Developing Thai Economic Model to Study Cost-Effectiveness of Switching to Bupropion Compared to Combination with Bupropion after the Failure of an SSRI for Major Depressive Disorder

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Objective: *To present an economic model and cost-effectiveness estimates of switching to bupropion compared to combination with bupropion after failure of an SSRI for major depressive disorder (MDD).*

Material and Method: *An economic model was developed to simulate the transitions of Thai outpatients with nonpsychotic MDD who had no remission or could not tolerate the SSRI citalopram and received either sustained-release bupropion monotherapy as switching strategy or sustained-release bupropion plus citalopram as combination strategy. Clinical data were obtained form 2 trials of the Sequenced Treatment Alternatives to Relieve Depression (STAR*D) study. The four event probabilities: remission rates, rates of non-remission, discontinuation rates due to intolerance, and incidence of serious adverse events were estimated. Direct costs included drug cost, hospitalizations, and electroconvulsive therapy (ECT). The primary outcome considered in the model was a remission of symptoms. Outputs were measured in terms of costs per remission and costs per quality-adjusted life-years (QALYs).*

Results: *In the base-case analysis, the total direct costs with a bupropion switch were 22,937 THB per remission and 29,346 THB per remission with a bupropion combination. Compared with combination option, switching to bupropion also had lower total cost per QALY (28,672 THB vs. 36,682 THB) and had cost saving of 21.8%. The incremental cost-effectiveness of the combination regimen compared with the switching regimen was 6,409 THB per remission gained and 8,011 THB per QALY gained. In a sensitivity analysis, combination strategy dominated switching strategy if the value of the transitional probability of remission changed to a value of greater than 0.547.*

Conclusion: *The economic model indicated that treatment of MDD patients who fail to achieve remission from an SSRI with a switch to bupropion is a cost-effectiveness treatment option compared with a combination of SSRI with bupropion.*

Keywords: *Cost-effectiveness, Bupropion, Switching, Combination, Major depressive disorder*

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Major depressive disorder is a debilitating disease that imposes a significant social and economic burden and is projected to be the first rank of leading causes of disability-adjusted life-year in 2030[1]. Since no single treatment is uniformly effective[2,3], subsequent interventions are often needed. Second-step treatments include discontinuing the first agent and beginning a second (switching), combining two antidepressants from different classes, or augmenting the first agent with a second[4].

The selective serotonin-reuptake inhibitors (SSRIs) are common first-step treatments, given their relatively low toxicity and high tolerability. The major types of switching strategies employed are switching to another antidepressant from a different pharmacological class (*e.g.*, from an SSRI to a serotonin-norepinephrine reuptake inhibitor [SNRI] or to a norepinephrine-dopamine reuptake inhibitor [NDRI])[5,6] and switching to another antidepressant within the same pharmacological class (*e.g.*, from an SSRI to another SSRI)[7,8].

The advantage of a switch to another antidepressant class is that it minimizes polypharmacy, which helps prevent toxicity and negative drug-drug interactions, it may lead to fewer or more tolerable side effects and can, therefore, improve patient compliance[2,9] while reasons in support of combining

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two antidepressants from different classes include avoidance of loss of partial response with a monotherapy and less risk of worsening of depressive symptoms when a partially effective medication is discontinued. Disadvantages of combination strategy are increase risk of drug-drug interactions, potentiating of side effects and drug cost[4].

Bupropion, an NDRI, is an antidepressant with novel neurotransmitter properties that not only seems to augment SSRI or SNRI effectiveness and/or help relieve or reverse certain adverse events associated with these agents[10,11] but also resulted in an improvement of treatment response after switching from an SSRI[8]. In step 2 of the Sequenced Treatment Alternatives to Relieve Depression (STAR*D) study, which included a switch from citalopram to bupropion and combination of citalopram with bupropion, showed that approximately one in five patients had a remission of symptoms after switching to bupropion[12] and one-third of the participants remitted with bupropion combination[13]. However, bupropion is not approved for the treatment of MDD in Thailand.

Critical reviews, there is no publicating study evaluating economic aspect of bupropion in terms of switching strategy and combination strategy in those with inadequate benefit (intolerance or lack of remission) with an SSRI. Therefore, the current study aims to present an economic model and cost-effectiveness estimates for bupropion in treatment of MDD after failure of an SSRI using outcomes form the STAR*D study. The main comparator treatments were a switch to bupropion and a combination with bupropion.

