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Cost-Effectiveness of Typical and Atypical Drugs Combination for Outpatients at RSJD Surakarta

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ABSTRACT

Introduction: Schizophrenia treatment requires an analysis of more effective drug combinations, resulting in shorter treatment durations and hospital stays, ultimately reducing overall treatment costs.
Objective: To analyze the cost-effectiveness of two classes of antipsychotic drugs in the treatment of schizophrenia inpatients at Dr. Arif Zainuddin Regional Mental Hospital, Surakarta, in 2022.
Methods: This study is a non-experimental analytical study using purposive sampling. The inclusion criteria were schizophrenic patients in the inpatient unit of the Dr. Arif Zainuddin Regional Mental Hospital in Surakarta. The data used for this study were medical records, drug costs, and the National Assessment and Assessment System (PAANS) obtained from the Administration Department of the Dr. Arif Zainuddin Regional Mental Hospital. This study employed cost-effectiveness analysis techniques using the drug effectiveness formula, ACER, and ICER, which were then analyzed descriptively.
Results: The results of this study concluded that the cost-effectiveness of treating schizophrenic patients with a combination of typical and atypical antipsychotic drugs in the inpatient unit of the Dr. Arif Zainuddin Regional Mental Hospital in Surakarta was significant. The combination of atypical typical antipsychotics, a combination of olanzapine and haloperidol with an ACER value of Rp. 333,620.5 and an ICER value of Rp. 60,005.8/day of treatment with a treatment duration of around 9 to 10 days.
Keywords : Antipsychotics, Drug Costs, Schizophrenia

INTRODUCTION

Mental disorders in individuals are a common issue faced by society, typically caused by worsening economic problems, family conditions, inappropriate parenting patterns, and natural disasters affecting our region. Such situations can lead to various psychological and economic problems, which can negatively impact the mental health of sufferers (Kurniawan et al., 2020). A mental disorder is a syndrome or behavior associated with symptoms of distress that affect one of the body's primary functions. Individuals experiencing mental health problems should be treated in a psychiatric hospital (Devi and Nurjayanti, 2020).

Schizophrenia, as revealed in research by Hasni et al. (2020), is the most severe form of functional mental disorder and can cause significant disruption to self-identity, with a global prevalence of schizophrenia ranging from 0.6% to 1.9%. Schizophrenia contributes approximately 2.6% to the burden of disease in developed countries and 0.8% in developing countries. The causes of schizophrenia are generally related to impaired brain function and structural abnormalities, as well as genetic and environmental factors (WHO, 2018). One treatment method for schizophrenia is the use of antipsychotic medications.

Overall expenditures for schizophrenia are high, with a significant risk of lifelong morbidity. In developed countries, direct costs associated with schizophrenia, including hospital costs, community-based therapy, medications, and services, account for between 1.4% and 2.8% of total national health

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expenditures and nearly one-third of the direct costs for mental disorders (Saputra et al., 2021). According to the American Psychiatric Association, one treatment strategy for schizophrenia involves a combination of clozapine and a first-generation antipsychotic (AGP) such as haloperidol or a second-generation antipsychotic (AGK) such as risperidone. The choice of drug combination can also impact the total costs borne by schizophrenia patients.

In practice, schizophrenia patients often use two drug combinations: haloperidol and risperidone (Putri et al., 2020). Haloperidol is a typical antipsychotic with low potency for treating symptoms such as anxiety, hyperactivity, and difficulty sleeping, known as positive symptoms. Approximately 80% of patients treated with haloperidol experience extrapyramidal reactions (Saputra et al., 2021).

A comparison of the effectiveness of typical and atypical drug combinations for the treatment of schizophrenia patients conducted by Karaeng and Liaury (2018) showed that the average percentage reduction in the PANSS (Positive and Negative Scale Score) in the risperidone combination group reached 25.09% (±10.038), compared to only 15.29% (±10.940) in the haloperidol combination group. From the cost aspect, Nareza (2019) noted that the price per tablet of haloperidol 5 mg is Rp 115 and risperidone 2 mg Rp 2,184. This shows that the unit price of atypical combination tablets is much higher compared to typical combinations, especially when viewed from the frequency and dosage given to patients, where the average cost for risperidone (atypical) is greater than that of haloperidol (typical). For treatment using injections, the latest information shows that the cost for a combination of risperidone injections per unit is Rp 151,800, while the combination of haloperidol injections (with certain trade names) costs Rp 14,260, and haloperidol drops Rp 19,544, and haloperidol injections (with certain trade names) Rp 100,625 in 2021 (Ahyari, 2017). The difference in price and effectiveness between these two drugs underlies the researchers' decision to conduct further research on the effectiveness of drug combinations in schizophrenia patients hospitalized at Surakarta Mental Hospital, considering the high costs that schizophrenia patients have to bear so that the use of drug combinations needs to be studied more deeply.

