Cost-Effectiveness Analysis of Long-acting Injectable Once-monthly of Aripiprazole Compared with Long-acting Injectable Once-monthly Paliperidone Palmitate for the Treatment of Stable Schizophrenia Patients in Thailand

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ABSTRACT

Objective: Long-acting injectable (LAI)-aripiprazole and LAI-paliperidone palmitate are both second-generation antipsychotics that have been introduced to increase drug compliance in patients. These attributes are expected to enhance drug compliance, particularly in stable patients. The previous studies demonstrated that the efficacy of LAI-aripiprazole and LAI-paliperidone palmitate is controversial. Nevertheless, the costs of treatments and adverse events of both LAI-aripiprazole and LAI-paliperidone palmitate are unlikeness. As there had been no previous cost-effectiveness studies comparing the use of LAI-aripiprazole and LAI-paliperidone palmitate in Thailand, this study was carried out to investigate the matter.

Materials and Methods: This study analysed the cost-effectiveness of LAI-aripiprazole compared with LAI-paliperidone palmitate in the treatment of stable schizophrenia, by using the Markov model from a societal perspective.

Results: The total cost of treatment with LAI-aripiprazole and LAI-paliperidone palmitate was 1,334,919.05 baht and 1,329,818.79 baht, respectively, while the quality-adjusted life years (QALYs) were both 16.35 years. Life-year of the treatment with LAI-aripiprazole and LAI-paliperidone was 24.27 years and 24.25 years, respectively. The cost-effectiveness ratios (CER) of the treatment with LAI-aripiprazole and LAI-paliperidone palmitate were 81,652.85 baht/QALY gained and 81,330.94 baht/QALY gained, respectively.

Conclusion: In Thailand, the treatment of stable schizophrenia with LAI-aripiprazole was shown to provide similar benefits to LAI-paliperidone palmitate in terms of QALYs, despite being more costly. Comparatively, LAI-aripiprazole exhibited better clinical efficacy and led to a longer average life expectancy than LAI-paliperidone. Treatment with LAI-aripiprazole may be dominant strategy, especially with a 2% reduction in drug cost. The results could contribute to appropriate decision-making by policymakers.

Keywords: Aripiprazole; cost-effectiveness; long-acting injectable antipsychotics; paliperidone; stable schizophrenia patients (Siriraj Med J 2023; 75: 725-735)

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INTRODUCTION

Schizophrenia is a chronic mental illness affecting cognition, emotion, and behaviour. Over 24 million people around the world are impacted by the illness. With about 5.5 million sufferers, China has the highest rate of schizophrenia in the entire globe.[1] Schizophrenia incidence rates range from 8 to 43 per 100,000 individuals.[2,3] It is a considerable economic and social burden worldwide since the afflicted patients are hardly able to work. Nowadays, schizophrenia is one of the 25 leading causes of disability worldwide4 and one of the top ten causes of Disability-Adjusted Life Years (DALYs).[4,5] In Thailand, approximately 8.8 per 1000 of the population suffer from schizophrenia, and was the eighth or ninth leading cause of years lived with disability.[6] It also consumed a large amount of annual cost of treatment (i.e., estimated to be THB 87,000 (USD 2,600) per person or THB 31,000 million (USD 925 million) for the entire schizophrenic population in Thailand.[7]

Treatment of schizophrenia includes both pharmacological and non-pharmacological therapies.[8] The goal of treatment is to improve the patient's quality of life by reducing the symptoms and preventing relapse of patients. For example, conventional and atypical antipsychotics are commonly used for the treatment of schizophrenia[9], but conventional antipsychotics produces extrapyramidal symptoms (EPS) while atypical antipsychotics have been reported as metabolic adverse events, e.g., weight gain, hyperlipidemia, and hyperglycemia. Both adverse events have affected patients' compliance.[9,10] Therefore, for some patients, even if they control their symptoms and are discharged from the hospital, 30-40% of discharged patients relapse within 1-2 years.[11] Patient compliance is one of the important factors associated with relapse.[12-15] Non-adherent patients were approximately three times more likely to be hospitalized in a given year, according to a study conducted in the United States.[16]

Recently, long-acting injection (LAI) antipsychotics have been suggested to be used[17], particularly in the prevention of relapse for non-compliant patients, according to the most evidence-based guidelines for the maintenance treatment of schizophrenia.[18] LAIs are recommended as a first-line treatment.[18] Thai clinical guidelines[19] have been updated to include LAI first-generation antipsychotics (e.g., Fluphenazine decanoate and Haloperidol decanoate) as well as LAI second-generation antipsychotics (e.g., LAI-aripiprazole and LAI-paliperidone palmitate) to improve medication compliance in stable schizophrenia patients. Currently, LAI second-generation have been used more than first-generation antipsychotics because they have lower EPS side effects.[19]

LAI-aripiprazole and LAI-paliperidone are both second-generation antipsychotics that have been introduced to increase drug compliance[20] since they are LAIs and administered once a month. These attributes are expected to enhance drug compliance, particularly for stable patients who are not inpatients. However, they have different pharmacological mechanisms.[21] Aripiprazole is a partial agonist at dopamine D2 and serotonin 5-HT1A receptors and an antagonist at 5HT2A receptors while Paliperidone is an antagonist at D2 and 5HT2A receptors. The different mechanisms may contribute to different effectiveness and tolerability.[22] The previous comparative studies[23,24] demonstrated that the efficacy of LAI-aripiprazole and LAI-paliperidone is controversial. Nevertheless, the costs of treatments and adverse events of both LAI-aripiprazole and LAI-paliperidone are unlikeness.[22,23] Utilizing the economic evaluation as a tool for selecting the optimal LAI strategy would be reasonable.

Previously, no cost-effectiveness studies have been carried out that compared the use of LAI-aripiprazole and LAI-paliperidone palmitate in Thailand from the societal perspective. A cost-effectiveness study is crucial in order to evaluate and compare these antipsychotics. Therefore, the cost-effectiveness of LAI-aripiprazole and LAI-paliperidone palmitate was investigated in this study.