Material and Method

Model Structure

A schematic representation of the model structure is given in Fig. 1. Adult Thai outpatients with a nonpsychotic MDD who had no remission or could not tolerate the SSRI citalopram received either sustained-release bupropion (at a dose of up to 400 mg per day) monotherapy as switching strategy or sustained-release bupropion (at a dose of up to 400 mg per day) plus citalopram as combination strategy. A 12-week time horizon was applied because the STAR*D trials from which the parameters were taken had 12-week observation periods[12,13].

At the end of each treatment, patients could have 4 possible health states: remission, non-remission, discontinuation due to intolerance, and occurrence of serious adverse events. Those who had non-remission, discontinuation due to intolerance, or serious adverse events were assumed to be hospitalized and, received electroconvulsive therapy (ECT). During this process, the patients accumulated costs and outcomes, which were evaluated at the end of treatment.

Transitional Probabilities

The modelled transitional probabilities given in Table 1 were derived from Rush trial[12] and Trivedi trial[13]. Both trails recorded remission rates, rates of non-remission, discontinuation rates due to intolerance, and incidence of serious adverse events. These event probabilities were used in the model to calculate weighted cost of each treatment outcome.

Cost and Resource-Use Estimates

The model take a direct-payer costing perspective (year 2009 Thai Baht; THB). Modeled resource-use items were drug costs for acute treatment. If patients experience non-remission, intolerance, or serious adverse events (worsening depression, suicidal ideation/attempt, or other psychiatric condition), the model account for the following: cost of hospitalization; cost of drugs; cost of ECT. The model do not consider costs and outcomes arising from possible adverse events, indirect costs, or premature mortality. All the resource-use assumptions, unit costs, and data sources are presented in Table 1, 2, respectively.

Health-State Utilities

The health-state utilities used in the model were based on a report by Revicki and Wood[15], which used the standard gamble interviews and the 36-short form (SF-36) values to examine differences in utilities for 11 hypothetical depression-related states in MDD. The utility values were collated as part of bupropion trials[12,13]. Consequently, this analysis assumed utility values of 0.8 for remission (or euthymic state).

Model Outcomes

The primary outcome considered in the model was a remission of symptoms - defined as a total score of 7 or less on the 17-item Hamilton Depression Rating Scale (HDRS-17)[16] at the end of 12-week treatment period. Quality-adjusted life-years (QALYs) were derived as a secondary outcome because utility assessment was not performed in the trials. The incremental cost-effectiveness ratios (ICERs) examine the additional costs that one strategy incurs over another and compare this with the additional benefits. Therefore, ICERs were calculated to assess the cost

per remission gained and the incremental cost per QALY gained was also investigated.

Sensitivity Analyses

In order to test the sensitivity of the model outputs to the input assumptions, the study undertook the one way sensitivity analysis and threshold analysis. Selecting clinical input variables were based on the greatest influence on model results. For the one way sensitivity analysis, the following parameters were varied individually: probability of remission, duration of treatment, and cost of citalopram. Other variables that had a relatively small effect on direct costs (*e.g.*, discontinuation due to intolerance and incidence of serious adverse events) were not undertaken.

Results

Base-Case Treatment Analysis

Over 12-week period with the 2 treatment options using effectiveness data from pivotal trials including patients with a non-psychotic MDD, the model estimated that patients treated with bupropion monotherapy (switching strategy) experienced a remission at 21.3% whereas bupropion plus citalopram (combination strategy) provided 29.7% of remission. The mean times to reach remission were 8.3 weeks for bupropion switch and 10.2 weeks for bupropion combination, respectively. Number of discontinuation and serious adverse events are summarized in table 1. The model estimated that the total direct costs with a bupropion switch were 22,937 THB per remission and 29,346 THB per remission with bupropion combination (Table 3). Compared with combination option, switching to bupropion also had lower total cost per QALY (28,672 THB vs. 36,682 THB) and had cost saving of 21.8%. The incremental cost-effectiveness of a combination regimen compared with a switching regimen was 6,409 THB per remission gained and 8,011 THB per QALY gained (Table 4).

Sensitivity Analyses

Table 5 presents the proportional change in remission rates (40%, 50%, and 60%) and duration of treatment (4, 6, and 8 weeks) as well as cost of citalopram (30%, 50% and 70% discounts) for combination strategy relative to switching strategy. Incremental cost per remission gained and incremental cost per QALY gained (combination compared with switching) which resulted

Table 1. Transitional Probability Estimates and Resource Use Assumptions

Transitional probability and resource variable	Switching (n = 239)	Combination (n = 279)
Transitional probability		
Remission	0.213	0.297
Non-remission	0.511	0.571
Discontinuation due to intolerance	0.272	0.125
Serious adverse events: Hospitalization for worsening depression, suicidal ideation/attempt or other psychiatric condition	0.004	0.007
Resource use variable		
Duration of treatment (wk)	8.3	10.2
Dose at end of study (mg/d)	282.7	267.5
Citalopram dose at end of study	-	54.2
Source	Rush et al[12]	Trivedi et al[13]

