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Cost-utility analysis of olanzapine versus combination of haloperidol-diazepam in patients with acute phase schizophrenia: An Indonesian context

Hesty Utami Ramadaniati[1*], Yusi Anggriani[1], Fredrick Dermawan Purba[2], Desweri Muhareni[1]

[1]Faculty of Pharmacy, Pancasila University, South Jakarta, Indonesia.
[2]Faculty of Psychology, Padjadjaran University, Bandung, Indonesia.

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ABSTRACT

This study aimed to estimate the cost per quality-adjusted life-year (QALY) of olanzapine versus the combination of haloperidol-diazepam in acute phase schizophrenia. An observational study was conducted in a psychiatric hospital in Indonesia involving acute phase schizophrenic patients receiving either olanzapine or combination of haloperidol and diazepam. The outcome measures included Positive and Negative Syndrome Scale (PANSS) score, length of stay in acute room, utility score, and QALY. PANSS score and utility score were rated by psychiatrists and nurses, respectively, at the initiation of study medicines and after patient stabilization (postintervention). Calculated costs were direct medical costs with third-party payer perspective. QALY was determined by multiplying the utility score by the duration of the treatment effect to provide the number of QALY gained. A total of 193 patients (102 in olanzapine group/OG *vs*. 91 in haloperidol-diazepam group/HG). Postintervention, PANSS score significantly decreased by 16.09 in OG and 14.64 in HG. Patients in the two groups spent similar amount of time in acute room (i.e., 3–6 days). Both groups showed no significant difference in utility score and QALY post-treatment. Olanzapine incurred higher costs (US 20.89/QALY) than the comparator ($US 18.10/QALY). In conclusion, the combination of haloperidol-diazepam was a cost-effective option for treating acute phase schizophrenia.

INTRODUCTION

Schizophrenia is a psychiatric disorder characterized by symptoms of chronic or recurrent psychosis. It is commonly associated with social and occupational impairments. Unsurprisingly, this debilitating medical condition was among the major causes of disability worldwide (Institution of Health Metrics and Evaluation, 2019). The 2018 World Health Organization Report highlighted the low prevalence of schizophrenia as opposed to other mental disorders. It was cited in the report that depression is the most common mental disorder with 300 million patients globally followed by bipolar disorders (60 million), while the prevalence of schizophrenia and other psychoses constituted less than one-tenth of those with depression, i.e., 23 million cases (World Health Organization, 2018). In the context of Indonesia, the Basic Health Survey conducted by the Ministry of Health in 2013 reported the prevalence of schizophrenia was 1.7% corresponding to two households with schizophrenia in every 1,000 study households. Over the next 5 years, a similar survey signified the considerable increase of prevalence to 7% which is equivalent to 470,000 schizophrenia cases (Indonesian Ministry of Health, 2018).

Despite its low prevalence, schizophrenia is associated with a higher risk of mortality where schizophrenic patients are nearly three times more likely to die earlier than the general population mainly due to cardiovascular disease, metabolic disorders, and infections (Ringen *et al*., 2014). In addition, this condition has significant ramifications on social and economic

**Corresponding Author*
Hesty Utami Ramadaniati, Faculty of Pharmacy Pancasila University, South Jakarta, Indonesia.
E-mail: hesty.utami @ univpancasila.ac.id

aspects for patients, families, healthcare providers, and society (Chong *et al*., 2016). Mental health disorders including schizophrenia are part of the main causes of the global burden of disease, and around one-third of the disease burden is attributable to productivity losses (Vos *et al*., 2015). A systematic review to investigate the economic burden of schizophrenia in some countries revealed that annual costs for patients with schizophrenia in each country ranged from US $94 million to US $102 billion with indirect costs accounting for the largest proportion of the total costs. The aforementioned review also estimated that the economic burden of this disease was approximately 0.02%–1.65% of the gross domestic product (Chong *et al*., 2016). A more recent review to estimate the societal cost of schizophrenia across middle- and high-income countries signified the large economic burden of schizophrenia. It was revealed that the annual societal cost per patient varied considerably from just below US $6,000 in Thailand to almost US $100,000 in Norway. Furthermore, that review also highlighted direct medical costs and productivity losses as the major contributor (Jin and Mosweu, 2017). In reference to a report from Indonesia's Social Security Agency for Health, total direct medical costs for mental disorders in 2016 were IDR 730 billion (US $50 million) with inpatient care-related cost dominating the proportion. Schizophrenia accounted for the highest amount of healthcare spending in comparison to other mental disorders (Badan Penyelenggara Jaminan Sosial-Kesehatan (Indonesian Social Security Agency for Health), 2017). Schizophrenia was still responsible for the highest economic burden of mental disorders in 2020 where the costs for treating inpatients and outpatients with schizophrenia were approximately IDR 282 billion (US $19.6 million) (Badan Penyelenggara Jaminan Sosial-Kesehatan (Indonesian Social Security Agency for Health), 2022).

