The Treatment of Major Depressive Disorders (MDD) in Thailand Using Escitalopram Compared to Fluoxetine and Venlafaxine: A Pharmacoeconomic Evaluation

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A decision analytical model was used to compare expected health outcomes and costs of treating patients with major depression using new selective serotonin reuptake inhibitor (SSRI) escitalopram versus the other SSRI fluoxetine and the serotonin norepinephrine reuptake inhibitor (SNRI) venlafaxine. The primary health outcome measure was an overall treatment success, defined as a remission (Montgomery-Åsberg Depression Rating Scale (MADRS) ≤ 12), achieved over the 6 months of treatment. Estimated costs consisted of those directly related to treatment (drug acquisition costs, costs of psychiatric visits, hospital outpatient visits, hospitalization, and electroconvulsive therapy) and indirect costs associated with productivity lost due to depression. Clinical input parameters for the economic analyses were derived from published literatures. Resource utilization estimates were obtained from a survey of psychiatrists, while medical treatment patterns were determined from focus groups participated consisting from both general and family practitioners and psychiatrists. Unit costs (including daily cost of patient's absence from work due to depression) were obtained from the standard sources. The unit cost of hospitalization was derived based on the average of factual service rates charged by the local hospital.

The results show that escitalopram is more effective and less costly compared to fluoxetine and venlafaxine. Treatment using escitalopram produced the best-expected success rate and the lowest expected per patient cost. Escitalopram earned a savings of Baht 2,002 and Baht 1,768 compared to fluoxetine and venlafaxine respectively over a six-month period.

Keywords: *Major depression, Escitalopram, Fluoxetine, Venlafaxine, Cost-effectiveness, SSRIs, SNRI*

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The Global Burden of Disease study by the World Health Organization (WHO) and other sources indicate that depression is one of the most debilitating health problems in the world[1,2]. In 1990, depression ranked fourth among all diseases. The WHO researchers predicted that, by the year 2020, depression would rank second after heart disease, accounting for 15% of the disease burden in the world[1]. It is clear that depression has been the focus of intense clinical research and policy concern in both general medical and mental health specialty practices.

Pharmacological treatment appears to be the most common treatment for major depressive disorder (MDD). Worldwide, selective serotonin reuptake inhibitors (SSRIs) are recommended as first-line treatment of MDD [NICE, 2004; Kennedy et al., 2001; APA, 2006; Norwegian Medicines Agency, 2004][3-6]. An observational study found that 98% of patients were prescribed an antidepressant, of which SSRIs were the most frequently prescribed[7]. SSRIs are also recommended as first-line treatment of MDD in Thailand. However, there are still unmet needs in treatment of depression,

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including real-life efficacy (e.g., remission of symptoms), tolerability and, given scarce healthcare resources, cost savings/ost effectiveness versus standard alternatives.

Lexapro® (escitalopram), the S-enantiomer of citalopram, is the most selective SSRI available[8]. It was more effective than the SSRIs in clinical studies[9] and at least as effective as SNRIs (venlafaxine and duloxetine) in MDD, but with better tolerability profile[10,11]. Health economic models have demonstrated escitalopram to be cost-effective[12-16].

In an increasingly cost-conscious environment, it is necessary to examine the cost-effectiveness of escitalopram compared to relevant alternatives from Thai perspectives. So far, no study has been published evaluating the cost effectiveness of escitalopram in Thailand. The present report therefore evaluates the economic benefits of escitalopram compared to venlafaxine and fluoxetine, the most relevant pharmacologic treatment alternatives in MDD in Thailand. The cost-effectiveness analyses were performed over a 6-month time horizon from the perspectives of the health care provider and Thai society.

Insights gained from these perspectives will be useful to policy makers. The results of this pharmacoeconomic study will help clinicians and health-care policy makers to determine which treatment will provide the most benefit to patients with major depression in term of patient functioning and well-being at the most acceptable medical cost.

Objectives

1. To assess the cost effectiveness of escitalopram versus fluoxetine and venlafaxine in the treatment of major depressive disorder in Thailand from the viewpoint of health-care providers and society over a six month period.

2. To perform a sensitivity analysis of the main variables that affected the analysis.

Material and Method

Study design

The present study was an economic evaluation of the treatment of major depression disorder in Thailand for 6-months using a clinical decision analysis model. Parameter estimations were based on information obtained through the review of published randomized clinical trials and other medical literature and, when needed, clinical judgment in the treatment of major depression disorder from the perspective of health-care provider and society.

The target population for the present study consisted of patients with major depressive disorder.