MATERIALS AND METHODS

Study design

This study was health economic evaluation using a Markov model to compare the cost-effectiveness of LAI-aripiprazole with LAI- Paliperidone palmitate for the treatment of stable schizophrenia. The analysis was carried out using cost-effectiveness ratios (CER) and presented humanistic outcomes in Quality-Adjusted Life Years (QALYs). The perspective of this study was societal. Future costs and utilities were discounted at 3 percent per year.[24] This study has been reviewed and approved by the Human Research Ethics Committee of Silpakorn University (COE 65.1007-165)

Treatments

This study compared monthly dosages of LAI-aripiprazole 400 mg and LAI-paliperidone palmitate 156 mg (equivalent dose of Paliperidone 100 mg).[25-28] Patients with schizophrenia who did not respond to LAI-aripiprazole or LAI-paliperidone palmitate treatment were switched to 300 mg per day of clozapine[29], which is the only antipsychotic medicine approved by the FDA for treatment-resistant schizophrenia.[30]

Decision model

The decision model was developed based on previously studies of antipsychotics used in the treatment of schizophrenia patients.[31] A Markov model was used to perform decision analysis through Microsoft Excel 2020. The model and assumptions were validated for the disease sequence to ensure its appropriateness for the treatment of stable schizophrenia in Thailand by three psychiatrists.

The model comprises three main health states including remission under the first antipsychotic, relapse, and death, see Fig 1. A 'death state' is a state where a patient dies for any reason. 'Relapse state' denotes patients who have suffered an exacerbation of their condition and hospital admission, due to non-compliance or the inefficacy of LAI-aripiprazole or LAI-paliperidone. Patients who are not in the death or relapse state are in the 'remission state' Transition probabilities and health state utilities were reviewed and derived from published literature.

The model simulated stable schizophrenia patients over the period of their lifetime. Patients were assigned 400 mg LAI-aripiprazole every 4 weeks or 156 mg LAI-paliperidone palmitate (equivalent dose of Paliperidone 100 mg) every 4 weeks. All stable patients under first LAI antipsychotic entered the model in the 'remission state' at the beginning of the simulation. It was assumed that the health transition state cycle was 4 weeks. At the end of each cycle, mortality rate, the probability of relapse status, and any adverse events occurrence (i.e., akathisia, dystonia, parkinsonism, dyskinesia, diabetes mellitus, hyperprolactinemia, and weight gain) were assessed for each group of LAI antipsychotics until all the patients died. Patients with 'remission state' were not changed health state if they did not experience any adverse events. Patients who did not respond to LAI due to inefficacy of the treatment were switched to 300 mg per day of clozapine as a second antipsychotic. Patients who experienced relapse due to one of two conditions: (1) Non-compliance with, or inefficacy of LAI-aripiprazole or LAI-paliperidone palmitate, or (2) Relapse from remission with taking clozapine were moved to the relapse state and were switched to 300 mg per day of clozapine as a second antipsychotic. Assumingly, patients who switched to clozapine would continue receiving it until the end of the study. Patients in all states could be moved to the death state throughout the study period according to the probability of death.

Assumptions of the model

1. Patients did not withdraw from the treatment during the study and remained until the end of study.

2. Patients who received LAI-aripiprazole were initially administered with a single injection of 400 mg aripiprazole followed by 20 mg of oral aripiprazole for the first 14 days (i.e., concurrent with the first dose of LAI). This was followed by monthly injections of 400 mg aripiprazole thereafter.

3. Patients who received LAI-paliperidone palmitate were initially administered with injection of 400 mg (equivalent dose of Paliperidone 250 mg) in the first month. This was followed by monthly injections of 156 mg paliperidone palmitate (equivalent dose of Paliperidone 100 mg) thereafter.

4. Patients administered with LAI-aripiprazole or LAI-paliperidone could potentially experience common adverse drug reactions, i.e., akathisia, dystonia, parkinsonism, dyskinesia, diabetes mellitus, hyperprolactinemia, and weight gain.

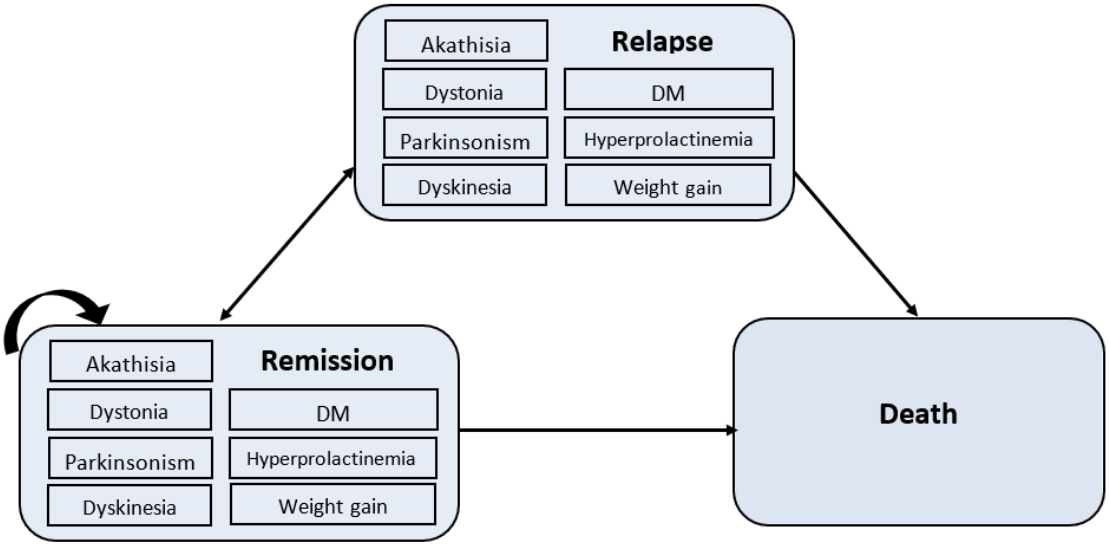

Fig 1. Markov model structure of Schizophrenia disorder.