Antipsychotic medications are the first-line medication treatment for acute psychosis, symptom reduction, and relapse prevention in patients with schizophrenia. It is recognized in numerous national and international guidelines that patients with schizophrenia should be treated with first- or second-generation antipsychotics. The choice of antipsychotics should be based on a combination of treatment efficacy, tolerability, and patient/carer preference (Kementerian Kesehatan Republik Indonesia (Indonesian Ministry of Health), 2015; National Institute for Health and Care Excellence, 2014; Remington *et al*., 2017; The American Psychiatric Association, 2020). The management of acute psychosis requires timely intervention using injectable antipsychotics to control severe symptoms and to minimize any harm to patients and others. Treatment with conventional (first-generation) antipsychotics such as haloperidol in conjunction with benzodiazepines has been used as the mainstay treatment for acute psychosis, yet the poor tolerability of conventional antipsychotics due to their side effects (e.g., extrapyramidal symptoms, tardive dyskinesia) was experienced by many patients compromising their benefit for long-term treatment (Uçok and Gaebel, 2008). Meanwhile, second-generation antipsychotics offer a more favorable side-effect profile despite their considerable costs (Wei Xin Chong *et al*., 2016). Olanzapine injection (second-generation antipsychotic) and a combination of haloperidol and diazepam injections constituted the most highly used antipsychotics in one of the major public psychiatric hospitals in Jakarta, Indonesia. Interestingly, the price of olanzapine was 44 times higher than that of the combination of haloperidol and diazepam necessitating pharmacoeconomic evaluation to justify the costs and the treatment outcomes.

In addition to epidemiological measures such as morbidity and mortality, the economic burden of mental disorders including schizophrenia should be thoroughly investigated through cost-of-illness studies within health economics. Cost-effective analysis (CEA) comparing antipsychotics in schizophrenia is widely available, yet the studies focusing on the cost-utility analysis of schizophrenic treatments are less common than their CEA counterpart. Quantifying patients' quality of life through utility analysis is of importance in economically catastrophic and disabling medical conditions like schizophrenia. Thus, the objective of this study was to estimate the cost per quality adjusted life-year (QALY) of olanzapine injection versus the combination of haloperidol and diazepam injections in patients with acute-phase schizophrenia.

METHODS

Study design and patient selection

A prospective cohort observational three-month study was conducted in a public psychiatric hospital in Jakarta, Indonesia. A purposive sampling approach was applied in our study. Sample size was determined using Krejcie and Morgan's table. It was estimated that over three months there were 160 patients receiving olanzapine injections and 120 patients receiving a combination of haloperidol-diazepam injections. Based on Krejcie and Morgan's table, the sample size for the olanzapine group was 113 patients and for the haloperidol-diazepam group was 92 patients (Krejcie and Morgan, 1970). The inclusion criteria were acute schizophrenic inpatients (aged >17 years) who were treated in an acute room and received either olanzapine intramuscular injections or a combination of haloperidol and diazepam intramuscular injections during the study period. Deceased patients during hospitalization, patients referred to other hospitals, patients admitted several times during the study, and patients readministered the study medicine after being transferred to a quiet room were excluded. An acute room is an isolation room designed for schizophrenia patients with acute agitation and PANSS-EC score $\geq$ 20. This study had been approved by the Institutional Ethics Committee (No. Sket/02/2019/KEPK), and patient confidentiality was maintained throughout the study.