The alternatives or choices of comparators in the present study were as follows.

Alternative 1: escitalopram (SSRI), the primary antidepressant of interest

Alternative 2: fluoxetine (SSRI), selected as an alternative SSRI due to its frequent use as a first-line therapy of MDD in Thailand

Alternative 3: venlafaxine (SNRI), as a representative of another group of medication, which is a relatively new antidepressant drug

As no head-to-head comparison exists between all three agents, two parallel cost effectiveness analyses were carried out; one comparing escitalopram to fluoxetine and the other one comparing escitalopram to venlafaxine.

Model outcomes

The primary effectiveness outcome of the model was the overall treatment success, defined as remission (MADRS $\leq$ 12) achieved over 6 months of treatment. Other effectiveness outcomes of the model included first-line success (defined as remission achieved during the first 8 weeks of treatment with an initial therapeutic agent and maintained for a further 4 months), as well as expected rates of titration, switch and hospitalization/electroconvulsive therapy (ECT) associated with lack of treatment effect and/or tolerability issues (Fig. 1).

Cost outcomes included direct depression-related costs, consisting of the cost of drugs, medical services (consultation fees), and hospitalization/ECT charges, and indirect cost associated with productivity lost due to depression.

Decision analytic model

A decision analytic model[12] was adapted to the Thai setting, reflecting local key treatment options for the first-line treatment, most likely scenarios in the case of adverse events, and lack of treatment response, etc. The model takes into account the direct access to psychiatrists that depressed patients have in Thailand; according to expert opinion, 80% of depressed patients seek treatment directly from psychiatrists. The final model used in the present study is depicted in Fig. 1.

Data inputs

The treatment outcomes in the model depend on the probabilities of certain clinical events, determined by clinical properties of an antidepressant used (i.e.,

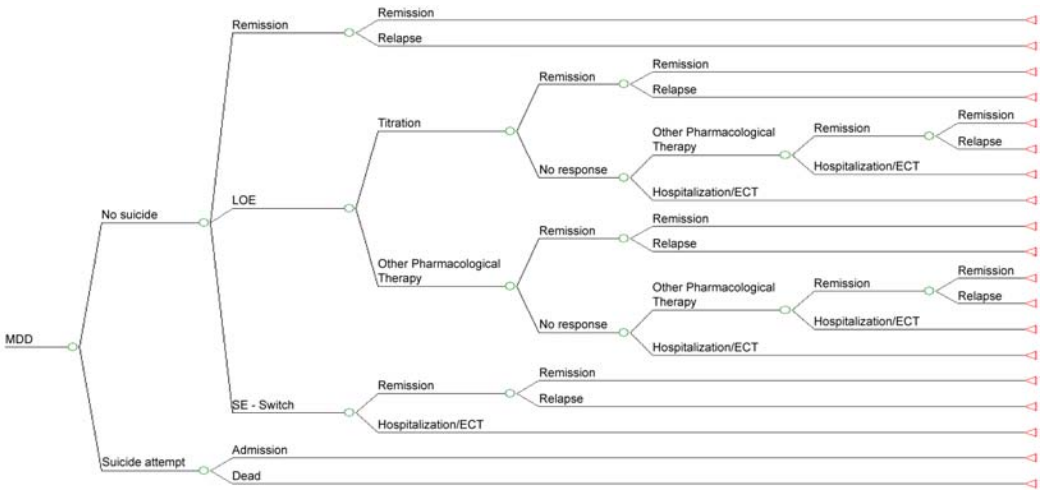

Fig. 1 Decision tree vs. treatment diagram of major depressive disorder

its efficacy and tolerability), and/or clinical practice patterns. The model input probabilities (clinical parameters) and inputs related to patient management and healthcare resource utilization are based on sources considered most relevant for this context.

Drug-specific clinical parameters

Drug-specific input probabilities used in the two cost-effectiveness models (i.e., escitalopram versus fluoxetine and escitalopram versus venlafaxine) are presented in Table 1. Due to lack of published data on head-to-head comparison of escitalopram to fluoxetine at the time of the present analyses, the clinical data comparing escitalopram to citalopram were used as a proxy, derived from the meta-analysis on all available relevant clinical trials[17]. This substitution is justified by the equal efficacy and safety profile of fluoxetine compared to citalopram[18]. For escitalopram, the remission rate at week 8 of 49.2% was derived from the remission rate estimate for citalopram (43.3%) and the adjusted odds ratio of remission for escitalopram vs. citalopram (1.27, 95% CI 1.03-1.57)[a]. For the cost-effectiveness analysis of escitalopram versus venlafaxine, *remission rates at week 8* were derived from the meta-analysis of head-to-head clinical trials[9]. In this pooled analysis, the remission rate for venlafaxine (the reference treatment arm) was 55.0%. For escitalopram, the remission rate of 61.2% was derived from the remission rate estimate for venlafaxine and the adjusted odds ratio of remission for escitalopram vs. venlafaxine (1.29, 95% CI 0.84-1.98)[a].

