The Cost-Effectiveness of Aripiprazole as Adjunctive Therapy in Major Depressive Disorder: Thai Economic Model

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Background: *Aripiprazole is the first atypical antipsychotic approved for adjunctive treatment to antidepressant therapy in patients with major depressive disorder (MDD). The current study aims to present an economic model and cost-effectiveness estimates for aripiprazole compared with placebo as adjunctive therapy to antidepressant treatment in patients with MDD who showed an incomplete response to a prospective 8-week trial of antidepressant therapy*

Material and Method: *An economic model of MDD treatment was developed to estimate the clinical and economic outcomes in Thai patients. Efficacy data were derived from a pooled analysis of two studies. A cost-effectiveness analysis was constructed in simulate the impact of treatment outcomes and costs over a 6-week time horizon. The primary outcome of the model was remission of symptoms. Quality-adjusted life-year (QALYs) was the secondary outcome. The event probabilities were used to derive the transitional probability used in the model and to calculate the weighted cost of each treatment outcome. Only direct costs were considered. One-way sensitivity analysis was performed to test the sensitivity of the model outputs.*

Results: *Treatment with aripiprazole came at the total costs per remission of 30,970 Baht while treatment with placebo came at the total costs per remission of 28,409 Baht. Placebo had lower total costs per QALY than aripiprazole (35,511 Baht vs. 38,713 Baht). The incremental cost-effectiveness ratio (ICER) of augmentation with aripiprazole compared with placebo was 2,561 Baht per remission gained and 3,201 Baht per QALY gained. Aripiprazole dominated placebo if the value of transitional probability of remission changed to a value of greater than 0.348 from the base-case value of 0.257. Aripiprazole was more cost-effective than placebo as adjunctive therapy if the unit cost of aripiprazole is more than 48.9% discount.*

Conclusions: *Adjunctive aripiprazole is not more cost-effective than adjunctive placebo in Thai patients with MDD who showed an inadequate response to at least one prospective antidepressant therapy. Remission rates and unit cost are the key parameters involving the cost-effectiveness of aripiprazole.*

Keywords: *Aripiprazole, Major depressive disorder, Cost-effectiveness*

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The ultimate goal of treatment of major depressive disorder (MDD) is to help patients to reach and sustain remission[1-3]. Despite the availability of a board array of antidepressants in the treatment of MDD, approximately one third of the patients achieve remission after an adequate course of at least one antidepressant and a significant number of patients do not remit after multiple coursed of pharmacotherapy[4,5]. Residual depressive symptoms are common and are associated with many negative outcomes, including increased relapse rates, more severe future episodes, risk of comorbid medical and psychiatric illness, and psychological impairment[6-8].

Various alternative treatment strategies have been proposed for the non- or partially responsive depressions. Augmenting antidepressants with atypical antipsychotics to enhance antidepressant efficacy is one of these alternative strategies[9-12]. Aripiprazole, an atypical antipsychotic, is the first medication that has received U.S. Food and Drug Administration (FDA) approval as an adjunctive treatment to antidepressant therapy in patients with MDD. Aripiprazole has potent partial agonist activity at the dopamine D2 and D3 receptors and partial agonism at serotonin (5-HT) 1A receptors and antagonism at 5-HT2A receptors[13,14]. These pharmacological properties may contribute to the antidepressant effect as an adjunctive therapy to

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antidepressants[14-16].

The efficacy and tolerability of aripiprazole as adjunctive therapy to antidepressants has been demonstrated in 3 large, identical, randomized, double-blind, placebo-controlled trials in MDD patients who have a history of an inadequate response to at least 1, and no more than 3, adequate antidepressant trials (>6 weeks' duration at adequate dose) and who exhibited an inadequate response to a prospective 8-week trial of a different antidepressant therapy[17-19]. A pooled analysis of 2 studies extended previous results from the individual trials and demonstrated significant efficacy benefits of augmentation of antidepressant therapy with aripiprazole across a range of subgroups of patients with MDD[20].

The cost-effectiveness of aripiprazole as adjunctive therapy in MDD has not yet reported. Thus, the current study aims to present an economic model and cost-effectiveness estimates for aripiprazole compared with placebo as adjunctive therapy to standard antidepressant treatment in the treatment of patients with MDD who have shown an incomplete response to a prospective 8-week trial of the same antidepressant agent and at least one historical antidepressant trial, based on a recent pooled analysis[20].