Study instrument and data collection

The principal researcher collected the patients' sociodemographic information and clinical characteristics from medical records. The direct medical costs (medicine, medical devices, medical consumables, physician visits, laboratory testing, radiology examination, and patient accommodation) were sourced from financial records. The perspective of the study was the third-party payer. The outcome measures included Positive and Negative Syndrome Scale Excited Component (PANSS-EC) score, length of stay in the acute room, utility score, and QALY. The PANSS-EC consisted of five items: excitement, tension, hostility, uncooperativeness, and poor impulse control. The five items from the PANSS-EC were rated from 1 (not present) to 7 (extremely severe); scores ranged from 5 to 35; mean scores $\geq$ 20

clinically correspond to severe agitation (Montoya *et al*., 2011). Patients were transferred from the acute room to the quiet room if they demonstrated symptom improvement and had PANSS-EC ≤ 15 or the score for each item was ≤ 3. Meanwhile, the utility score (between 0.0 and 1.0) was measured using the Indonesian EQ-5D-5L questionnaire. The questionnaire was the most frequently used instrument to evaluate health-related quality of life. The EQ-5D-5L consisted of five dimensions: mobility, self-care, usual activities, pain/discomfort, and anxiety/depression. Each dimension had five levels: no problems, slight problems, moderate problems, severe problems, and unable/extreme problems. This EQ-5D-5L descriptive system was followed by rating of overall health status on a visual analog scale ranging from 0 ("worst health you can imagine") to 100 ("best health you can imagine") (Purba *et al*., 2017).

The PANSS-EC score and utility score were rated by psychiatrists and nurses, respectively. The rating of PANSS-EC score and utility score was done two times, i.e., at the initiation of study medicines in the acute room (baseline assessment) and immediately before patient transfer from the acute room to the stabilization room (after intervention). The measure for the economic evaluation was QALYs. QALYs were calculated by multiplying the utility score by the duration of the treatment effect to provide the number of QALYs gained. Utility estimates were determined by converting the results of the five dimensions obtained from the EQ-5D-5L questionnaire using the Indonesian EQ-5D-5L value set validated by Purba *et al*. (2017). According to Purba *et al*. (2017), there were approximately 3,125 combinations of five dimensions to specify health states. The resulting utility values were obtained by entering each health state combination (e.g., 12,311) into the model of the final value set. Furthermore, the duration was determined by calculating the difference between the average of life expectancy and the average age at diagnosis. The average of life expectancy was set at 69.3 years (men) and 71 years (women), whilst the average onset at diagnosis was 25 years for both genders. The cost-utility ratio was calculated by dividing the direct medical costs by the QALYs.

Data analysis

Categorical data were presented as numbers and percentages, whilst continuous data were presented as mean ± standard deviation (SD). The chi-square test was used to compare categorical data. Continuous data, i.e., PANSS-EC score, utility score, and QALY, between the two treatment groups were compared using the Mann-Whitney test. The differences in PANSS score, utility score, and QALY between the baseline and final assessment (after intervention) in each group were analyzed using the Wilcoxon test. Data were analyzed using IBM SPSS Statistics for Windows (version 23.0). A p value < 0.05 was considered to be statistically significant. For pharmacoeconomic analysis, a cost-utility analysis was conducted to calculate the cost-utility ratio (CUR) for each treatment and incremental cost-utility ratio (ICUR).

RESULTS

There were 193 patients in this study of whom 102 patients received olanzapine injections and 91 patients were administered a combination of haloperidol and diazepam injections for treating acute-phase schizophrenia. As depicted in Table 1, both groups were comparable in regard to sociodemographic and clinical characteristics. The aforementioned characteristics have been published elsewhere previously (Muhareni *et al*., 2021). It can be seen in Table 1 that patients aged 26–45 years accounted for more than half of the patients in each group. There was no discernible difference in terms of gender as more males than their counterparts were observed in either group. With respect to residential status, a similar proportion of patients either lived with their families or resided in social housing managed by the government. It is quite interesting that approximately 1 in 2 patients had normal body mass index indicating that more patients had an overall good nutritional status. A similar profile of coexisting diseases was found in both groups with the majority of the patients not having any comorbidity. Nearly all patients had a baseline PANSS-EC score > 20, and they required acute treatment to manage their schizophrenia.