MATERIALS AND METHODS

This research is a non-experimental analytical study analyzed using a descriptive approach. Data were collected retrospectively from secondary data consisting of medical records and patient administrative data. The subjects in this study were all medical records of patients treated at the inpatient unit of Dr. Arif Zainuddin Surakarta Mental Hospital in 2024.

The sampling method used in this study was purposive sampling, which is a sampling technique based on specific criteria established for the population (Sugiyono, 2016). The sample in this study consisted of a portion of the medical records of schizophrenia patients treated at the inpatient unit of Dr. Arif Zainuddin Surakarta Mental Hospital, with the following inclusion criteria:

1. Patients with schizophrenia (excluding other illnesses) treated at Dr. Arif Zainuddin Surakarta Mental Hospital.
2. Patients receiving therapy using a combination of typical and atypical medications.
3. Patients who showed a calm outcome in 2022.

The exclusion criteria in this study included:

1. Patients who were discharged involuntarily.
2. Patients who absconded during treatment.
3. Patients who died.

This study employed a cost-effectiveness analysis, a pharmacoeconomic method used to compare the effectiveness and cost-efficiency of treatment for schizophrenia patients using a combination of typical and atypical medications. The analysis was conducted by calculating the costs incurred compared to the therapeutic outcomes obtained, using an effectiveness formula based on the outcome scores from the PANSS (Positive and Negative Syndrome Scale Component), ACER (Average Cost-Effectiveness Ratio), and ICER (Incremental Cost-Effectiveness Ratio) (Adisaputra et al., 2021).

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Microsoft Excel was used for data processing in this study. After the necessary data were collected, they were entered into the software to be processed according to the ACER and ICER formulas. Finally, the ACER and ICER values were obtained, which served as the basis for assessing the cost-effectiveness of the two types of antipsychotic therapy being compared.

$$drug\ effectivity = \frac{PANSS\ Score \leq average}{Sample\ total} 100\% \quad \text{.....1}$$

$$ACER = \frac{Direct\ Medical\ cost}{Clinical\ Outcome} \quad \text{.....2}$$

$$ICER = \frac{A\ cost - B\ cost}{A\ drug\ effectivity - B\ drug\ Effectivity\ (\%)} \quad \text{.....3}$$

RESULTS

A. Demographic Data of RSJD Patients in the Period January – June 2024

Table 1. Demographic distribution according to ages, genders, education background and jobs

Demographic criteria	Criteria (years old)	Patients number	Percentage (%)
Ages	< 20	2	3,33
	21 – 30	10	16,67
	31 - 40	22	36,67
	41 - 50	14	23,33
	51 - 60	9	15
	>60	3	5
	Total	**60**	**100%**
	Criteria	**Patients number**	**Percentage (%)**
Genders	Men	45	75
	Woman	15	25
	Total	**60**	**100%**
	Criteria	**Patients number**	**Percentage (%)**
Education Level	no school	10	16,67
	elementary school	15	25
	junior high school	16	26,67
	senior high school	16	26,67
	Diploma/bachelor	3	5
	Total	**60**	**100%**
	Criteria	**Patients number**	**Percentage (%)**
Jobs	unemployment	37	61,67
	employment	21	35
	student	2	3,33
	Total	**60**	**100%**

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B. Profile of Antipsychotic Used in RSJD Patients in the Period January – June 2024

Table 2. Profile of typical and atypical combination drug use and length of treatment of patients at Surakarta Mental Hospital

Antipsychopatic combinations	Number of Days	Percentage (%)
CPZ dan risperidone (first combination)	20	33,33
Haloperidol dan risperidone (second combination)	25	41,67
Olanzepin dan haloperidol (third combination)	5	8,33
Klozapin dan haloperidol (fourt combination)	10	16,67
Total	**60**	**100%**