Material and Method

Model Overview

An economic model of MDD treatment was developed to estimate the clinical and economic outcomes associated with its treatment in Thai patients. Efficacy data were derived from a pooled analysis of two studies[20]. Data for other model inputs were obtained from the published literature. The model is probabilistic in those uncertainties in parameter estimates are characterized by assigning probability distributions. The model estimates costs were determined for the fiscal year 2009 and expressed in Thai Baht. Only direct costs were considered. A cost-effectiveness analysis was constructed in simulate the impact of treatment outcomes and costs over a 6-week time horizon.

Aripiprazole Pooled Analysis

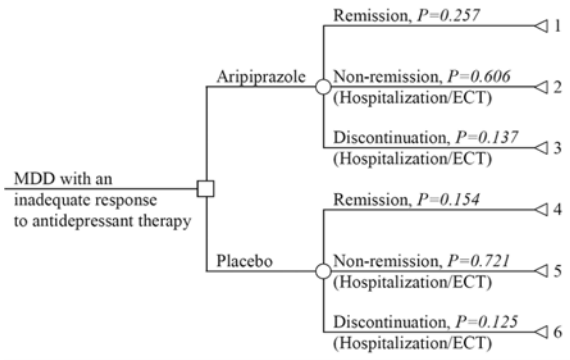
The pooled analysis were performed on 2 identical 14-week studies (8-week prospective antidepressant therapy treatment phase followed by 6 week randomized double-blind phase) evaluating the efficacy of adjunctive aripiprazole (2-20 mg/day) in DSM-IV-TR-defined MDD patients with an inadequate response to antidepressant therapy[20]. The primary efficacy endpoint was the mean change in Montgomery-Asberg Depression Rating Scale (MADRS) total score from the end of the prospective phase (week 8) to the end of randomized phase (week 14). Remission rate and discontinuation rates were also analyzed.

Model Structure

An overview of the model structure is shown in Fig. 1. Patients with an inadequate response to antidepressant therapy continued antidepressant therapy and were randomly assigned to an adjunctive aripiprazole or adjunctive placebo. Aripiprazole or placebo was discontinued in patients who have no remission or discontinuation from treatment. After that, those with non-remission or discontinuation will be hospitalized for electroconvulsive therapy (ECT). The model was assumed that all patients will achieve remission of symptoms after hospitalization for ECT.

Model Outcomes

The primary outcome of the model was remission of symptoms, defined by a total score of 10 or less of MADRS. Symptom remission measured in terms of quality-adjusted life-years (QALYs) was the secondary outcome in the present study. Both primary and secondary outcomes were estimated in the model in a similar way to costs, with a utility value being calculated for the remission state. The incremental cost-effectiveness ratio (ICER) examines the additional cost the one strategy incurs over another and compared this with the additional benefits. Therefore, the ICER of the primary outcome is the additional cost per remission gained and the ICER of the secondary outcome is the additional cost per QALY gained, respectively.



ECT = Electroconvulsive therapy

Fig. 1 The Model Structure and Transitional Probability

Transitional Probabilities

Table 1 shows the transitional probability presented in the pool analysis. These event probabilities were used to derive the transitional probability used in the model and to calculate the weighted cost of each treatment outcome. The placebo outcomes were used as a comparator for aripiprazole outcomes.

Resource-Use and Cost Estimates

The modeled resource-use items were drug acquisition cost for acute treatment. Cost for hospitalization and cost for ECT were calculated in those who experienced non-remission or discontinued to treatment. The cost of aripiprazole and various antidepressants was based on the mean dosage given in the pooled analysis and drug prices listed in Phramongkutklao Hospital. The Unit cost of drugs, cost per inpatient bed day, and cost per time of ECT are presented in Table 2. Indirect costs, such as productivity loss due to absenteeism or mortality, were not estimated in the model.