Data related to patients' outcome measures during acute schizophrenia treatment are detailed in Table 2. At baseline, there was no significant difference in PANSS score where the patient on average had severe acute schizophrenia. After administration of study medicines, the PANSS score significantly decreased by 16.09 in the olanzapine group and 14.64 in the other group. After the intervention, there was a significant difference in change of PANSS score between both groups (p = 0.021) indicating that the administration of olanzapine injection generated greater improvement in patients' symptoms than its counterpart. With respect to the length of stay in the acute room, there was no significant difference in duration of stay between the patients in the two groups as more than three-quarters of the patients spent around 3–6 d. Data related to the PANSS score and length of stay of this study have been published elsewhere (Muhareni *et al*., 2021). Similar baseline utility scores and QALYs were observed in both groups. Patients in each group had a baseline utility score of approximately 0.62 for each year of life saved, and the score increased significantly by 0.18 and 0.15 in the olanzapine group and the combination of haloperidol-diazepam group, respectively. It is worth noting that any of the study medicines was able to improve patients' utility scores to a similar extent. In line with the postintervention utility score, there was no significant difference in additional QALYs at the final assessment of the acute phase. Patients receiving olanzapine injection could gain approximately an extra seven years versus eight years in those taking the combination of haloperidol-diazepam injections.

Table 3 outlines the direct medical cost for each patient during acute treatment. As detailed in Table 3, the total cost in the olanzapine group was significantly higher (p = 0.000) than its counterpart with nearly IDR 2.5 million per patient being documented in patients receiving olanzapine as opposed to approximately IDR 1,8 million in those taking haloperidol-diazepam. Furthermore, a remarkable difference was also observed in the cost of medicine in which the cost of the olanzapine injection was almost eight times higher than that of the haloperidol-diazepam injections.

The administration of either of these acute treatments was associated with increase in QALY at a relatively low increase in cost. As described in Table 4, acute treatment using olanzapine injection would cost approximately IDR 300,000 (US $20.89)

Table 1. Socio-demographic and Clinical Characteristics of Acute Phase Schizophrenic Patients (Muhareni *et al*., 2021).

Characteristics	Olanzapine (N=102) No. (%)	Combination of Haloperidol and Diazepam (N=91) No. (%)	P-value*
Age (years)			**0.325**
17-25	18 (17.6)	13 (14.3)	
26-35	39 (38.2)	35 (38.5)	
36-45	21 (20.6)	23 (25.3)	
46-55	13 (12.7)	17 (18.7)	
56-65	10 (9.8)	3 (3.3)	
>65	1 (1.0)	0	
Gender			**0.140**
Male	65 (63.7)	67 (73.6)	
Female	37 (36.3)	24 (26.4)	
Residential Status			**0.458**
Living with family	57 (55.9)	46 (50.5)	
Living in government-owned social housing	45 (44.1)	45 (49.5)	
Body Mass Index			**0.347**
Underweight	11 (10.8)	16 (17.6)	
Normal	66 (64.7)	48 (52.7)	
Overweight	13 (12.7)	13 (14.3)	
Obese	12 (11.8)	14 (15.4)	
Comorbidities			**0.830**
No comorbid	63 (61.8)	53 (58.2)	
Anemia	10 (9.8)	6 (6.6)	
Dermatitis	1 (0.9)	2 (2.2)	
Dyspepsia	1 (0.9)	2 (2.2)	
Epilepsy	9 (8.8)	3 (3.3)	
Hypertension	0	1 (1.1)	
Hypokalemia	11 (10.8)	12 (13.2)	
Scabies	9 (8.8)	9 (9.9)	
Upper respiratory infection	1 (0.9)	2 (2.2)	
Baseline PANSS Score			**0.167**
Moderate (15-20)	4 (3.9)	4 (4.4)	
Moderate Severe (21-25)	29 (28.4)	34 (37.4)	
Severe (26-30)	51 (50.0)	31 (34.1)	
Extreme (31-35)	18 (17.0)	22 (24.2)	

*Statistical analysis used Chi-Square test

per extra QALY, whilst a lower cost was observed in patients taking haloperidol-diazepam injection where this combination would cost around IDR 260,000 (US $18.10) for each additional QALY. When taking QALY into consideration, both acute treatments demonstrated the same effectiveness with a higher cost found in the olanzapine group than its counterpart indicating the combination of haloperidol-diazepam was a cost-effective option compared with olanzapine (see Table 5). In this sense, the combination of haloperidol-diazepam was the dominant choice, and ICUR calculation was not necessarily conducted.

