. Data tersebut kemudian diolah dan dianalisis menggunakan analisis univariat. Pasien skizofrenia rawat jalan didominasi laki-laki 62,8%, usia 26-35 tahun 32,4%, lama sakit lebih dari 12 bulan 92,3%, menggunakan asuransi kesehatan 82,8%, rata-rata jumlah obat yang diresepkan 3,5 obat. Kombinasi dengan dua antipsikotik adalah 58%. Kombinasi atipikal-tipikal (30,9%) lebih tinggi dengan kebanyakan risperidone-clozapine. Kombinasi tipikal-tipikal (19,3%) termasuk klorpromazin-haloperidol, trifluoperazin-klorpromazin. Kombinasi atipikal-atipikal termasuk risperidon-clozapine. Kombinasi ketiga antipsikotik mencapai 7,7%. Kesimpulan penelitian ini menunjukkan bahwa kombinasi antipsikotik banyak digunakan dalam pengobatan skizofrenia, dengan dua jenis antipsikotik yang paling banyak digunakan. Kombinasi risperidone-klorpromazin adalah yang paling umum yaitu 21,7%.
Kata kunci: antipsikotik kombinasi, pasien rawat jalan, Skizofrenia.

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INTRODUCTION

Mental disorders are currently a health challenge and contribute 14% to the global burden of disease. About 450 million people are declared to suffer from mental disorders. Mental disorders are the main cause of long-term and dependent disability (Semahegn et al., 2018). Depression, bipolar disorder and schizophrenia are the most common psychiatric disorders (WHO, 2019). Schizophrenia is one of the diseases in the last three decades (1990-2017) that experienced an increase in DALYs (Disability Adjusted Life Years). In 1990, it was in fourth place while in 2017 it was in third place after depression and anxiety (Kementrian Kesehatan RI, 2019).

Schizophrenia disorder is a chronic disease, relapsing, and causes a decrease in function that is getting more and more severe, especially if it does not get adequate management. In other words, schizophrenia disorder clearly results in disability which is often irreversible and creates a heavy burden for both the individual and his family (PDSKJI, 2011). Pharmacological therapy for schizophrenia has developed rapidly after the discovery of the second generation of antipsychotics. The success of pharmacological therapy will facilitate the success of psychosocial therapy and rehabilitation (PDSKJI, 2011).

Antipsychotics have been the mainstay of treatment for schizophrenia since their discovery in the 1950's. These antipsychotics are used in various phases of schizophrenia. Its use to prevent relapse has been shown to be effective in reducing mortality compared to no antipsychotics. However, it is necessary to be aware of the side effects that can cause disability or death. Switching between antipsychotics is often done to increase their efficacy and tolerance, although their effectiveness has not been investigated in a randomized controlled-trial (RCT) (Hadda & Correl, 2018; Huhn et al., 2019).

Many guidelines recommend the latest generation of antipsychotics, second generation or called atypical antipsychotics as a treatment option. The older generation of antipsychotics are cheaper and are still used in many parts of the world, especially in low-income countries (Hadda & Correl, 2018). Research at the Tampan Mental Hospital in Pekanbaru for the January-June 2015 period and the Madani Hospital in Central Sulawesi Province for the January-April 2014 period showed that typical antipsychotics were more dominant than atypical antipsychotics, respectively 78% and 56.8% (Aryani & Sari, 2016). In contrast to research conducted by X Hospital in Bantul, the use of atypical antipsychotics reached 91%, while typical was 51% (Dania et al., 2019).

There have been no studies on the use of antipsychotic combinations at Mental Health Hospital. The purpose of this study was to describe the pattern of antipsychotic combinations. Based on this background, the researcher will see how the combination of antipsychotics is used at Mental Hospital in the Lampung Province. Mental hospital is the one and only specialized hospital in mental disease at Lampung Province. Pattern of antipsychotic combinations can be the first step or basis for seeing effectiveness of drugs and can be related to medication cost.

MATERIAL AND METHODS

Study Design

This descriptive study was quantitative approach and was cross-sectional study. Outpatient's schizophrenia monthly treatment to this hospital and take chronic treatment. The sampling technique used is purposive sampling. Every outpatient who take prescription to the pharmacy from September-October 2019 was sampled by inclusion and exclusion criteria. An outpatient prescription and patient medical records data as a secondary data.