5. Hyperprolactinemia was defined as a serum prolactin level greater than or equal to 25 ng/mL and patients who experienced hyperprolactinemia were switched to clozapine 300 mg per day (or 100 mg three times per day).

6. Weight gain was defined as body weight increased to greater than or equal to 7 percent of basal body weight, and patients who experienced weight gain were provided with counselling.

7. Diabetes mellitus was defined as plasma glucose levels greater than or equal to 200 mg/dl or fasting blood glucose levels greater than or equal to 126 mg/dl which could be reversed when treated with 1,000 mg of metformin daily to control diabetes.

8. Patients who had akathisia were treated with 40 mg per day of propranolol.

9. Patients who had dyskinesia were switched to clozapine 300 mg per day (or 100 mg three times per day).

10. Patients who had dystonia were assumed to be suffering from only mild dystonia and were treated with 6 mg of trihexyphenidyl per day (or 2 mg three times per day).

11. Patients who had parkinsonism were treated with 6 mg of trihexyphenidyl per day (or 2 mg three times per day).

12. Patients who switched to clozapine and experienced a form of agranulocytosis, which is defined as ANC <500 cells per microlith, received 300 micrograms of filgrastim daily, for 7 days.

13. Patients who did not respond to LAI due to inefficacy were switched to 300 mg per day of clozapine as a second antipsychotic.

14. Patients in a relapsed state of health relapsed due to one of two conditions: (1) Non-compliance with, or inefficacy of LAI-aripiprazole or LAI-paliperidone palmitate, or (2) Relapse from remission while taking clozapine.

15. Patients had not received other antipsychotics or other co-interventions.

16. Patients in all health states who received LAI-aripiprazole or LAI-paliperidone palmitate could be moved to the death state based on the normal mortality rate of the Thai population.[32] In the case of patients who received clozapine, the mortality rate was based on the mortality rate of schizophrenia patients.[33]

Time horizon

A Markov model was developed to imitate the treatment of adult schizophrenia patients over a lifetime period from the age of 18 until death with a life expectancy of not more than 75.7 years.[34] A cycle length of 4 weeks was considered appropriate to capture both the clinical treatment and associated events such as relapses and adverse drug reactions from a survey of treatment in Thailand.[7]

Probability of clinical outcomes

A systematic search was conducted in Medline, SCOPUS and Cochrane databases. The keywords were "schizophrenia, Paliperidone, and Aripiprazole", with filtering by randomized controlled trial, meta-analysis, systematic reviews, full text and English published literature. Two reviewers independently reviewed abstracts, and articles sequentially to select studies for data abstraction based on the study eligibility criteria. All searched literature was evaluated and given a JADAD score. All probabilities were converted into risks over 4 weeks because of the cycle length and are shown in Table 1.

Studies were identified as eligible for inclusion if they were published as full papers and in the English language. All transition probabilities were obtained from studies involving schizophrenia patients who have used LAI-aripiprazole or LAI-paliperidone. The utility of health states was obtained from studies involving Thai schizophrenia patients who used LAI-aripiprazole or LAI-paliperidone with/or without any adverse events. Where search results were inconclusive, the study proceeded as follows: (i) involving schizophrenia patients controlled by antipsychotics drug and whether they had side effects, or (ii) other patients who had utility of health state and side effects, or (iii) utility was retrieved from international studies due to the limited data in Thailand. Articles were excluded from the review if they met any of the following criteria: (i) non-full text papers, (ii) editorials and opinions, letters, research protocols, conference abstracts, duplicate reports of the same study, and notes and books.

Costs

All costs are expressed in Thai baht and are shown in Table 1. Drug treatment costs were derived from the Drug and Medical Supply Information Center (DMSIC) and the Ministry of Public Health, Thailand.[35]

All drug costs (i.e., LAI-aripiprazole, LAI-paliperidone palmitate, Clozapine, metformin, propranolol, trihexyphenidyl, and filgrastim) were obtained from the drug's median price in Thailand. Costs of meals, nursing care costs, and laboratory costs including tests for FBS, haemoglobin A1c, serum prolactin, and complete blood counts were obtained from the mean cost per unit of secondary care by standard cost lists for health

TABLE 1. All parameters used in the Markov model.