Table 2. Outcome Measures of the Study Patients.

Variables	Olanzapine (N=102)	Combination of Haloperidol and Diazepam (N=91)	P-value*
PANSS Score (Mean±SD)			
Baseline	28.28±3.80	28.14±4.09	0.624
Post intervention	12.47±2.49	13.52±1.95	0.030
Difference within group	16.09±4.39 (0.000)	14.64±4.50 (0.000)	0.021
(p-value)#			
Length of stay in acute room in days (No, %)			0.699
1-2	2 (1.9)	2 (2.2)	
3-4	38 (37.3)	32 (35.2)	
5-6	46 (45.1)	40 (43.9)	
7-8	13 (12.8)	16 (17.6)	
9-10	3 (2.9)	1 (1.1)	
Utility Score (Mean±SD)			
Baseline	0.62±0.09	0.62±0.08	0.899
Post intervention	0.79±0.04	0.77±0.06	0.017
Difference within group	0.18±0.07 (0.000)	0.15±0.06 (0.000)	0.083
(p-value)			
Quality Adjusted Life Years (Mean±SD)			
Baseline	28.34±4.35	28.08±3.75	0.668
Post intervention	36.3±2.34	34.92±3.15	0.000
Difference within group (p-value)#	7.96±3.21 (0.000)	6.85±2.87 (0.000)	0.180

PANSS = Positive and Negative Syndrome Scale
SD = Standard Deviation
*Mann-Whitney was employed for statistical analysis for PANSS score, utility value and Quality Adjusted Life Years, whilst Chi-Square test was used for analyzing length of stay in acute room
#Difference within group pre- and post-treatment was analyzed using Wilcoxon test

Table 3. Direct Medical Cost Per Patient During Acute Schizophrenia

Direct Medical Cost in IDR (Mean±SD)	Olanzapine (N=102)	Combination of Haloperidol and Diazepam (N=91)	P-value*
Medicine	678,128±202,258	86,928±8,567	0.000
Medical device and consumables	6,946±8,567	20,704±16,029	0.000
Physician visit	211,764±74,891	199,560±57,405	0.283
Accommodation	1,298,872±375,956	1,238,120±330,439	0.552
Laboratory testing	244,166±100,442	251,648±111,768	0.752
Radiology Examination	6,764±3,054	0	0.033
Total cost	**2,446,644±814,719**	**1,796,962±408,376**	**0.000**

*Mann-Whitney was employed for statistical analysis
IDR= Indonesian Rupiah

Table 4. Cost Utility Ratio Calculations.

Variables	Olanzapine (N=102)	Combination of Haloperidol and Diazepam (N=91)	P-value*
Total direct medical cost per patient in IDR (Mean)	2,446,644	1,796,962	0.000
QALY difference pre- and post-intervention within group (Mean)	7.96	6.85	0.180
Average cost per QALY	307,367	262,330	

IDR = Indonesian Rupiah, QALY= quality-adjusted life years
*Statistical analysis used Chi-Square test

Table 5. Alternative Position of Olanzapine Injection and Combination of Haloperidol-Diazepam Injections (Rascati, 2009).