The inclusion criteria in this study were outpatients with a diagnosis of schizophrenia, prescription and medical records completed. The exclusion criteria in this study were patient with same number medical record only take once between those months.

The number of samples in this study was found to be 207. This research has obtained ethical approval from the Health Research Ethics

Committee of the Tanjungkarang Health Polytechnic with Number 275/EA/KEPK-TJK/IX/2019.

Collecting and Analysis Data

The collected data consists of age, gender, duration of illness, financing status, number of drugs, and the name of the antipsychotic used. The data obtained were then processed and analyzed using univariate analysis, include patient characteristic, type and class of antipsychotics, and number of antipsychotic combinations.

RESULTS AND DISCUSSION

Patients Characteristics

Outpatient schizophrenia are predominantly male than female as presented in table 1. Several studies state that men have a higher prevalence than women (Aryani & Sari, 2016; Li et al., 2016; Ochoa et al., 2012; Yulianty et al., 2017). Estrogen has a neuromodulatory role in the pathogenesis and treatment of neuropsychiatric disorders including schizophrenia. Estrogen in the form of 17-β estradiol is not only produced in the ovaries, but also in fat, breast, and brain. Its neuroprotective properties make it one of the targets of adjunct therapy in schizophrenia (Gogos et al., 2015). In an RCT, it was shown that the administration of transdermal estrogen adjunctive therapy in schizophrenia women who had given birth was effective in reducing negative symptoms (Weiser et al., 2019).

Schizophrenia patients in this study (table 1) were in various age ranges forming a mountain-like curve with one peak, which was mostly in the age range of 26-35 years. As adults, the incidence of schizophrenia will increase to a peak in the age range of 26-35 years and decrease with increasing age. This could be because gender differences affect the onset of schizophrenia. The onset of occurrence in men is slightly earlier than in women. The peak onset of events in men is at the age of 21-25 years, while women have two peaks, namely at the age of 25-30 years and after 45 years (Li et al., 2016). In addition, those aged 25-35 years are 1.8 times more likely to experience schizophrenia than those aged 17-24 years (Zahnia & Wulan Sumekar, 2016).

Table 1. Characteristics of Schizophrenia Outpatients

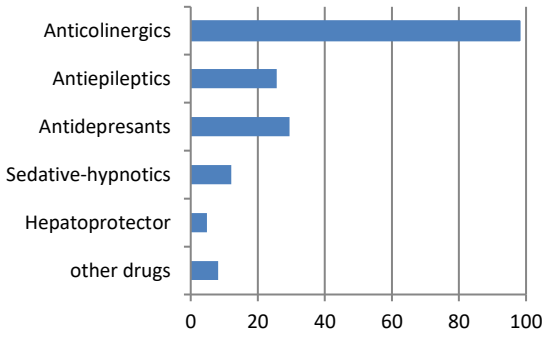
Characteristics	Frequency (n = 207)	Percentage (%)
Gender		
Male	130	62,8
Female	77	37,2
Age (years)		
0-5	1	0,5
6-11	1	0,5
12-16	5	2,4
17-25	33	15,9
26-35	67	32,4
36-45	50	24,2
46-55	38	18,4
56-65	11	5,3
>65	1	0,5
Length of illness		
< 12 months	16	7,7
≥12 months	191	92,3
Financing Status		
Assurance	185	89,4
Out of pocket	22	10,6
Number of drugs prescribed		
1	1	0,5
2	8	3,9
3	92	44,4
4	92	44,4
5	13	6,3
6	1	0,5
Average number of drugs prescribed	3,5	

The high incidence of schizophrenia in this study was in the productive age range, namely 15-64 years. At productive age, humans are required to perform their functions economically and socially so that factors such as interpersonal relationships, work, and finances can appear which will be factors that cause schizophrenia (Kementrian Kesehatan RI, 2019).