Parameters	Distribution	Mean ± SE	References
Probabilities			
Transition probabilities			
LAI-aripiprazole			
Relapse from Inefficacy	Beta	0.02260 ± 0.00797	25-28
Relapse from non-compliance	Beta	0.00355 ± 0.00859	26
Probabilities of adverse drug reaction			
Hyperprolactinemia	Beta	0.00000 ± 0.00000	28
Akathisia	Beta	0.00229 ± 0.00217	22, 23, 25
Dyskinesia	Beta	0.00057 ± 0.00146	23
Dystonia	Beta	0.00132 ± 0.00185	22, 23
Parkinsonism	Beta	0.00356 ± 0.00302	22, 23
Weight gain	Beta	0.00277 ± 0.00172	22, 23, 28, 43, 44
Diabetes	Beta	0.00015 ± 0.00124	43
LAI-paliperidone palmitate			
Relapse from Inefficacy	Beta	0.02497 ± 0.00880	26-28
Relapse from non-compliance	Beta	0.00378 ± 0.00575	26
Probabilities of adverse drug reaction			
Hyperprolactinemia	Beta	0.00002 ± 0.00000	25
Akathisia	Beta	0.00169 ± 0.00213	22, 23, 25
Dyskinesia	Beta	0.00047 ± 0.00169	23
Dystonia	Beta	0.00066 ± 0.00155	22, 23
Parkinsonism	Beta	0.00197 ± 0.00203	22, 23
Weight gain	Beta	0.00900 ± 0.00295	22, 23, 25, 44, 45
Diabetes	Beta	0.00008 ± 0.00001	45
Clozapine			
Remission	Beta	0.09109 ± 0.02877	43
Relapse	Beta	0.09136 ± 0.00342	28, 46
Agranulocytosis	Beta	0.00077 ± 0.00278	47
Weight gain	Beta	0.02269 ± 0.01489	47
Diabetes	Beta	0.00124 ± 0.00352	47
Costs			
Medicine costs			
LAI-aripiprazole 400 mg	Gamma	6,848.00 ± 684.80	35
Aripiprazole 10 mg (per tablet)	Gamma	99.74 ± 9.97	35
LAI-paliperidone palmitate 156 mg (equivalent dose of paliperidone 100 mg)	Gamma	6,947.51 ± 694.75	35
LAI-paliperidone palmitate 234 mg (equivalent dose 150 mg)	Gamma	8,914.16 ± 891.41	35
Clozapine 100 mg (per tablet)	Gamma	1.57 ± 0.16	35
Metformin 500 mg (per tablet)	Gamma	0.36 ± 0.04	35
Trihexyphenidyl 2 mg (per tablet)	Gamma	0.20 ± 0.02	35
Propranolol 40 mg (per tablet)	Gamma	0.23 ± 0.02	35
Filgrastim 300 micrograms	Gamma	432.45 ± 43.25	35

TABLE 1. All parameters used in the Markov model. (Continue)

Parameters	Distribution	Mean ± SE	References
Laboratory costs			
HbA1c (per unit)	Gamma	237.21 ± 23.72	48
Serum prolactin (per unit)	Gamma	475.60 ± 47.56	48
Complete blood count (per unit)	Gamma	142.09 ± 14.21	48
Treatments and Additional Procedures			
Hospitalization (per admission)	Gamma	25,610.53 ± 2,561.05	7
OPD service (per visit)	Gamma	592.53 ± 59.25	7
Psychoeducation (per year)	Gamma	3,143.11 ± 314.31	7
Direct non-medical costs			
Travel (per visit)	Gamma	256.11 ± 25.61	7
Meal (per visit)	Gamma	61.66 ± 6.17	48
Utility			
Remission state	Beta	0.690 ± 0.026	40, 41
Relapse state	Beta	0.578 ± 0.028	40, 41
Hyperprolactinemia	Beta	0.618 ± 0.027	38, 41
Akathisia	Beta	0.639 ± 0.056	39-41
Dyskinesia	Beta	0.608 ± 0.040	39-41
Dystonia	Beta	0.449 ± 0.054	40-42
Parkinsonism	Beta	0.626 ± 0.011	39-41
Weight gain	Beta	0.664 ± 0.027	40, 41
Diabetes	Beta	0.664 ± 0.027	40, 41
Agranulocytosis	Beta	0.460 ± 0.059	49

technology assessment in Thailand.[35] Costs of Out-Patient Department (OPD) services, hospitalization, psychoeducation, travel expenses and family time were obtained from previous studies carried out in Thailand.[7] The frequencies of outpatient visits and admissions per year from surveys of mental illness in Thailand were 7.7 and 0.5, respectively.[36]

All costs were adjusted to 2021 values using the consumer price index from the Bureau of Trade and Economic indices, The Ministry of Commerce, Thailand.[37]

Utility values

Quality-adjusted life-years (QALYs) were used for outcomes measurement. The humanistic outcomes were measured in utility weights for different health states and side effects, ranging from 0 (death) to 1 (perfect health). Utility weights were multiplied by life expectancies to generate QALYs.

Utility values of remission states were estimated based on the disability weights according to previous studies.[31] Utility values of other health states were obtained from previous studies.[38-42] All utility values are shown in Table 1.

One-way sensitivity and probabilistic sensitivity analysis

Random Monte Carlo Simulation was applied for probabilistic sensitivity analyses using Microsoft Excel 2020. All variables were randomized and run 1,000 times to generate the probability distribution and the ICER estimation. Beta distribution was used for transition probabilities and utility value, and gamma distribution was used for costs. The results are shown as a cost-effectiveness plane between incremental costs and incremental QALYs. One-way sensitivity analysis was performed using Microsoft Excel 2020. The parameter values were changed individually and regularly to the lowest and highest values. The results of one-way sensitivity analyses were presented in tornado diagram.

RESULTS

Cost-effectiveness analysis

The cost-effectiveness analysis results (presented in Table 2) showed that the total cost of treatment with LAI-aripiprazole and LAI-paliperidone palmitate was LAI-aripiprazole 1,334,919.05 baht and 1,329,818.79 baht, respectively, while the QALYs were 16.35 years for both. Life years of the treatment with LAI-aripiprazole and LAI-paliperidone was 24.27 years and 24.25 years, respectively.

The CER of the treatment with LAI-aripiprazole and LAI-paliperidone palmitate was 81,652.85 baht/QALY gained and 81,330.94 baht/QALY gained, respectively. Due to the significantly lower CER, treatment with LAI-paliperidone palmitate is more cost-effective than treatment with LAI-aripiprazole.

One-way sensitivity and probabilistic sensitivity analysis

Fig 2 presented the one-way sensitivity analysis result in a tornado diagram. According to the findings, the probability of LAI-aripiprazole-induced dyskinesia was the variable with the greatest influence on the ICER. The probabilistic sensitivity analysis result is presented in Fig 3 as a cost-effectiveness plane between the incremental cost and the incremental QALYs of treatment with LAI-aripiprazole compared with LAI-paliperidone palmitate. The Monte Carlo simulations randomized each variable 1,000 times. The red point represents the base-case ICER.

DISCUSSION

A previous economic evaluation study of aripiprazole in Thailand[31] suggested that oral aripiprazole was the dominant strategy, showing greater QALYs and lower

TABLE 2. Cost-effectiveness results.