Cost or Outcome	Lower Cost	Same Cost	Higher Cost
Less Effective	A (ICUR calculation is required)	B	C
Same Effectiveness	D **Haloperidol and Diazepam Injections**	E	F **Olanzapine Injection**
More Effective	G	H	I (ICUR calculation is required)

DISCUSSION

Our study uncovered that the improvement of positive and negative symptoms of schizophrenia during exacerbation was statistically higher in patients given olanzapine than in those given haloperidol (in combination with diazepam). The PANSS score of olanzapine recipients decreased by 16.09 which was considerably lower ($p = 0.02$) than haloperidol recipients (PANSS score = 14.64). The superiority of olanzapine in reducing schizophrenia symptoms was also documented in some published studies (Beasley *et al*., 2003; Bhana *et al*., 2001; Leucht *et al*., 2009; Pinem, 2010; Tollefson *et al*., 1997). Consistent with our finding, a study involving schizophrenia patients with moderately severe to very severe agitation in an Indonesian hospital reported that olanzapine significantly decreased PANSS score within 2 h and 4 h following administration of the study medicines. That study also demonstrated significantly greater improvement in agitation severity ($p = 0.015$) at 4 hours after injection with 80% of olanzapine recipients having mild agitation compared to 50% of haloperidol recipients (Pinem, 2010). A multicenter six-week study conducted in 174 sites in Europe and North America also demonstrated better improvements in behavioral agitation during acute-phase schizophrenia in olanzapine recipients than in haloperidol counterparts (Tollefson *et al*., 1997). The superiority of olanzapine to haloperidol was observed not merely during acute psychosis. Olanzapine-treated patients showed a significantly lower one-year risk of psychotic relapse than those given haloperidol during long-term maintenance treatment (Beasley *et al*., 2003). Likewise, a meta-analysis comparing the efficacy of first-generation antipsychotics and that of second-generation comparators revealed that four second-generation antipsychotics (i.e., amisulpride, clozapine, olanzapine, and risperidone) outperformed the older antipsychotics (including haloperidol) in the improvement of positive and negative symptoms and overall symptoms (Leucht *et al*., 2009). Nonetheless, our results were somewhat different from those documented in a 24-week effectiveness study by Gründer *et al*. (2016) with no differential effects on PANSS score between typical antipsychotics (i.e., haloperidol, flupentixol) and atypical antipsychotics (i.e., aripiprazole, olanzapine, and quetiapine).

In addition to PANSS score improvement, we also assess the effectiveness of olanzapine and haloperidol on the patients' quality of life. When comparing the findings of this study with other studies, we have found mixed findings. To some extent, the result of the present study was consistent with that of an American study where olanzapine demonstrated no significant advantages in improving compliance to treatment and overall quality of life compared with haloperidol (in combination with benztropine). Further, that study observing patients over a year found olanzapine and haloperidol had similar effectiveness in controlling positive and negative symptoms notwithstanding olanzapine's superiority in reducing akathisia and improving cognition. Olanzapine was also associated with significantly higher costs and incidence of weight gain (Rosenheck *et al*., 2003). Another study conducted in the USA by Hamilton *et al*. (1999) also found that olanzapine was not significantly superior ($p = 0.094$) in improving patients' quality of life during six-week treatment in the acute phase. It was reported in that study that 33% of olanzapine recipients and 25% of haloperidol recipients showed clinical improvement in quality of life. Contrary to our result, Hamilton *et al*. (1999) observed that olanzapine treatment had significantly lower inpatient total medical costs than its haloperidol counterpart (US $5,125 *vs.* US $5,795, $p = 0.038$) despite the medicine cost of olanzapine being significantly higher than haloperidol (US $5,125 *vs.* US $5,795, $p = 0.038$). These findings indicated that olanzapine would be a cost-effective option compared to haloperidol. In two six-month observational Spanish studies, patients receiving olanzapine experienced significantly greater improvement in all dimensions of the EQ-5D visual analog scale than those given haloperidol (median change 20.5 in the olanzapine group *vs.* 12.5 in the haloperidol group, $p < 0.05$) (Gómez *et al*., 2000; Sacristán *et al*., 2000). Olanzapine as the dominant strategy in improving patients' quality of life was also reported by Tunis *et al.* in which olanzapine could save US $1,632.50 per unit improvement in physical health and functioning score and US $5,654.74 per additional gain in the mental health and functioning factor (Tunis *et al*., 1999). Similarly, better improvement in quality of life related to olanzapine use has been uncovered in a randomized double-blinded study involving schizophrenia outpatients recruited from some hospitals in Germany. This six-month study reported that patients receiving one of the second-generation antipsychotics (aripiprazole, olanzapine, and quetiapine) demonstrated significantly greater improvement in quality of life than those taking either first-generation antipsychotic (haloperidol or flupentixol). However, this German study did not report any cost calculation, so it is unlikely to assess the cost-effectiveness of the antipsychotics (Gründer *et al*., 2016).