C. Cost Analysis of the Used of Atypical and Typical Combination Antipsychotic Drugs

Table 3. Overview of the number of patients using a combination of typical and atypical patients at Surakarta Mental Hospital

Antipsychopatic combinations	Number of Patients	Percentage (%)
CPZ dan risperidone	12	20
Haloperidol dan risperidone	28	46,67
Olanzepin dan haloperidol	10	16,67
Klozapin dan haloperidol	10	16,67
Total	**60**	**100%**

Table 4. Average direct medical costs for outpatients with schizophrenia at Surakarta Mental Hospital in 2024

Costs	Fisrt Combination	Second Combination	Third Combination	Fourth Combination	p value
Psychotic cost	Rp 34.809	Rp 24.104	Rp 122.382	Rp 70.206	0,000<0,05
Doctor cost	Rp 80.000	Rp 80.000	Rp 80.000	Rp 80.000	-
Registration	Rp 25.000	Rp 25.000	Rp 25.000	Rp 25.000	-
Acomodation cost	Rp 1.240.417	Rp 1.434.000	Rp 1.107.000	Rp 1.551.990	0,297>0,05
Total cost	Rp 1.380.225	Rp 1.563.104	Rp 1.334.382	Rp 1.727.196	0,406>0,05

D. Effectiveness of Therapy for Schizophrenia Patients at Surakarta Mental Hospital for the Period January – June 2024

Table 5. Description of the effectiveness value of each antipsychotic combination in outpatients at Surakarta Mental Hospital for the period January – June 2024

Mantainance Groups	PANSS scoring average	Average improvement (days)	Length of treatment	Amount of medication used to treat side effects
Fisrt combination	82,91	13,82	16,18	112,73
Second combination	66,44	20,93	13,44	128,26
Third combination	41,55	8,82	9,63	28,82
Fourt combination	41,55	8,82	9,63	28,82

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E. Cost-Effectiveness of Schizophrenia Patients at Surakarta Mental Hospital for the Period January – June 2024 based on ACER

Table 6. Cost-effectiveness overview of outpatient schizophrenia patients at Surakarta Mental Hospital based on ACER value

Criterias	Fisrt Combination	Second Combination	Third Combination	Fourth Combination
Direct medical average (C)	Rp 1.380.225	Rp 1.563.104	Rp 1.334.482	Rp 1.727.196
Therapy Effectiveness (E)	4	4	4	4
ACER value(C/E)	Rp 345.056,25	Rp 390.776,-	Rp 333.620,5	Rp 431.799,-

F. Cost Effectiveness of Schizophrenia Patients at Surakarta Mental Hospital for the Period January – June 2024 based on ICER

Table 7. Cost-effectiveness overview of outpatient schizophrenia patients at Surakarta Mental Hospital based on ICER value

Categories	Cost Difference (ΔC)	Treatment duration difference (ΔE)	ICER value (ΔC/ ΔE)
combination 1 dan 2	-182.879	2,74	-Rp 66.744,2/treatment day
combination 1 dan 3	45.743	6,55	Rp 6.983,7/ treatment day
combination 1 dan 4	-346.971	6,55	-Rp 52.972,7/ treatment day
combination 2 dan 3	228.622	3,81	Rp 60.005,8/ treatment day
combination 2 dan 4	-164.092	3,81	-Rp 43.068,8/ treatment day
combination 3 dan 4	-392.714	0	undefined

DISCUSSION

This study aimed to analyze the cost-effectiveness of typical combination therapy for schizophrenia outpatients at Surakarta Regional Mental Hospital (RSJD) in 2024, including chlorpromazine (CPZ), haloperidol, flupentixol, and trifluoroperazine, and atypical risperidone, olanzapine, aripriprazole, quetiapine, paliperidone, clozapine, and ziprasidone. However, most typical psychotic patients seen at Surakarta Regional Mental Hospital used haloperidol and CPZ, while atypical psychotic patients used olanzapine, clozapine, and risperidone.

Based on patient medical records from January to June 2024, 230 patients used both atypical and typical medications for schizophrenia. However, only 60 patients met the inclusion and exclusion criteria, using a combination of atypical and typical medications. Those who did not meet the criteria used only typical or atypical psychotic medications.