	Total cost (Baht)	Life Years (Years)	QALYs (Years)	CER (Baht/QALY)
LAI-aripiprazole	1,334,919.05	24.27	16.35	81,652.85
LAI-paliperidone palmitate	1,329,818.79	24.25	16.35	81,330.94

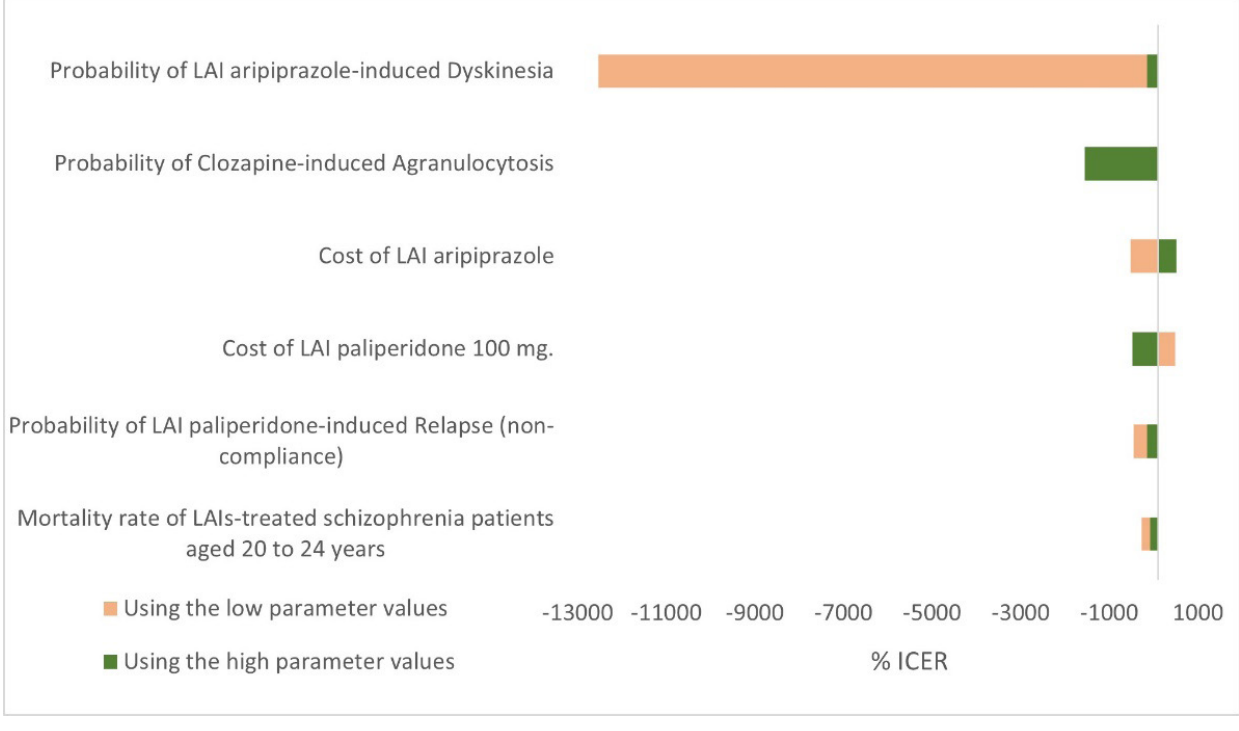

Fig 2. The tornado diagram depicts the results of a one-way sensitivity analysis.

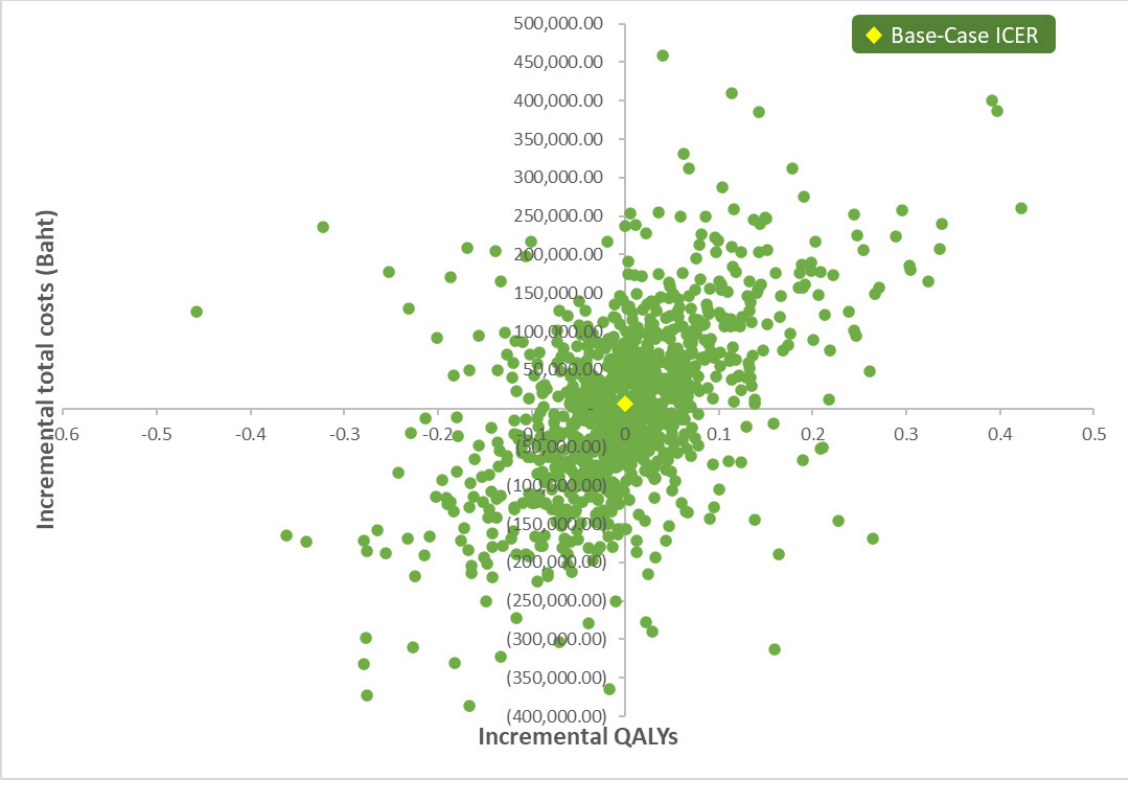

Fig 3. The cost-effectiveness plane of treatment with LAI-aripiprazole compared with LAI paliperidone palmitate.