The *probabilities of remission after titration* were derived from a post-hoc analysis of the 8-week head-to-head flexible-dose randomized European clinical trial comparing escitalopram with citalopram (unpublished data). Due to lack of data, the rate for venlafaxine was assumed to be the same as that of escitalopram. These estimates were used in the cost-effectiveness analysis of escitalopram vs. SSRIs and venlafaxine in Norway[19].

No head-to-head comparisons of *relapse rates* between escitalopram and fluoxetine (or citalopram) were available. Therefore relapse rates (specific and non-specific to treatments) were estimated based on all placebo-controlled relapse prevention studies available for escitalopram and citalopram, including two relapse prevention studies for escitalopram[20,21] and three for citalopram[22-24], as a meta-analysis of all the studies for each compound.

For the model comparing escitalopram to fluoxetine, *switch due to adverse events* were based on published meta-analysis of clinical trials of escitalopram vs. citalopram[25], assuming similar clinical profile between citalopram and fluoxetine[18]. For the model of escitalopram versus venlafaxine, rates of switch due to adverse events were derived from the meta analysis[17].

Sensitivity analysis

To test the robustness of model outcomes to uncertainty in key input probabilities, several univariate

[a] *This approach accounts for heterogeneity between individual clinical trials, in contrast to the use of pooled unadjusted remission probabilities for escitalopram and citalopram treatment arms reported in the meta-analysis.*

Table 1. Drug-specific probabilities

Parameter	Base-case value	95% CI	Distribution	Reference
Remission rate				
OR escitalopram vs. fluoxetine	1.27	1.03-1.57	Exp (Normal)	Lançon et al, 2007[17]
Escitalopram vs. fluoxetine	49.2%[a] vs. 43.3%	39.7-46.9	Normal	Lançon et al, 2007[17]
OR escitalopram vs. venlafaxine	1.29	0.84-1.98	Exp (Normal)	Kennedy et al, 2006[9]
Escitalopram vs. venlafaxine	61.2%[b] vs. 55.0%	52.3-57.7	Normal	Kennedy et al, 2006[9]
Remission rate after titration				
Escitalopram	36.2%	24.9-49.2	Normal	François et al, 2003[19]
Fluoxetine	23.8%	14.9-35.8	Normal	François et al, 2003[19]
Venlafaxine	36.2%	24.9-49.2	Normal	François et al, 2003[19]
Relapse rate				
OR escitalopram vs. real practice	0.36	0.23-0.58	Exp (Normal)	Rapaport et al, 2004; Gorwood et al, 2007[20,21]
OR fluoxetine vs. real practice	0.33	0.25-0.43	Exp (Normal)	Montgomery et al, 1993; Robert and Montgomery, 1995; Klysner et al, 2002[23,24]
OR venlafaxine vs. real practice	0.36	0.19-0.66	Exp (Normal)	Simon et al, 2004[26]
Rate of switch due to adverse events				
Escitalopram vs.	4.4%	2.4-6.8	Beta	Einarson, 2004[25]
fluoxetine	7.0%	4.5-10.1	Beta	Einarson, 2004[25]
escitalopram vs.	6.8%	4.3-10.3	Beta	Lançon et al, 2007[17]
venlafaxine	13.5%	9.4-18.1	Beta	Lanéon et al, 2007[17]

(a) Calculated from Lançon et al, 2007[17]
(b) Calculated from Kennedy et al, 2006[9]
(c) Remissio n for all SSRI and SNRI since remission rates for venlafaxine is not given in the publication

sensitivity analyses were carried out using the lower and higher boundaries of the 95% confidence intervals. For the variables on resource utilization, one-way sensitivity analyses were performed with the plausible ranges based on the estimation of the physician survey. A probabilistic sensitivity analysis using Monte Carlo simulations (1,000 trials) was also performed to account for the uncertainty around the clinical input parameters and unit costs. Cost-effectiveness planes were produced to depict the relationship between incremental effectiveness and incremental total cost for escitalopram versus fluoxetine and escitalopram versus venlafaxine.