A weighted daily drug cost of aripiprazole was calculated for a 6-week treatment phase for patients who have remission (outcome 1) and non-remission (outcome 2). Those who discontinued aripiprazole (outcome 3) were assumed to receive 0 day of treatment. Treatment periods of antidepressants were 6 weeks for those with remission (outcome 1 and 4), 6 weeks plus 20 days (bed day for ECT) in those with non-remission (outcome 2 and 5), and 20 days for patients who discontinued from the trial (outcome 3 and 6). The resource-use assumptions are summarized in Table 3.

Table 1. Transitional Probability Estimates

Transitional probability	Aripiprazole (n = 368)	Placebo (n = 356)
Discontinuation from treatment (due to lack of efficacy, adverse events, subject withdraw consent or lost to follow-up)	0.137	0.125
Completed randomization phase	0.863	0.875
Remission	0.257	0.154
Non-remission	0.606	0.721
Source	Thase et al[20]	Thase et al[20]

Health-State Utility Estimates

The health-state utilities used in the model were based on a report by Revicki and Wood[22] which determined utility values using the 36-item Short Form (SF-36) Health Survey and standard gamble interviews to obtain utilities for 11 hypothetical depressive-related states, varying depression severity, antidepressant treatment, and the patient's current health state. The mean utility for antidepressant maintenance therapy was 0.72-0.83. Consequently, the present study assumed utility values of 0.8 for remission state which is the clinical status during the maintenance phase.

Sensitivity Analyses

One-way sensitivity analysis was performed

Table 2. Unit Cost (in Thai Baht)

Cost	Unit resource /Cost	Source
Drug		
Aripiprazole 15 mg/tab	195.5	Phramongkutklao Hospital
Escitalopram 10 mg/tab	52.25	Phramongkutklao Hospital
Fluoxetine 20 mg/tab	55.0	Phramongkutklao Hospital
Paroxetine 20 mg/tab	58.0	Phramongkutklao Hospital
Sertraline 50 mg/tab	44.0	Phramongkutklao Hospital
Venlafaxine 75 mg/tab	62.0	Phramongkutklao Hospital
Hospitalization/ECT		
Cost per inpatient bed day	600	Phramongkutklao Hospital
ECT per time	1,700	Phramongkutklao Hospital

ECT = Electroconvulsive therapy

to test the sensitivity of the model outputs to the input assumptions. The following key parameters were tested for in the sensitivity analyses: drug acquisition cost (varied by -20 % to -40%) and remission rates at week 6 varied from the relative risk of aripiprazole. Other parameters, for example, cost of adverse effects and mortality risk, were not taken into account.

Another approach, a threshold analysis, was to undertake. Here the critical values of both key parameters were analyzed by varying across the value ranges until the alternative decision strategy is found to have an equal outcome.

Table 3. Resource Use Assumptions and Sources

Resource use variable	Aripiprazole (n = 368)	Placebo (n = 356)	Source
Mean daily dose (mg/d)			Thase et al[20]
Aripiprazole	11.1	-	
Escitalopram	20.0	19.6	
Fluoxetine	39.6	37.7	
Paroxetine	48.4	46.8	
Sertraline	141.3	143.9	
Venlafaxine	215.3	214.2	
Time to receive drug*	6.0 wks	6.0 wks	Thase et al[20]
Time to receive antidepressant			
Outcome 1 and 4	6.0	6.0	Thase et al[20]
Outcome 2 and 5	6.0 wks +20 days	6.0 wks +20 days	Thase et al[20] +Survey
Outcome 3 and 6	20 days	days	Survey
Hospitalization/ECT			
Days hospitalized for ECT	20	20	Survey
ECT (times)	8	8	Kennedy and Giacobbe[21]

*6-week for those with remission and non-remission
ECT = Electroconvulsive therapy

Results

Base-Case Analysis

In base-case analysis, adjunctive treatment to antidepressant therapy for 6 weeks with aripiprazole was assessed compared with placebo. At the end point, the remission rates were 25.7% and 15.4% in adjunctive aripiprazole and adjunctive placebo groups, respectively; this difference was statistically significant (relative risk, 1.66; 95% CI = 1.23 to 2.24; $p < .001$)[20]. From the healthcare provider perspectives, treatment with aripiprazole came at the total costs per remission of 30,970 Baht while treatment with placebo came at the total costs per remission of 28,409 Baht (Table 4). The distribution of the total costs observed was shown in Fig. 2. Aripiprazole group had drug cost greater than the placebo group whereas the placebo group had costs for hospitalization/ECT greater than aripiprazole group. In terms of health-state utility, placebo had lower total costs per QALY than aripiprazole (35,511 Baht vs. 38,713 Baht). The more cost-effective of placebo provided 8.27% of cost saving. The incremental cost-effectiveness of augmentation with aripiprazole compared with placebo was 2,561 Baht per remission gained and 3,201 Baht per QALY gained (Table 5).