Schizophrenia is a chronic mental disorder (WHO, 2019). Most of the patients in this study as seen in table 1 had suffered from schizophrenia for more than 12 months, which was 92.3%. Schizophrenia patients require long-term treatment and the costs can cause economic problems (Oommen et al., 2019). The government with a national health insurance system implements a mutual cooperation insurance system. The availability or participation of health

insurance plays an important role as a factor medication adherence. With the existence of health insurance it is easy to find financing so that it is more obedient compared to those who do not have health insurance insurance (Liberty et al., 2018). In several studies, participation of health insurance as one determinant factor in adherence (Budiman et al., 2013; Emiliana et al., 2021).

The average number of drugs prescribed to schizophrenia patients is 3.5 drugs as seen in table 1. This point is higher than the results of Oommen's (2019) research, which is 2.28. The high number of drugs prescribed can be due to the emergence of non-psychotic symptoms, overcoming drug side effects, drug availability, and the addition of other drugs that are in accordance with clinical symptoms, and previously unresponsive drugs (Ballon & Stroup, 2013; Heald et al., 2017).



Picture 1. Drug Class Therapy's in Schizophrenia Patients

Table 2. Five Mostly Antipsychotics Prescribed in Schizophrenia Outpatient

Antipsychotics	Frequency	Percentage (N=207)
Risperidon	132	63,8
Haloperidol	73	35,3
Klorpromazin	104	50,2
Klozapin	28	13,5
Trifluoperazin	19	9,2
Olanzapin	3	1,4
Fluphenazin	2	1,0

Drugs prescribed to schizophrenia patients are dominated by antipsychotics, but it is also possible to use antidepressants, anticholinergics (Heald et al., 2017). In this study as seen picture 1, anticholinergics prescribe almost for all patients (98,6%), followed by antidepressants (29,5%), antiepileptics (25,6%), and other drugs. Other drugs in this study only take small percentage (under 5% for each drug), including hepatoprotector, vitamine, antihypertensive, antibiotic, antidiabetic, and analgesic.

All of patients in this study (100%) used antipsychotics either as monotherapy or in combination with other antipsychotics. Risperidone being the most widely used both in single and combination therapy, which was 63.8% as seen in table 2. Risperidone is an antipsychotic with a mechanism of action as an antagonist of serotonin (2A) and dopamine (D2). This causes risperidone to have low extrapyramidal effects compared to the first generation, namely typical antipsychotics such as haloperidol (Hs et al., 2018).

Treatment in schizophrenia patients is changing trends. There was a decrease in monotherapy treatment for schizophrenia, either between antipsychotics or with other drug classes from 1980 by 48% to 20% in 1991-2000 (Heald et al., 2017).

The number of antipsychotics combinations is shown in table 3. The use of two types antipsychotics combinations reached 57.5% as the largest percentage, followed by monotherapy 34.8%, and combinations of three types of antipsychotics 7.7%. Combining three antipsychotics may be extremely dangerous, may caused mortality (Pandarakalam, 2019).

The use of combinations between antipsychotics in practice can reach 50% to 68% (Alessi-Severini et al., 2013; Kasteridis et al., 2019). The use of combinations between antipsychotics in this study reached 65.7%, either two or three combinations. The use of combinations can be due to the fact that single therapy does not provide an adequate effect or aims to achieve a greater or faster effect than monotherapy, as well as the availability of antipsychotic drugs in health care facilities (Ballon & Stroup, 2013; Barnes & Paton, 2011; Faden et al., 2021). The effect of therapy felt by the patient also determines the choice of single or combination therapy, such as patients who are discontinued one of their antipsychotics show a decrease in side effects, but these patients still choose the combination based on the comfortable that their feels (Ballon & Stroup, 2013).

Table 3. Type of Combination Based on Class Antipsychotics

Class Antipsychotics	Frequency	Percentage
Monotherapy	**72**	**34,8**
Typical	24	11,6
Atypical	48	23,2
Two Antipsychotics	**119**	**57,5**
Typical-Atypical	64	30,9
Typical-typical	40	19,3
Atypical-atypical	15	7,2
Three Antipsychotics	**16**	**7,7**
atypical-typical-typical	11	5,3
atypical-atypical-typical	2	1,0
atypical-atypical-atypical	1	0,5
Typical-typical-typical	2	1,0
Total	**207**	**100,0**