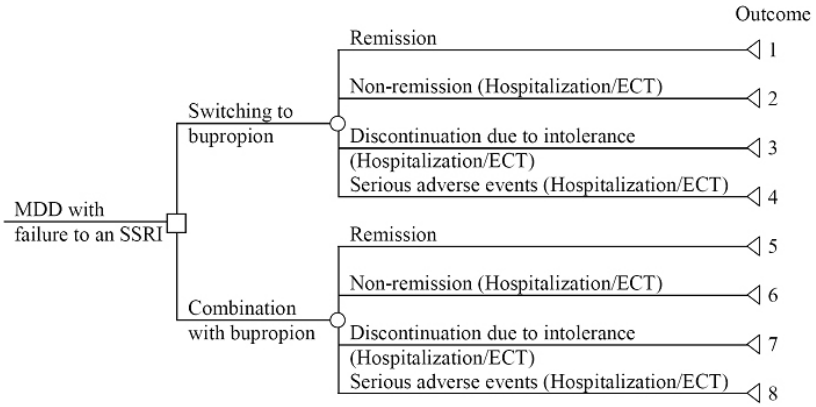

Fig. 1 The Model Structure

from having changed clinical input variables of combination strategy are also presented.

An increase in remission rates of combination strategy produced a decrease (26,709 THB to 21,589 THB) in total costs of treatment. Besides, a shorter period of getting remission and a decrease of the price of citalopram resulted in a decrease in direct cost outcomes. Consequently, the ICERs for a remission gained and a QALY gained were sensitive to the probability of remission, duration of treatment to achieve one remission, and cost of citalopram.

Since switching strategy is more cost-effective than combination strategy, a threshold analysis sought out the value of clinical input variables of combination strategy that were varied until switching strategy was found to have equal outcomes, and there is no benefit of switching strategy over combination strategy in terms of estimated outcome (remission). Combination strategy dominated switching strategy if the value of the transitional probability of remission changed to a value of greater than 0.547 from the base-case value of 0.297. In other words, combination strategy needs 25% of difference in remission rate compared with switching strategy to be a more cost-effectiveness regimen.

Likewise, the threshold values of means duration of achieving remission and cost of citalopram for combination strategy compared with switching strategy are 4.4 weeks and 6.15 THB, respectively. In other words, combination strategy is more effective and cost saving than switching strategy if it provides a remission period before 4.4 weeks and the cost of citalopram is less than 6.15 THB.

Table 2. Unit Cost (THB)

Cost	Unit resource /Cost	Source
Drug		
Bupropion 150 mg/d	35	Phramongkutklao Hospital
Citalopram 20 mg/d	44	Phramongkutklao Hospital
Cost per day		
Switching	65.96	
Combination	181.66	
Hospitalization/ECT		
Days hospitalized for ECT	20	Survey
Cost per inpatient bed day	600	Phramongkutklao Hospital
ECT (times)	8	Kennedy and Giacobbe[14]
ECT per cost	1,700	Phramongkutklao Hospital

THB = Year 2009 Thai Baht, ECT = Electroconvulsive therapy

Discussion

This study is the first to evaluate the cost-effectiveness of bupropion, an NDRI antidepressant, as a switching strategy and a combination strategy in adult outpatients with a nonpsychotic MDD who had not achieve remission or had withdrawn from treatment because of intolerance to a previous SSRI trial.

Table 3. Weighted Cost of Each Outcome (THB)

Health effects	Medication	Hospitalization	ECT	Total cost	Probability	Weight cost
Switching						
Outcome 1	3,832.47			3,832.47	0.213	816.316
Outcome 2	3,832.47	12,000.00	13,600.00	29,432.47	0.511	15,039.99
Outcome 3	0.00	12,000.00	13,600.00	25,600.00	0.272	6,963.20
Outcome 4	3,832.47	12,000.00	13,600.00	29,432.47	0.004	117.73
				Total	1.000	22,937.24
Combination						
Outcome 5	12,970.29			12,970.29	0.297	3,852.17
Outcome 6	12,970.29	12,000.00	13,600.00	38,570.29	0.571	22,023.63
Outcome 7	0.00	12,000.00	13,600.00	25,600.00	0.125	3,200.00
Outcome 8	12,970.29	12,000.00	13,600.00	38,570.29	0.007	269.99
				Total	1.000	29,345.80

THB = Year 2009 Thai Baht, ECT = Electroconvulsive therapy

Although a combination of bupropion with an SSRI is more effective than a switch to monotherapy and was well tolerated[13,17] and is one of the more popular combinations used in clinical practice in MDD patients who fail to reach remission[18], this strategy is not more cost-effective in short-term than bupropion alone for treating adults with MDD after failure of an SSRI.