Results

Result on the efficacy and resource utilization is presented in Table 1, 2, and 3.

Non-drug specific clinical parameters

Table 2 presents non-drug specific input probabilities used in the analyses, based on the published literature or, whenever necessary, on the Thai psychiatrist survey.

Resource utilizations

Resource utilization input parameters were based on the Thai psychiatrist survey. For switch or combination, only major drugs were considered:

- Switch due to lack of efficacy: venlafaxine (sertraline was considered if venlafaxine was the first-line treatment).

- Switch due to adverse events: sertraline and escitalopram (sertraline was considered alone if escitalopram was the first-line treatment).

- Combination: as TCAs are used in the case of a combination of antidepressant treatments, amitriptyline 75mg/day was considered.

The resource utilization data are presented in Table 3. The number of psychiatrist visits was estimated separately for the acute and follow-up phases. Additional professional visits included those due to the occurrence of relapse, switch, and titration.

Unit costs

Unit costs used in the model were determined for the fiscal year 2007 and expressed in Thai Baht for each intervention encountered in each alternative.

Table 2. Non-drug specific probabilities

Parameter	Base-case Value	95% CI	Distribution	Reference
Remission/Relapse				
Remission rate after switch	44.7%	29.1-59.8	Beta	Posternak and Zimmerman, 2001[27]
Relapse rate				
OR relapse rate vs. real practice	0.34	0.27-0.42	Exp (Normal)	Rapaport et al, 2004; Gorwood et al, 2007; Montgomery et al, 1993; Robert and Montgomery, 1995; Klysner et al, 2002; Simon et al, 2004[20-24,26]
Relapse rate after 4 months (real practice)	21.8%	16.8-27.4	Beta	Mulder et al, 2006[28]
Suicide				
Suicide attempt	6.3%			Khan et al, 2001[29]
Completed suicide	0.6%			Khan et al, 2001[29]
In case of lack of efficacy				
Titration	61.4%	16.5-100	Normal	Survey
Switch/Combination/Augmentation	38.6%			Survey
Switch	42.0%			Survey
Combination	30.7%			Survey
Augmentation	27.3%			Survey
In case of no response after titration				
Switch/Combination/Augmentation - after titration	69.1%	24.0-100	Normal	Survey
Switch	51.6%			Survey
Combination	22.0%			Survey
Augmentation	26.5%			Survey
Hospitalization/ECT	30.9%			Survey
In case of no response after switch[a]				
Titration/Switch/Combination/Augmentation - after switch	54.5%	0-100	Normal	Survey
Titration	28.6%			Survey
Switch	22.1%			Survey
Combination	27.1%			Survey
Augmentation	22.2%			Survey
Hospitalization/ECT	45.5%			Survey

[a] Options after augmentation or combination were assumed to be similar to patterns after switch

There is no discount rate applied in the present study because the duration of the model was less than one year. All unit costs are shown in Table 4.

Direct costs included drug acquisition cost, professional consultation cost, and hospitalization cost. Direct medical cost considered the actual charges from the Department of Pharmacy Unit, which was calculated by the dose used in one year. The daily-defined dose (DDD) of escitalopram is 10 mg, fluoxetine 20 mg, venlafaxine 75 mg, and augmentation with a 600-900 mg/day dose of lithium. The professional consultation cost was calculated using a consultation fee per psychiatrist visit.

Indirect costs due to absenteeism from work were estimated using the human capital approach. The number of working days lost for a patient seeking a treatment was estimated based on survey results. Indirect costs were calculated by multiplying the number of working days lost by the daily cost of absence from work (i.e., Baht 191 per day [30]) in Thailand.

Cost effectiveness analysis

Results on effectiveness and costs of escitalopram versus fluoxetine and venlafaxine in the base-case analyses are shown in Table 5. Escitalopram appeared superior to both fluoxetine and venlafaxine

Table 3. Resource utilization

Parameter	Unit(s)	95% CI	Distribution	Source
Psychiatrist visit				
Acute phase	1.8	1.0-3.2	Normal	Survey
Follow-up phase	4.6	2.6-5.0	Normal	Survey
Relapse	4.9	1.0-9.8	Normal	Survey
Switch	4.3	2.0-10.0	Normal	Survey
Titration	3.9	1.0-9.6	Normal	Survey
Hospitalization/ECT				
Hospitalization - Duration	19.6	7.0-41.4	Normal	Survey
ECT	10	8.0-12	Uniform	Thai Psychiatric Text Book[10]
Sick leave				
Proportion of patients	31.1%	5.0%-70.5%	Normal	Survey
Due to MDD	13.5	5.0-35.1	Normal	Survey
Additional due to lack of efficacy	17.1	3.0-85.3	Normal	Survey
Additional due to adverse events	6.5	1.0-20.0	Normal	Survey