The use of combinations is more in countries in Asia and Europe than North America. The decline in combination use in North America may be due to the availability of second-generation (atypical) antipsychotics. The most common types of combinations as seen in table 3 are between the first (typical) and second (atypical) generations, followed by the two first generations, and two second generations. No more than 1% of patients use more than two drug combinations (Faden et al., 2021). Similarly, in this study, the two most common types of combinations were typical-atypical (30.9%), typical-typical (19.3%), and atypical-atypical (7.2%), and the combination of three drugs did not more than 4.5%. Second generation antipsychotics or better known as atypical antipsychotics have a lower risk of extrapyramidal syndrome and tardive dyskinesia than first generation. Besides being able to overcome delusions and hallucinations, second generation antipsychotics have neuroprotective benefits compared to first generation antipsychotics which are associated with neutotoxic effects (Chen & Nasrallah, 2019; Warnez & Alessi-Severini, 2014).

Although combination antipsychotic therapy is greater than single therapy, the evidence is still highly variable based on the results of a systematic review (Kasteridis et al., 2019). A significant risk from combination therapy is generally due to overdosage is an increase in side effects, such as syndrome metabolic, cognitive impairment, extrapyramidal syndrome, and cardiac disorders, as well as the presence of non-adherence with increasing complexity of management, increased side effects (Barnes & Paton, 2011; Kasteridis et al., 2019). A study conducted in the United Kingdom (UK) showed that combination therapy did not correlate significantly with the incidence of PICU visits, hospital admission, and mortality when compared with single therapy (Kasteridis et al., 2019). In contrast to another study which showed that the combination of clozapine and aripiprazole was associated with a relative risk reduction of up to 10 %-13% of hospital readmissions versus monotherapy (Faden et al., 2021; Tiihonen et al., 2019).

Table 4. Type of combination based on antipsychotic active pharmaceutical ingredient

Type of antipsychotic	Frequency	% (N=207)
Monotherapy	**72**	**34,8**
HALO	14	6,8
CPZ	6	2,9
TFPZ	4	1,9
RPD	47	22,7
OLZ	1	0,5
Two Antipsychotics	**119**	**57,5**
RPD+FPZ	1	0,5
HALO+CLZ	8	3,9
RPD+CLZ	15	7,2
HALO+CPZ	31	15,0
CPZ+TFPZ	9	4,3
RPD+CPZ	45	21,7
RPD+TFPZ	3	1,4
RPD+HALO	7	3,4
Three antipsychotics	**16**	**7,7**
HALO+CPZ+TFPZ	1	0,5
RPD+CPZ+TFPZ	1	0,5
RPD+HALO+TFPZ	1	0,5
RPD+HALO+CPZ	9	4,3
HALO+CPZ+FPZ	1	0,5
RPD+CLZ+OLZ	1	0,5
RPD+CPZ+OLZ	1	0,5
RPD+HALO+CLZ	1	0,5
Total	**207**	**100,0**

Abbreviation: RPD=risperidone; HALO=haloperidol; CPZ=chlorpromazine; CLZ=Clozapine; TFPZ=Trifluoperazine; OLZ=Olanzapine; FPZ= Fluphenazine

The most widely used combination of two antipsychotics was risperidone-chlorpromazine (21.7%) as seen in table 4. In contrast to the study of Dania et al (2019), it was risperidone-clozapine while according to research Indriani (2019), the combination was haloperidol-clozapine (18.2%). The consensus on the management of schizophrenia disorders (2011) states that stabilization or maintenance therapy for schizophrenia can use several types of combinations according to the patient's clinical condition (PDSKJI, 2011).

The type of combination antipsychotic will also affect the outcome of therapy. For example, the addition of a partial D2 receptor agonist such as aripiprazole to clozapine can improve negative symptoms and reduce some side effects, such as weight gain, increased prolactin levels. While the combination of two dopamine receptor antagonists showed a greater increase in prolactin levels but reduced insomnia (Faden et al., 2021; Tiihonen et al., 2019).