This study used a pharmacoeconomic analysis focused on cost-effectiveness, a method used to assess and select the best program from among several available options (Prawati, 2017). This analysis examined and evaluated the medical costs incurred by patients and the effectiveness of each combination of antipsychotics, both atypical and typical. The results of the study at the Mental Hospital (RSJD) included patient demographic data, treatment data, patient treatment costs, and the cost-effectiveness of patient treatment.

This patient data distribution by age was used to determine the age range most likely to experience schizophrenia during the observation year. Furthermore, this age distribution was also used to analyze the potential association between age and the incidence of schizophrenia. Table 1 above shows that the most common age group treated at Surakarta Mental Hospital (RSJD) was 31–40 years old, accounting for 36.67%. The second most

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common age group was 41–50 years old, accounting for 23.33%. This finding aligns with research conducted by Safitri (2018), which found that 38.46%, or 10 individuals, of patients suffering from schizophrenia treated at the RSJD (Surakarta Mental Hospital) were aged 31–40. The peak age for schizophrenia in both men and women is the age group 30, which occurs due to high stress levels at this age (Rahaya dan Cahaya, 2016). This age group is considered productive, but the burden of problems is quite high (Mora et al., 2012). This is what causes the emergence of schizophrenia.

The distribution of patient data by gender aims to analyze which groups are vulnerable to schizophrenia. Gender-based differences in schizophrenia have been noted since the onset of the disease. Based on the results in Table 1 above, it shows that the majority of patients were male, with a total of 45 people, or 75%. This may be due to the effects of neuropathy in women, while men are more likely to experience head trauma (Seeman, 2004). Women have higher estrogen levels than men, which can protect women from prenatal complications and excessive sleep apnea (Rahaya dan Cahaya, 2016). Estrogen can provide neuroleptic effects by altering postsynaptic dopaminergic signal transduction, thereby inhibiting psychotic symptoms (Falkenburg and Tracy, 2013).

Education level is an important aspect of treatment. Patients with low education levels tend to be less concerned about their quality of life, which can impact the treatment process (Prawati, 2017). Conversely, patients with high education levels are more likely to be critical of their health. Based on the analysis of patient data distribution by educational background, the majority of patients had junior high and high school degrees, representing 26.67%.

Employment status is an important aspect of treatment, alongside educational background. The distribution analysis above shows that nearly 61.67% of patients are unemployed. This occurs because they experience psychosis, making it difficult to focus on work (Prawati, 2017). Furthermore, employment status also impacts the quality of therapy. Working individuals tend to be critical of their own health, making them more concerned about the continuity of their treatment if they experience psychosis. Research by Safitri (2018) found that patients undergoing psychosis therapy experience cognitive impairment, making it difficult to perform tasks. This was why most patients are unable to function effectively and decide to temporarily leave work.

The length of a patient's treatment period will impact the cost of outpatient treatment. According to the WHO, the length of treatment for schizophrenia patients is divided into three categories: acute (<35 days); subacute (35–103 days); and chronic (>103 days). This study found that the maximum length of treatment was 25 days, with a combination of the psychotic drugs haloperidol and risperidone (41.67%), while the minimum length of treatment was 5 days (8.33%).

The use of antipsychotic combinations is believed to reduce positive symptoms, followed by a reduction in negative symptoms (Yulianty et al., 2017). The drug combinations used are based on empirical data or practice, and consideration of patient comfort, with the choice of those with the fewest side effects. Based on the research results in Table 2, the combination of haloperidon and risperidone provided the longest treatment (25 days), followed by CPZ and risperidone (20 days), clozapine and haloperidol (10 days), and olanzapine and haloperidol (5 days). The most effective combination treatment is olanzapine and haloperidol.

The longer the treatment, the higher the patient's costs, making treatment duration a key factor in calculating the cost-effectiveness of schizophrenia treatment. Patients with reduced or stable positive and negative symptoms, those who are able to care for themselves, take their medication, and participate in activities, are considered to be experiencing successful treatment.