Table 4. Weighted Cost and Total Cost (in Thai Baht)

Health outcome	Medication		Hospitalization / ECT	Total cost	Path prob.	Weighted cost
	ARP	AD				
1	6,076.14	5,511.12	-	11,587.26	0.257	2,977.92
2	6,076.14	8,135.46	25,600.00	39,811.60	0.606	24,125.83
3	0	2,624.34	25,600.00	28,224.34	0.137	3,866.73
				Total	1	30,970.49
4	-	5,429.22	-	5,429.22	0.154	836.10
5	-	7,756.03	25,600.00	33,356.03	0.721	24,049.70
6	-	2,585.34	25,600.00	28,185.34	0.125	3,523.17
				Total	1	28,408.96

ARP = aripiprazole; AD = antidepressant; ECT = Electroconvulsive therapy

Sensitivity Analyses

In the sensitivity analyses, two key parameters in the model were varied, to capture the uncertainty in the total direct costs and ICER. All results from the one-way sensitivity analysis and the threshold analysis are summarized in Table 6. Varying the remission rate estimated from the relative risk resulted in a range of 28,436-32,849 Baht for total direct costs. Furthermore, incremental cost per remission gained and incremental cost per QALY gained were in a range of 27-4,440 Baht and 34-5,551 Baht, consecutively. By varying acquisition costs of aripiprazole from 20%-40% discount, total direct costs were in range of 28,873-29,921 Baht. In the same manner as remission rate, incremental cost per remission gained were in range of 464-1,513 Baht and incremental cost per QALY gained were in range of 580-1,891 Baht.

Because of the more cost-effectiveness of placebo than aripiprazole, a threshold analysis sought out the threshold value of the two key parameters that were varied until augmentation with aripiprazole was found to have an equal outcome, and there is no benefit of placebo over aripiprazole. Aripiprazole dominated placebo if the value of transitional probability of remission changed to a value of greater than 0.348 from the base-case value of 0.257. For drug cost, aripiprazole was more cost-effective than placebo as adjunctive therapy to an antidepressant if the unit cost of aripiprazole is more than 48.9% discount.

Table 5. Cost-Effectiveness Analysis of Aripiprazole vs. Placebo in Base-Case Analysis (in Thai Baht)

Cost-effectiveness analysis	Aripiprazole	Placebo
Total cost per remission	30,970.49	28,408.96
Incremental cost per remission gained	-2,561.52	
Total cost per QALY	38,713.11	35,511.20
Incremental cost per QALY gained	-3,201.91	
Cost saving (%)		8.27

QALY = Quality Adjusted Life Year

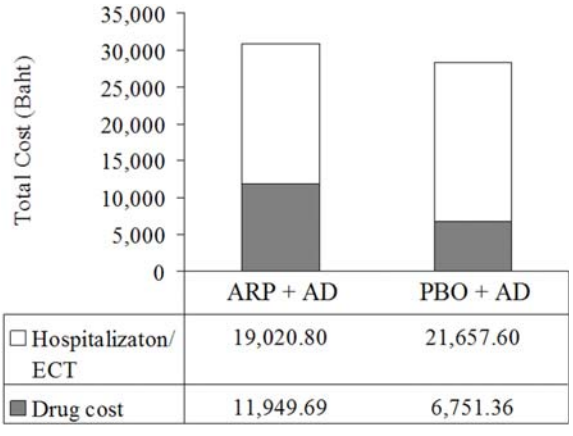
Table 6. One-Way Sensitivity Analysis of the Key Parameters of Aripiprazole Compared with Placebo