cost than risperidone in acute schizophrenia patients. However, no previous studies have investigated the economic evaluation of LAI-aripiprazole's use in treating patients with stable schizophrenia. This analysis represented the first economic evaluation comparing LAI-aripiprazole with LAI-paliperidone palmitate for the treatment of stable schizophrenia patients in Thailand. The study revealed that both LAI-aripiprazole and LAI-paliperidone palmitate were similarly beneficial in terms of QALYs, despite the fact that the drug cost of LAI-aripiprazole was cheaper than LAI-paliperidone palmitate. This notion may be considered LAI-aripiprazole as a cost-effective strategy for the treatment of stable schizophrenia patients in Thailand.

Regarding the possible adverse events associated with LAI-aripiprazole or LAI-paliperidone palmitate treatment, such as hyperprolactinemia, akathisia, dyskinesia, dystonia, parkinsonism, diabetes, and weight gain, previous studies conducted in the United States[25,50], the United Kingdom[51], Finland[52] and France[45], only considered and included some of these events in their economic models. In contrast, this study took into consideration all potential adverse events that could impact both costs and utilities, providing a more realistic model that aligns with clinical practices. However, it's worth noting that adverse drug reactions were assumed to be mild, as they were closely monitored every 4 weeks in accordance with the cycle length in the model. Nevertheless, it is important to recognize that despite such monitoring, some adverse events can still occur and may be severe, especially in the short term. The probability of patients experiencing relapse symptoms with once-monthly LAI-aripiprazole treatment was lower than that of those receiving once-monthly LAI-paliperidone palmitate. This could lead to savings in long-term treatment costs. However, from an economic perspective, efficacy is not the only consideration; overall costs, including the treatment of adverse drug events, must also be taken into account. The use of LAI-aripiprazole may result in higher total costs due to the management of side effects, leading to a higher CER. Considering that both LAIs have similar QALYs, LAI-aripiprazole's superior clinical efficacy and longer life expectancy compared to LAI-paliperidone. It's possible that LAI-aripiprazole justifies a 2% price decrease and might be offered LAI-aripiprazole as a dominating strategy for compensating the costs associated with treating side effects, particularly dyskinesia management.

This study encountered some limitations regarding data availability. Specifically, there were few randomized controlled trials (RCTs) that directly compared the efficacy and adverse drug reactions of LAI-aripiprazole with LAI-paliperidone palmitate, and no previous studies were conducted in Thailand. Consequently, the probabilities

of transitioning between health states and experiencing adverse drug reactions were derived from international resources. To enhance the probabilities' validity and minimize the effects of confounding factors, sensitivity analysis was performed based on global data. Additionally, utility values were obtained and recalculated into utility weights specifically for Thai schizophrenia patients. The use of different values from various data sources and diverse populations resulted in a notable variation in the likelihood of side effects and efficacy for each patient receiving LAI treatment. This variability holds the potential to significantly impact the overall treatment outcome, as manifested by the conspicuous amplitude of sensitivity dispersion observed among the sensitivity results. Moreover, this study did not include sexual dysfunction and neuroleptic malignant syndrome (NMS) as adverse drug reactions of antipsychotics due to their rarity and the limited availability of relevant data.

Further economic evaluation studies are required to evaluated the cost-effectiveness of LAI-aripiprazole and LAI-paliperidone palmitate using the real-word data in Thai stable schizophrenia patients to provide a more accurate and reliable evaluation.

CONCLUSION

In Thailand, the treatment of stable schizophrenia with LAI-aripiprazole was found to yield similarly beneficial results in terms of QALYs when compared to treatment with LAI-paliperidone palmitate, despite being more costly. Comparatively, LAI-aripiprazole exhibited better clinical efficacy and led to a longer average life expectancy than LAI-paliperidone. If the drug cost of LAI-aripiprazole were decreased by 2%, treatment with LAI-aripiprazole would become a dominant cost-effectiveness strategy. The results of this study could contribute to informed decision-making by policymakers.