Cost analysis was conducted by grouping the types of psychotic medications used in the treatment of schizophrenia patients, where therapy for these patients requires continuity and routine and is not inexpensive (Safitri, 2018). The cost of antipsychotics is the average cost of antipsychotic use based on the antipsychotic components used by the patient. Combination medications are administered simultaneously, and patients who receive additional therapy are expected to experience rapid

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improvement. If there is no improvement, the additional medication will be discontinued (Sukandar et al., 2008). The cost components of psychotic therapy include the cost of antipsychotic medication, non-antipsychotic costs (if any), registration fees, doctor's services/examination fees, and accommodation costs.

Based on the data in Table 3 above, it shows that the number of patients receiving the combination of CPZ and risperidone was 20%, the most patients receiving haloperidol and risperidone at 46.67%, then the combination of olanzepine and haloperidol and clozapine and haloperidol had the same number of patients, namely 16.67%. The analysis of treatment costs was seen based on direct medical costs and the total cost of therapy for each therapy group. Direct medical costs include: antipsychotic costs, nonpsychotic drug costs, registration, medical service costs, and accommodation costs (Parwati, 2017). An overview of the average direct medical costs for patients can be seen in Table 9 below.

Based on the analysis of the average use of direct medical costs, it was found that the psychotic costs between combinations showed a significant difference where the p value = 0.000 <0.05, while for accommodation costs and total costs there was no significant difference because the p value> 0.05. Based on the results in Table 4 above, the highest psychotic costs were in combination 3, namely the combination of olanzapine and haloperidol with an average cost of IDR 122,382. Haloperidol is a drug that has a strong antipsychotic function but has a low sedative effect, and is cheaper (Rahardja, 2015), while olanzapine, which is a long-acting derivative that is effective in inhibiting other neurotransmitters, has an extraordinary effect of increasing positive and negative symptoms compared to other antipsychotics. In addition, olanzapine has the smallest pyramidal effect (Rahmaningtyas et al., 2020). Next came combination 4, clozapine and haloperidol, at a cost of Rp 70,206. The cheapest was combination 2, haloperidol and risperidone.

The registration and doctor service fees charged to patients were the same, except for BPJS patients, where registration was Rp 25,000 and doctor services were Rp 80,000. Table 4.6 shows that the highest accommodation and total costs were for combination 4, followed by combination 2, combination 1, and combination 3. This indicates that effective and efficient use of antipsychotic medication will result in minimal patient expenditure during treatment. Accommodation costs represent the costs incurred by patients during treatment, including transportation and meals during hospitalization. However, there was no statistically significant difference between the accommodation costs for each combination, with a p-value >0.05, indicating that accommodation costs did not affect treatment costs.

The costs of antipsychotics, accommodation costs, registration fees, and doctor services were important components in this study. The total costs were a component used to calculate cost-effectiveness. The average total cost of each psychotherapy group is compared to the effectiveness of the therapy, making it a significant component.

The effectiveness of antipsychotics in treating schizophrenia is determined by improvements in the PANSS score, minimal pyramidal effects, and duration of treatment. A patient is considered stable if their PANSS score is also stable. Scoring is performed by completing a PANSS symptom checklist, which includes the number of symptoms occurring during treatment, the speed with which antipsychotics improve negative and positive symptoms, the duration of treatment for each therapy, and the amount of medication used to alleviate side effects (Tanti et al., 2012).

Scoring is based on the following criteria: 1 is given if the average daily PANSS symptoms are lower, and 0 is lower; 0 is given if the PANSS improvement is faster, and 0 is lower; 1 is given if the treatment duration is shorter, and 0 is lower; and 1 is given if the medication used to alleviate extrapyramidal symptoms (EPS) is lower, and 0 is lower.

Table 5 above shows that combination 1 had the highest PANSS score of 82.91, indicating that it required a longer treatment period to reduce both positive and negative symptoms. This was followed by combination 2, which showed a PANSS score of 66.44, and combinations 3 and 4, which had the same PANSS score, were the lowest. This indicates that combinations 3 and 4 were more

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effective than combinations 1 and 2 in terms of therapeutic effectiveness in reducing both positive and negative symptoms.

Based on the duration of PANSS improvement, combinations 3 and 4 remained the fastest, at approximately 8.82 days, while combination 1 still required approximately 13.82 days, and combination 2 took the longest, at 20.93. The shortest treatment duration is a combination of 3 and 4 followed by combination 2 and then the longest combination 1, in contrast to the number of drugs used to reduce EPS, which is the least combination of 3 and 4 then followed by combination 1 and the most combination 2. This could be concluded that the best therapeutic effectiveness is in combination 3 and 4.