Based on the results of two STAR*D trials, the economic model indicates that switching to bupropion is a cost-effectiveness treatment option compared to combination with bupropion strategy. The total cost distribution of the 2 strategies indicated that during the switching treatment, 66% of the total costs were attributable to the management of non-remission, compared with 75% of the total costs for combination treatment. Cost of drugs in combination strategy, an SSRI plus bupropion, is approximately 3 times higher than switching strategy. This difference in cost of drugs is due to the high cost of SSRI and resulted in the less cost effectiveness of combination treatment.

Table 4. Cost-Effectiveness Analysis (THB) of Switching vs. Combination in Base-Case Analysis

Cost-effectiveness analysis	Switching	Combination
Total cost per remission	22,937.24	29,345.80
Total cost per QALY	28,671.55	36,682.25
Cost saving (%)	21.84	
Incremental cost per remission gained		-6,408.56
Incremental cost per QALY gained		-8,010.70

THB = Year 2009 Thai Baht, QALY = Quality Adjusted Life Year

Table 5. One-Way Sensitivity Analysis on Clinical Input Variables for Combination Relative to Switching

Cost-effectiveness analysis	Total cost	Incremental cost per remission gained	Incremental cost per QALY gained
Probability of remission			
0.4	26,709.00	-3,771.76	-4,714.70
0.5	24,149.00	-1,211.76	-1,514.70
0.6	21,589.00	1,348.24	1,685.30
Duration of treatment (wk)			
4	22,447.39	489.85	612.31
6	24,672.68	-1,735.44	-2,169.31
8	26,897.98	-3,960.74	-4,950.92
Cost of citalopram (THB/tab)			
30.80 (-30%)	27,110.94	-4,173.71	-5,217.13
22.00 (-50%)	25,621.04	-2,683.80	-3,354.75
13.20 (-70%)	24,131.14	-1,193.90	-1,492.37

THB = Year 2009 Thai Baht, QALY = Quality Adjusted Life Year

In Thailand, SSRIs or other antidepressants (SNRIs or NDRI) are costly medications. Thus, combining two antidepressants yield a substantial high-costly treatment option. As such, clinical decision of selecting treatment option may be cautiously considered not only in healthcare provider perspectives but also in payer perspectives.

Compared with switching strategy, combination strategy provided only 8.4% of additional remission rates which are a little difference to achieve a cost-effectiveness treatment option as inferred in the model. In additions, time to remission of combination strategy that was longer than switching strategy (10.2 vs. 8.3 weeks) was lead to a higher cost of drugs and lastly, the less cost-effectiveness option. Although a combination of bupropion with an SSRI is more effective than a switch to monotherapy and was well tolerated[13,17] and is one of the more popular combinations used in clinical practice in MDD patients who fail to reach remission[18], this strategy is not more cost-effective in short-term than bupropion alone for treating adults with MDD after failure of an SSRI.

The first limitation of this study is determined largely by the simplifying assumptions that were made in constructing and populating the model. The validity of the model results is restricted to the subgroup of patients with MDD included in the STAR*D trials. The results should not be interpreted as relevant to patients excluded from the trials, for example, adolescents or psychotic depression. The model did not account for pharmacological or psychological treatment options which are often used in clinical setting before receiving ECT.

Secondly, the generalizability of the STAR*D results (clinical parameters) to MDD patient population in Thailand or Asian population is limited because the trials were conducted in a different race or ethnic group which may lead to differences in drug response, burden of side effects/adverse events and discontinuation due to intolerance.

Third, direct costs accounted for the present

study were based only on data from Phramongkutklao Hospital, the government general hospital, which may be unable to generalize to other psychiatric hospital, private hospital, or even general hospital in Thailand. However, healthcare providers in other hospitals can change the costs and resource use estimates in order to capture the critical variables of the model outcomes. Lastly, the study does not account for the indirect costs incurred as a result of MDD. Indirect costs, such as productivity loss due to absenteeism or loss productive time, pose a substantial economic burden upon society[19-21], especially in patients who had partial remission or persistent depression[21-23]. Because the accrual of indirect costs is associated with productivity loss (due to non-remission), a combination treatment such as SSRI plus bupropion that is able to increase the remission rate is likely to decrease the ICERs and provide further cost saving.