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REFERENCES

1. Institute for Health Metrics and Evaluation (IHME). GBD Compare Data Visualization. Seattle, WA: IHME, University of Washington, 2020. Available from http://vizhub.healthdata.org/gbd-compare.
2. McGrath J, Saha S, Chant D, Welham J. Schizophrenia: a concise overview of incidence, prevalence, and mortality. Epidemiol Rev. 2008;30(1):67-76.
3. McGrath J, Saha S, Welham J, El Saadi O, MacCauley C, Chant D. A systematic review of the incidence of schizophrenia: the distribution of rates and the influence of sex, urbanicity, migrant status and methodology. BMC Med. 2004;2:13.
4. Chong HY, Teoh SL, Wu DB-C, Kotirum S, Chiou C-F, Chaiyakunapruk N. Global economic burden of schizophrenia: a systematic review. Neuropsychiatr Dis Treat. 2016;12:357-73.
5. James SL, Abate D, Abate KH, Abay SM, Abbafati C, Abbasi N, et al. Global, regional, and national incidence, prevalence, and years lived with disability for 354 diseases and injuries for 195 countries and territories, 1990–2017: a systematic analysis for the Global Burden of Disease Study 2017. Lancet. 2018;392(10159):1789-858.
6. Phanthunane P, Vos T, Whiteford H, Bertram M, Udomratn P. Schizophrenia in Thailand: prevalence and burden of disease. Popul Health Metr. 2010;8(1):24.
7. Phanthunane P, Whiteford H, Vos T, Bertram M. Economic burden on schizophrenia: Empirical analyses from a survey in Thailand. J Ment Health Policy Econ. 2012;15(1):25-32.
8. Keepers GA, Fochtmann LJ, Anzia JM, Benjamin S, Lyness JM, Mojtabai R, et.al. The American Psychiatric Association Practice Guideline for the Treatment of Patients With Schizophrenia. Am J Psychiatry. 2020 Sep 1;177(9):868-72.
9. Crossley NA, Constante M, McGuire P, Power P. Efficacy of atypical v. typical antipsychotics in the treatment of early psychosis: meta-analysis. Br J Psychiatry. 2010;196(6):434-9.
10. Geddes J. Prevention of relapse in schizophrenia. N Engl J Med. 2002;346:56-58.
11. Olfson M, Mechanic D, Hansell S, Boyer CA, Walkup J, Weiden PJ. Predicting medication noncompliance after hospital discharge among patients with schizophrenia. Psychiatr Serv. 2000;51(2):216-22.
12. Alvarez-Jimenez M, Priede A, Hetrick S, Bendall S, Killackey E, Parker A, et al. Risk factors for relapse following treatment for first episode psychosis: a systematic review and meta-analysis of longitudinal studies. Schizophr Res. 2012;139(1-3):116-28.
13. Coldham E, Addington J, Addington D. Medication adherence of individuals with a first episode of psychosis. Acta Psychiatr Scand. 2002;106(4):286-90.
14. Pothimas N, Tungpunkom P, Chanprasit C, Kitsumban V. A Cross-sectional Study of Factors Predicting Relapse in People with Schizophrenia. Pacific Rim Int J Nurs Res. 2020;24(4):448-59.
15. Pitanupong J, Ratanaapiromyakij P, Teetharatkul T. Factors Associated with Readmission Among Individuals with One Previous Episode of Schizophrenia in Southern Thailand: A University Hospital-based Retrospective Study. J Hlth Sci Res. 2022;40(6):657-70.
16. Gilmer TP, Dolder CR, Lacro JP, Folsom DP, Lindamer L, Garcia P, et al. Adherence to treatment with antipsychotic medication and health care costs among Medicaid beneficiaries with schizophrenia. Am J Psychiatry. 2004;161(4):692-9.
17. Pitanupong J, Karakate A, Tepsuan L, Sritrangnant G. Attitudes Toward Long-Acting Injectable Antipsychotics among Schizophrenia Patients in Southern Thailand: A Multihospital-Based Cross-Sectional Survey. Siriraj Med J. 2022;74(3):193-201.
18. Kittipeerachon M, Sirivech P, Suraaroonsamrit B, Mekwilai W.