Cost-effectiveness was calculated by calculating the ACER (Acer-Effectiveness Indicator), which compares total direct medical costs with observed patient clinical outcomes. Based on the analysis, the lowest ACER value was obtained for combination 3, at IDR 333,620.5, followed by combination 1 with an ACER of IDR 345,056.25; combination 2 with an ACER of IDR 390,776; and finally, combination 4 with IDR 431,799. The best therapeutic effectiveness and cost analysis can be concluded as combination 3, which boasts very high therapeutic effectiveness, coupled with cost effectiveness, resulting in a short treatment period with minimal costs.

The Average Cost-Effectiveness Ratio (ACER) is calculated based on the ratio of therapeutic costs. In this study, the therapeutic costs are the direct medical costs of each antipsychotic drug combination compared to the therapeutic effectiveness of each combination (Afitriyani et al., 2024). The lower the ACER value, the more effective the therapy. The most effective combination in this study was the atypical-typical combination (olanzepine and haloperidol), as this combination had fewer side effects compared to the atypical and typical groups alone (Abdulah et al., 2020). This research aligns with research conducted by Azani et al. (2022), which stated that the most effective antipsychotic combination, in terms of minimizing the risk of extrapyramidal syndrome (EPS), was the combination of atypical and typical. The study also found that this combination was most effective in reducing PANSS scores, despite the high cost of therapy. This was the case with combination 4, clozapine and haloperidole (atypical-typical).

However, in alternative ACER measurements, the most cost-effective is not necessarily the lowest cost to achieve a more specific therapeutic goal (Andriani et al., 2015). ACER observed that the combination of antipsychotic drugs considered to be more cost-effective was not only based on the lowest cost, but also on cost optimization, which indicated improvements in health or symptoms (Afitriyani et al., 2024).

Cost-effectiveness analysis, as applied in pharmacoeconomics, is used to determine the most efficient therapeutic intervention alternatives at discounted costs to achieve better outcomes (Madania et al., 2022). Cost-effectiveness analysis based on the ICER value refers to the calculation of the costs incurred to increase therapeutic effectiveness by switching from one treatment to another (Yuswantina, 2018). Cost analysis calculations using the ICER are conducted to provide several applicable alternative options, where the choice of treatment alternative is adjusted based on budget considerations or the availability of the alternative (Andriani et al., 2015).

The results in Table 7 above show that the comparative value of each drug combination used per treatment varies per day. If a patient has received a combination of chlorpromazine and haloperidol (combination 1), switching to combination 2 would require an additional cost of Rp 66,744.2 per treatment day, with a shorter treatment duration (approximately 13 to 14 days). If the initial therapy was combination 1 and the patient wishes to switch to combination 3, the cost would be reduced by Rp 6,983.7 per treatment day, with a shorter treatment duration (between 9 and 10 days). If the patient started treatment with combination 2 and wishes to switch or is recommended to switch to combination 3, the cost would be lower than the original cost of Rp 60,005.8 per treatment day, with a treatment duration of approximately 9 to 10 days. These results indicate that combination 3 has a more effective switching effectiveness value compared to the other three combinations.

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The ICER value obtained represents the additional or reduced costs incurred by patients to receive more effective therapy. In this study, it was assessed based on the length of treatment. If the ICER value is negative, the additional costs required to achieve greater therapeutic effectiveness are greater. Conversely, if the ICER value is positive, there is a reduction in therapeutic costs to achieve higher effectiveness (Citraningtyas et al., 2018). The results of the study showed that it has better cost effectiveness compared to the three combination therapies used by patients to treat psychosis at Surakarta Mental Hospital (RSJD) as seen from its ICER value.

CONCLUSIONS

Based on this study, it could be concluded that the cost-effectiveness of treating schizophrenia patients with a combination of typical and atypical antipsychotic drugs in the inpatient installation at Dr. Arif Zainuddin Surakarta Mental Hospital was a combination of typical atypical antipsychotics, a combination of olanzapine and haloperidol with an ACER value of Rp. 333,620.5 and an ICER value of Rp. 60,005.8/day of treatment with a treatment duration of around 9 to 10 days.

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