Conclusions

The results of this economic evaluation suggest that switching to bupropion is a cost-effectiveness alternative to the combination of SSRIs and bupropion in the acute treatment after the failure of an SSRI in patients with nonpsychotic MDD. Specifically, the model indicates that a switch to bupropion, as compared with bupropion plus SSRI, results in lower costs and higher QALYs. Nevertheless, further clinical trials and economic analyses of direct comparison between these two strategies are needed to confirm the cost-effectiveness of bupropion in each treatment strategy.

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การพัฒนาแบบจำลองทางเศรษฐศาสตร์ของไทยเพื่อศึกษาต้นทุน-ประสิทธิผลของการเปลี่ยนการรักษาเป็น bupropion เทียบกับการรักษาผสมด้วย bupropion หลังจากการล้มเหลวต่อ SSRIs สำหรับโรคซึมเศร้า

ธวัชชัย ลีพหานาจ

วัตถุประสงค์*: เพื่อนำเสนอแบบจำลองทางเศรษฐศาสตร์และการประมาณการด้านต้นทุน-ประสิทธิผลของการเปลี่ยนการรักษาเป็น bupropion เทียบกับการรักษาผสมด้วย bupropion หลังจากการล้มเหลวต่อ SSRI ในการรักษาโรคซึมเศร้า*

วัสดุและวิธีการ*: แบบจำลองทางเศรษฐศาสตร์ได้ถูกสร้างขึ้นเพื่อเลียนแบบการเปลี่ยนแปลงต่างๆ ของผู้ป่วยนอกชาวไทยที่ป่วยเป็นโรคซึมเศร้าที่ไม่มีอาการโรคจิตที่ไม่เกิดการสงบของโรคหรือไม่สามารถทนต่อการรักษาด้วยยากลุ่ม SSRIs คือ citalopram ได้ และได้รับการรักษาด้วยวิธีการเปลี่ยนการรักษาเป็น bupropion หรือการรักษาผสมด้วย bupropion ร่วมกับ citalopram ข้อมูลทางคลินิกได้จากการศึกษา 2 ชิ้นของการศึกษา STAR*D ความน่าจะเป็นของเหตุการณ์ 4 อย่างได้แก่ อัตราการสงบของโรค อัตราการไม่สงบของโรค อัตราการออกจากการรักษาเนื่องจากการไม่สามารถ ทนต่อการรักษาได้ และอุบัติการณ์ของการเกิดอาการ ไม่พึงประสงค์ที่รุนแรงได้ถูกการประมาณการ ต้นทุนทางตรง ประกอบด้วยค่ายา ค่าพักรักษาตัวในโรงพยาบาล และค่าบำบัดด้วยการกระตุ้นให้ชักด้วยไฟฟ้า ผลลัพธ์ปฐมภูมิของ แบบจำลองคือการสงบของอาการของโรค ข้อมูลที่ได้จะถูกวัดเป็นต้นทุนต่อการสงบของโรคและต้นทุนต่อ QALYs*

ผลการศึกษา*: การวิเคราะห์ base-case พบว่า ต้นทุนทางตรงทั้งหมดของการเปลี่ยนการรักษาเป็น bupropion เท่ากับ 22,937 บาทต่อการสงบของโรค และ 29,346 บาทต่อการสงบของโรคของการรักษาผสมด้วย bupropion เมื่อเทียบกับการรักษาผสมพบว่า การเปลี่ยนการรักษามีต้นทุนต่อ QALY ต่ำกว่า (28,672 บาท เทียบกับ 36,682 บาท) และมีต้นทุนต่ำกว่าร้อยละ 21.8 ค่า incremental cost-effectiveness ของการรักษาผสมเทียบกับการเปลี่ยนการรักษาเท่ากับ 6,409 บาทต่อการสงบของโรคที่เพิ่มขึ้น 1 ราย และเท่ากับ 8,011 บาทต่อ QALY ที่เพิ่มขึ้น 1 หน่วย การวิเคราะห์ความไวพบว่า การรักษาผสมจะเหนือกว่าการเปลี่ยนการรักษาหากการรักษาผสมมีอัตราการสงบของโรคมากกว่า 0.547*

สรุป*: แบบจำลองทางเศรษฐศาสตร์แสดงให้เห็นว่า การรักษาผู้ป่วยโรคซึมเศร้าที่ล้มเหลวต่อ SSRI ด้วยการเปลี่ยนการรักษาเป็น bupropion เป็นวิธีที่มีต้นทุน-ประสิทธิผลเหนือกว่าการรักษาผสมด้วย SSRI กับ bupropion*