Clinical Guideline for Schizophrenia Patients in Hospitals (Medical Edition). 2nd ed. Nonthaburi: Department of Mental Health, Ministry of Public Health.; 2017.
19. Mantana Kittipeerachon, Pattama Sirivech, Burin Suraaroonsamrit, Wee Mekwilai. Clinical Guideline for Schizophrenia Patients in Hospitals (Medical Edition). 2nd ed. Nonthaburi: Department of Mental Health, Ministry of Public Health.; 2017.
20. Kishimoto T, Nitta M, Borenstein M, Kane JM, Correll CU. Long-acting injectable versus oral antipsychotics in schizophrenia: a systematic review and meta-analysis of mirror-image studies. J Clin Psychiatry. 2013;74(10):957-65.
21. Li H, Rui Q, Ning X, Xu H, Gu N. A comparative study of paliperidone palmitate and risperidone long-acting injectable therapy in schizophrenia. Prog Neuro-psychopharmacol Biol Psychiatry. 2011;35(4):1002-8.
22. Naber D, Hansen K, Forray C, Baker RA, Sapin C, Beillat M, et al. Qualify: a randomized head-to-head study of aripiprazole once-monthly and paliperidone palmitate in the treatment of schizophrenia. Schizophr Res. 2015;168(1-2):498-504.
23. Ceraso A, Lin JJ, Schneider-Thoma J, Siafis S, Tardy M, Komossa K, et al. Maintenance treatment with antipsychotic drugs for schizophrenia. Cochrane Database Syst Rev. 2020; 8(8):CD008016.
24. Subcommittee of Development of National Drug List Thailand. Handbook of Health Technology Assessment for Thailand. 2nd ed. Nonthaburi: Watcharin P.P. Printing; 2013.
25. Di Lorenzo R, Ferri P, Cameli M, Rovesti S, Piemonte C. Effectiveness of 1-year treatment with long-acting formulation of aripiprazole, haloperidol, or paliperidone in patients with schizophrenia: retrospective study in a real-world clinical setting. Neuropsychiatr Dis Treat. 2019;15:183-98.
26. Majer IM, Gaughran F, Sapin C, Beillat M, Treur M. Efficacy, tolerability, and safety of aripiprazole once-monthly versus other long-acting injectable antipsychotic therapies in the maintenance treatment of schizophrenia: a mixed treatment comparison of double-blind randomized clinical trials. J Mark Access Health Policy. 2015;3.
27. Taipale H, Mehtälä J, Tanskanen A, Tiihonen J. Comparative effectiveness of antipsychotic drugs for rehospitalization in schizophrenia—a nationwide study with 20-year follow-up. Schizophr Bull. 2018;44(6):1381-7.
28. Citrome L, Kamat SA, Sapin C, Baker RA, Eramo A, Ortendahl J, et al. Cost-effectiveness of aripiprazole once-monthly compared with paliperidone palmitate once-monthly injectable for the treatment of schizophrenia in the United States. J Med Econ. 2014;17(8):567-76.
29. National Institute for Health and Care Excellence. Psychosis and schizophrenia in adults: prevention and management Clinical guideline. London, United Kingdom. 2014.
30. Columbia University Medical Center. Better options for people with treatment-resistant schizophrenia: Research on the comparative effectiveness of antipsychotic medications [cited 2022 Aug 30]. Available from: https://www.sciencedaily.com/ releases/ 2015/11/151106062315.htm.
31. Thavornwattanayong W, Lertsirimunkong J, Thongkerd N, Pitakthanin N, Wettayanon P, Pongjakpanit H. Cost-effectiveness analysis of aripiprazole compared with risperidone in the treatment of acute schizophrenia patients in Thailand. TJPS. 2018;42(3): 169-75.
32. Health Information System Development Office. Trend of health in Thailand 2017 [cited 2022 Aug 30]. Available from: https://www.hiso.or.th/health/data/html/search1.php?menu=1&i.
33. Bitter I, Czobor P, Borsi A, Fehér L, Nagy B, Bacskai M, et al. Mortality and the relationship of somatic comorbidities to mortality in schizophrenia. A nationwide matched-cohort study. Eur Psychiatry. 2017;45:97-103.
34. World Health Organization. World health statistics 2016: monitoring health for the SDGs sustainable development goals: World Health Organization; 2016.
35. Drug and Medical Supply Information Center. In: Ministry of Public Health Thailand. Reference of Drugs Costs [cited 2022 Aug 30]. Available from: http://dmsic.moph.go.th/index/ drugsearch/1.
36. Kongsakon R, Leelahanaj T, Price N, Birinyi-Strachan L, Davey P. Cost analysis of the treatment of schizophrenia in Thailand: a simulation model comparing olanzapine, risperidone, quetiapine, ziprasidone and haloperidol. J Med Assoc Thai. 2005;88(9):1267.
37. Trade Policy and Strategy Office. Economic and Trade Indices Database: ETID [cited 2022 Aug 30]. Available from: http:// www.price.moc.go.th
38. Davies A, Vardeva K, Loze J-Y, L'Italien GJ, Sennfalt K, Baardewijk M. Cost-effectiveness of atypical antipsychotics for the management of schizophrenia in the UK. Curr Med Res Opin. 2008;24(11): 3275-85.
39. Lenert LA, Sturley AP, Rapaport MH, Chavez S, Mohr PE, Rupnow M. Public preferences for health states with schizophrenia and a mapping function to estimate utilities from positive and negative symptom scale scores. Schizophr Res. 2004;71(1):155-65.
40. Lin L, Zhao YJ, Zhou HJ, Khoo AL, Teng M, Soh LB, et al. Comparative cost-effectiveness of 11 oral antipsychotics for relapse prevention in schizophrenia within Singapore using effectiveness estimates from a network meta-analysis. Int Clin Psychopharmacol. 2016;31(2):84-92.
41. Phanthunane P, Vos T, Whiteford H, Bertram M. Health outcomes of schizophrenia in Thailand: Health care provider and patient perspectives. Asian J Psychiatr. 2010;3(4):200-5.
42. Skogseid I, Malt U, Røislien J, Kerty E. Determinants and status of quality of life after long-term botulinum toxin therapy for cervical dystonia. Eur J Neurol. 2007;14(10):1129-37.
43. Druais S, Doutriaux A, Cognet M, Godet A, Lançon C, Levy P, et al. Cost effectiveness of paliperidone long-acting injectable versus other antipsychotics for the maintenance treatment of schizophrenia in France. Pharmacoeconomics. 2016;34(4):363-91.
44. Seppälä A, Pylvänäinen J, Lehtiniemi H, Hirvonen N, Corripio I, Koponen H, et al. Predictors of response to pharmacological treatments in treatment-resistant schizophrenia–A systematic review and meta-analysis. Schizophr Res. 2021;236:123-34.
45. Fleischhacker WW, Gopal S, Lane R, Gassmann-Mayer C, Lim P, Hough D, et al. A randomized trial of paliperidone palmitate and risperidone long-acting injectable in schizophrenia. Int J Neuropsychopharmacol. 2012;15(1):107-18.
46. Masuda T, Misawa F, Takase M, Kane JM, Correll CU. Association with hospitalization and all-cause discontinuation among patients with schizophrenia on clozapine vs other oral second-generation antipsychotics: a systematic review and meta-analysis of cohort studies. JAMA Psychiatry. 2019;76(10):1052-62.
47. Treur M, Baca E, Bobes J, Canas F, Salvador L, Gonzalez B, et al. The cost-effectiveness of paliperidone extended release in Spain. J Med Econ. 2012;15(Suppl 1):26-34.

48. Health Intervention and Technology Assessment: HITAP Ministry of Public Health. Standard Cost Lists for Health Technology Assessment [cited 2022 Aug 30]. Available from: https://costingmenu.hitap.net/
49. Weeks JC, Tierney MR, Weinstein MC. Cost effectiveness of prophylactic intravenous immune globulin in chronic lymphocytic leukemia. NEJM. 1991;325(2):81-6.
50. Sapin C, Hartry A, Kamat SA, Beillat M, Baker RA, Eramo A. Pharmacoeconomic comparison of aripiprazole once-monthly and paliperidone palmitate from a head-to-head clinical trial in schizophrenia: a US analysis. Drugs Context. 2016;5:212301.
51. Hodgson RE. Evaluating the cost and clinical effectiveness of long-acting, injectable aripiprazole and paliperidone palmitate once a month in a real-world setting. ClinicoEconomics and Outcomes Research: Clinicoecon Outcomes Res. 2019;11:517-24.
52. Einarson TR, Pudas H, Goswami P, van Impe K, Bereza BG. Pharmacoeconomics of long-acting atypical antipsychotics for acutely relapsed chronic schizophrenia in Finland. J Med Econ. 2016;19(2):121-30.