The efficacy of antipsychotics is usually quantified by the reduction of psychopathological symptoms (e.g., positive and negative symptoms). Nevertheless, other effectiveness measures such as quality of life, subjective well-being, and social performance have been considered as important outcomes. Further, the importance of patients' perspectives should be taken into account when evaluating their quality of life. In this sense, the assessment of antipsychotic effectiveness including quality of life requires a combination of subjective self-rated and observer-rated examination (Hayhurst *et al*., 2014). The result of our study might differ considerably if self-rated assessment by patients was applied to

evaluate the quality of life. It has been suggested that the assessment of antipsychotic effectiveness solely based on objective examination may undermine the clinical profile of an individual antipsychotic (Gründer *et al*., 2016). Furthermore, the efficacy of antipsychotics should be balanced with their side effects. Olanzapine has a greater affinity for serotonin 5-hydroxytriptamine$_{2A}$ receptors than for the dopamine D_2 receptor and a high affinity for all muscarinic receptor subtypes. Meanwhile, haloperidol acts as an antagonist of D_2 receptors with very high affinity and has a low affinity for alpha$_2$ receptors and all muscarinic subtypes (Zhang and Stackman, 2015). As a consequence of their mechanism of action, it was noted in a meta-analysis that olanzapine was associated with significantly less incidence of extrapyramidal side effects (relative risk = 0.39, p value < 0.0001) than haloperidol (Leucht *et al*., 2009). However, olanzapine and most atypical antipsychotics were associated with an increased risk of metabolic adverse effects. Different properties of the efficacy and safety of each antipsychotic require individualization strategies for treating patients with schizophrenia (Gründer *et al*., 2016; Leucht *et al*., 2009).

The results of our study should be interpreted with caution as it has some limitations. This study was conducted in one hospital thus limiting its generalizability. Furthermore, it is difficult to determine the extent to which the results of our study are generalizable to other studies. The differences in study settings, i.e., the phase of schizophrenia (acute psychosis, stabilization, or remission), type of patients (inpatients or outpatients), heterogeneity in the measured costs, and distinction in study instruments, might lead to different results between ours and other published studies. In addition, the assessment of the quality of life in our study was merely undertaken during an acute exacerbation. The nature of an acute exacerbation is likely to correlate well with more ready outcome measures, i.e., symptom reduction. Thus, the impact of antipsychotics might require long-term study (not during acute psychosis) to adequately evaluate their roles in improving quality of life. In terms of the cost component, our study focused on direct medical costs. Social care elements for patients such as employment rates and reduced work-related productivity were not considered; thus, this analysis may underestimate the benefits of treatment with olanzapine. It has been evident that the direct costs of schizophrenia treatment are substantial, yet the indirect costs including societal costs may be at least as expensive as the direct costs (Bhana *et al*., 2001).

CONCLUSION

When compared with olanzapine, haloperidol (combined with diazepam) appears to be a dominant strategy for treating acute psychosis in schizophrenia, resulting in cost savings and similar QALYs. However, olanzapine may represent a cost-effective treatment option when considering psychopathological symptom reduction and length of stay during the acute phase. The selection of antipsychotics should also take into account patients' tolerability to their side effects and the outcome measures during long-term maintenance therapy.

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AUTHOR CONTRIBUTIONS

All authors made substantial contributions to conception and design, acquisition of data, or analysis and interpretation of data; took part in drafting the article or revising it critically for important intellectual content; agreed to submit to the current journal; gave final approval of the version to be published; and agree to be accountable for all aspects of the work. All the authors are eligible to be an author as per the international committee of medical journal editors (ICMJE) requirements/guidelines.

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CONFLICTS OF INTEREST

The authors report no financial or any other conflicts of interest in this work.

ETHICAL APPROVALS

This study had been approved by the Institutional Ethics Committee (No.Sket/02/2019/KEPK), and patient confidentiality was maintained throughout the study.

DATA AVAILABILITY

All data generated and analyzed are included within this research article.

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