Parameter range	Total cost	Incremental cost per remission gained	Incremental cost per QALY gained
Probability of remission (relative risk)			
0.1904 (1.23)	32,849.45	-4,440.48	-5,550.60
0.3468 (2.24)	28,436.08	-27.11	-33.89
0.3478 (2.246)*	28,408.96	0	0
Cost of aripiprazole			
-20% (156.4 Baht/tab)	29,921.75	-1,512.78	-1,890.98
-40% (117.3 Baht/tab)	28,873.00	-464.04	-580.05
-48.85% (100 Baht/tab)*	27,086.82	0	0

* = threshold value
QALY = Quality Adjusted Life Year

Discussion

Based on the pooled analysis assessing the efficacy of aripiprazole as adjunctive therapy in MDD, the present economic evaluation assessed the cost-effectiveness of this intervention. The results indicate that, compared to placebo to the patients with inadequate response to antidepressant therapy, aripiprazole is not likely to be cost-effective within the conventional margins of willingness to pay for health benefits in Thailand. This analysis indicates that remission rate and unit cost of aripiprazole are of important when assessing the economic benefits of adjunctive therapy in this patient group. However, the upper value of relative risk of remission in aripiprazole group reveals that total cost per remission of aripiprazole will be equal to placebo.



ARP = aripiprazole; AD = antidepressant; PBO = placebo

Fig. 2 Distribution of Total Direct Cost

Despite the fact that placebo is more cost-effective than aripiprazole, there are definite threshold limits regarding the highest acceptable cost per remission and cost per QALY. In the pooled analysis[20], aripiprazole results in only 10% difference in remission rate when comparing with placebo. Nevertheless, aripiprazole will be a more cost-effective option of adjunctive treatment to an antidepressant if it provides a difference in remission rate more than 19% compared with placebo.

The total cost distribution, as shown in Fig. 2, indicates that the less cost-effective of aripiprazole compared with placebo is due partly to the expensive cost of aripiprazole. Specifically, drug acquisition cost is one of the most important decision-making factors for healthcare providers, payers, or policy makers in Thailand, a developing country in Asia.

Even though the less cost-effectiveness of aripiprazole resulted from the present analysis, a recent benefit-risk analysis of adjunctive aripiprazole in the treatment of patients with MDD found that adjunctive aripiprazole was associated with an improved benefit-risk profile in MDD[23]. In addition, aripiprazole is the only medication approved for adjunctive treatment of antidepressants. Therefore, aripiprazole augmentation should be an alternative treatment strategy for patients who have inadequate response to antidepressant therapy, especially in affordable patients.

However, potential limitations are observed in the present study. First, the assumptions that were made in constructing and populating the model are based only on the results of the pooled analysis[20] which is limited by their post hoc nature, and no correction was made for multiple comparisons. Besides, the generalizability of the results to the population outside clinical trial setting is warranted. Second, the full range of possible treatment sequences that might be considered in patients and might be affected the health outcome are not possible to the model.

Another limitation associated with the current model is the exclusion of other direct costs, for instance, cost for psychiatric consultant and cost of adverse effects. Indirect costs that pose a substantial economic burden upon society[24-26], especially in patients who had partial remission or persistent depression[26-28] are also excluded from the present analysis. Moreover, unit cost employed in the current analysis is estimated from Phramongkutklao Hospital, a government general hospital. Certainly, differences in direct costs are existed and should be cautiously considered when applying the results of the present study. Fourth, this study does not account for the indirect costs incurred as a result of MDD. Indirect costs, such as productivity loss due to absenteeism or mortality, pose a substantial economic burden upon society. Finally, the results presented here are short-term, covering only the 6-week treatment period. The long-term cost-effectiveness of aripiprazole is unknown and required for further study.

Conclusions

Although adjunctive aripiprazole as a short-term augmentation strategy to conventional antidepressant therapy is efficacious and well tolerated in patients with MDD who showed an inadequate response to at least 1 and up to 3 historical and 1 additional prospective antidepressant therapy, the results of this Thai economic model with a 6-week time horizon suggest that adjunctive aripiprazole is not more cost-effective than adjunctive placebo. Remission rates and unit cost are the key parameters involving the cost-effectiveness of aripiprazole. Future researches that consider inclusion of indirect costs or a border costing perspectives are recommended and are likely to provide even more optimistic cost-effectiveness outputs.