Combination other antipsychotic with risperidone or clozapine are widely studied (Faden et al., 2021). Risperidone and clozapine have been shown to be more effective and well tolerated than first generation antipsychotics in chronic schizophrenia patients. Clozapine as monotherapy shows the best therapeutic effect compared to other antipsychotics and is gold standard for schizophrenia patients who are resistant to other antipsychotic combinations (Faden et al., 2021; Tiihonen et al., 2019; Warnez & Alessi-Severini, 2014). Although clozapine is the gold standard, the scope of its use is still low. This can be due to the agranulocytosis effect (Patel et al., 2014; Warnez & Alessi-Severini, 2014). In another study stated that single therapy of each of these antipsychotics showed clinical and behavioral effects that were not significantly different in outpatient stable patients (Kim et al., 2006).The results of another study showed that a comparison between risperidone and clozapine showed that risperidone had a faster onset of severe symptomatic reduction greater than clozapine (Bondolfi et al., 1998).

Risperidone as an atypical antipsychotic works as an antagonist of serotonin (5-HT2) and dopamine-D2 receptors, with a 20 times higher affinity for serotonin so that dissociation from dopamine receptors will be faster and ultimately reduce the extrapyramidal effect (Maylani et al., 2018). Another study stated that the use of a combination of risperidone was more cost effective than the combination of haloperidol (Karaeng et al., 2021). Risperidone compared to other second generation antipsychotics had the least criteria for atypical antipsychotics (Salwan et al., 2013). The drawbacks are more frequent occurrence of movement disorders and a tendency to increase prolactin levels compared to other second-generation antipsychotics (Komossa et al., 2011).

Clozapine has a unique spectrum of action with low affinity for dopamine-D2 so that a stronger dopamine-D2 antagonist or partial dopamine agonist can be added. The addition of a dopamine-D2 antagonist from risperidone can reduce positive symptoms (hallucinations and delusions), while partial agonists (aripiprazole) can improve negative symptoms (Faden et al., 2021). Clozapine has a delayed onset of 8 weeks to 6-9 months (Bondolfi et al., 1998). In addition, clozapine as an antipsychotic with the lowest mortality rate (Pandarakalam, 2019).

Chlorpromazine as the first antipsychotic or benchmark synthesized which was previously widely used as an antihistamine with a strong sedative effect. This first generation has a good reputation because positive symptoms can be overcome. Chlorpromazine is one of the drugs on the 2019 WHO essential list in addition to haloperidol, risperidone, and fluphenazine which are used in psychotic disorders. Newer antipsychotics than chlorpromazine are more expensive and less accessible especially in low and middle income countries (Rathbone et al., 2005). Chlorpromazine in this study reached 49.6% either alone or in combination with 21.7% in combination with risperidone. Chlorpromazine works by blocking alpha-1, 5-HT2A, Dopamine-1, and Dopamine-2 so that it has more side effects (Kb et al., 2016). Comparative studies between the use of clozapine and risperidone showed that there was no significant difference in clinical response but different from the side effects produced (Kb et al.,

2016).Research conducted at a Special Hospital in South Sulawesi showed that the combination of risperidone and chlorpromazine was better in treating agitation symptoms in patients in the first three days of the acute phase but not for long-term use when compared to the combination of risperidone and haloperidol (Syamsuddin et al., 2020).

The combination of haloperidol and chlorpromazine is up to 15%, both of which are typical antipsychotics. Both work as dopamine-2 and dopamine-3 antagonists. Haloperidol has a greater dopamine antagonist effect than chlorpromazine, but has low adrenergic, cholinergic, and histaminergic side effects (Handayani et al., 2017). The purpose of this combination is to strengthen the sedative effect and overcome the positive symptoms of schizophrenia. The disadvantage of this combination is the greater extrapyramidal effect. Overall, the study results show that the haloperidol-chlorpromazine combination leads to a poor quality of life (Hendra, 2020). The research is limited by time then the researcher suggests to have long period as sample. Limitation of this research then about only describe the combination pattern. Effectiveness and cost from first time become an outpatient should be analysis.

CONCLUSION

Risperidone as an antipsychotic is the most widely used either as a single or a combination therapy. The highest number of antipsychotic combinations used two antipsychotics with typical-atypical types of antipsychotics at 30.9%. The three most common combinations were risperidone-chlorpromazine, haloperidol-chlorpromazine, and risperidone-clozapine. Further research needs to be done to see the effectiveness of the combination with different methods.

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