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ต้นทุน-ประสิทธิผลของ aripiprazole ในการใช้เสริมการรักษาในโรคซึมเศร้า: แบบจำลองทางเศรษฐศาสตร์ของไทย

ธวัชชัย ลีพหานาจ

ภูมิหลัง*: aripiprazole เป็นยาต้านโรคจิตขนานแรกที่ได้รับการรับรองสำหรับการเสริมการรักษาของยาแก้ซึมเศร้าในผู้ป่วยโรคซึมเศร้า การศึกษานี้มีวัตถุประสงค์ที่จะนำเสนอแบบจำลองทางเศรษฐศาสตร์และการประมาณต้นทุน-ประสิทธิผลของ aripiprazole เทียบกับยาหลอกในการใช้เสริมการรักษาของยาแก้ซึมเศร้าในการรักษาผู้ป่วยโรคซึมเศร้าที่มีการตอบสนองไม่สมบูรณ์ต่อการรักษาด้วยยาแก้ซึมเศร้าเป็นระยะเวลา 8 สัปดาห์*

วัสดุและวิธีการ*: แบบจำลองทางเศรษฐศาสตร์ของการรักษาโรคซึมเศร้าถูกพัฒนาขึ้น เพื่อใช้สำหรับการประมาณผลลัพธ์ทางคลินิก และผลลัพธ์ทางเศรษฐศาสตร์ในผู้ป่วยไทย ข้อมูลเกี่ยวกับประสิทธิภาพของยาได้จากการศึกษาที่นำการศึกษาสองชิ้นมารวมกัน การวิเคราะห์ต้นทุน-ประสิทธิผลกระทำเพื่อจำลองผลลัพธ์ของการรักษากับต้นทุนในช่วง 6 สัปดาห์ ผลลัพธ์ปฐมภูมิของแบบจำลองคือการสงบของอาการของโรค ผลลัพธ์ทุติยภูมิคือ QALYs จะเป็นของเหตุการณ์นำมาใช้เป็นเป็น transitional probability เพื่อคำนวณต้นทุนเฉลี่ยของแต่ละผลลัพธ์ เฉพาะต้นทุนทางตรง ที่ถูกพิจารณา การวิเคราะห์ความไวแบบทางเดียวกระทำเพื่อทดสอบความไวของผลลัพธ์ตามแบบจำลอง*

ผลการศึกษา*: การรักษาด้วย aripiprazole มีต้นทุนต่อการสงบของโรคเท่ากับ 30,970 บาท ส่วนยาหลอกมีต้นทุนต่อการสงบของโรค 28,409 บาท ยาหลอกมีต้นทุนต่อ QALY ต่ำกว่า aripiprazole (35,511 บาทเทียบกับ 38,713 บาท) ค่า incremental cost-effectiveness ratio ของ aripiprazole เทียบกับยาหลอกเท่ากับ 2,561 บาทต่อการสงบของโรคที่เพิ่มขึ้นหนึ่งหน่วย และเท่ากับ 3,201 บาทต่อ QALY ที่เพิ่มขึ้นหนึ่งหน่วย aripiprazole เหนือกว่ายาหลอกหากค่า transitional probability ของการสงบของโรคมีค่ามากกว่า 0.348 จากค่าฐานที่ 0.257 aripiprazole มีต้นทุน-ประสิทธิผลเหนือกว่ายาหลอกหากราคายาของ aripiprazole ลดลงร้อยละ 48.9*

สรุป*: การเสริมการรักษาด้วย aripiprazole ไม่ได้มีต้นทุน-ประสิทธิผลเหนือกว่าการเสริมการรักษาด้วยยาหลอกในการรักษาผู้ป่วยไทยที่เป็นโรคซึมเศร้าที่ไม่ตอบสนองอย่างเพียงพอต่อยาแก้ซึมเศร้ามากก่อนหน้าอย่างน้อยหนึ่งขนาน อัตราการสงบของโรคและราคายาต่อหน่วยเป็นตัวแปรสำคัญที่เกี่ยวข้องกับต้นทุน-ประสิทธิผลของ aripiprazole*