Table 4. Unit cost (in Thai Baht) and resources used in model

Cost category	Unit cost (Thai Baht)	Source
Drugs		
Escitalopram 10mg/d	44	
Fluoxetine 20 mg/d	52	
Venlafaxine 75 mg/d	53	
Sertraline 50 mg/d	47	
Lithium 600/900 mg/d	6	
Amitriptyline 75 mg/d	3	
Consultation fee per visit		Faculty of Medicine, Ramathibodi Hospital
Psychiatrist - 1st visit	500	
Psychiatrist - follow-up visit	300	
Hospitalization/ECT		
Hospitalization fee per day	694	
Hospitalization for suicide attempt fee per day	1,446	
ECT	407	
Indirect costs		
Cost per working day lost	191	Ministry of Labour Thailand, 2006[30]

in terms of cost and effectiveness. Direct cost was a major portion of total cost; cost of medication was the key component of the direct cost, followed by cost of hospitalization. Cost savings with escitalopram mostly resulted from reduced use of health care services, e.g., hospitalization/ECT.

Sensitivity analysis on clinical input parameters

Escitalopram versus fluoxetine

Table 6 demonstrates the one-way analyses on clinical input parameters between escitalopram and fluoxetine. The results show that escitalopram remained more effective and cost saving when key clinical input parameters (including the odds ratio of remission with escitalopram vs. fluoxetine) were varied within the range of their 95% CIs. The cost and effectiveness results were only somewhat sensitive to remission rate and rate of remission after titration. Otherwise, the results clearly indicated that the model findings were robust to changes in the input parameters tested.

Escitalopram versus venlafaxine

The one-way analyses of clinical input parameters between escitalopram and venlafaxine are

Table 5. Cost and effectiveness of escitalopram vs. fluoxetine and venlafaxine in the base-case analysis

	Escitalopram vs. fluoxetine			Escitalopram vs. venlafaxine		
	ESC	FLU	Incr	ESC	VEN	Incr
Effectiveness (%)						
Overall success	69.32	64.56	4.76	73.76	70.64	3.12
First-line success	53.55	45.73	7.82	61.38	55.82	5.56
Switch	33.41	40.52	-7.11	26.74	32.72	-5.98
Titration	27.31	29.25	-1.94	18.73	18.64	0.09
Hospitalization/ECT	25.25	30.52	-5.27	20.60	23.90	-3.3
Cost (in Baht 2007)						
Total	17,460	19,462	-2002	15,994	17,762	-1768
Direct	15,704 (89.9%)	17,560 (90.2%)	-1856	14,525 (90.8%)	16,233 (91.4%)	-1708
Medications	7,955 (45.6%)	8,821 (45.3%)	-866	7,757 (48.5%)	8,846 (49.8%)	-1089
Visits	2,737 (15.7%)	2,796 (14.4%)	-59	2,579 (16.1%)	2,616 (14.7%)	-37
Hospitalization	3,984 (22.8%)	4,700 (24.1%)	-716	3,351 (21.0%)	3,800 (21.4%)	-449
ECT	1,028 (5.9%)	1,242 (6.4%)	-214	839 (5.2%)	973 (5.5%)	-134
Indirect	1,756 (10.1%)	1,902 (9.8%)	-146	1,469 (9.2%)	1,529 (8.6%)	-60

Table 6. One-way sensitivity analysis on clinical input parameters (escitalopram vs. fluoxetine)

Variable		Value	Effect on total costs			Effect on effectiveness		
			Escitalopram	Fluoxetine	Incremental	Escitalopram	Fluoxetine	Incremental
Drug specific clinical probabilities								
Remission: odds ratio of ESC vs. FLU	Low	1.03	18,051	19,462	-1,411	67.25	64.56	2.69
	High	1.57	16,859	19,462	-2,603	71.41	64.56	6.85
Remission: after titration	Low	0.249	17,673	19,462	-1,789	67.29	64.56	2.73
	High	0.492	17,215	19,462	-2,247	71.64	64.56	7.08
Adverse events rate for ESC	Low	0.024	17,518	19,462	-1,944	69.54	64.56	4.98
	High	0.068	17,389	19,462	-2,073	69.05	64.56	4.49
Relapse: odds ratio of ESC vs. real practice	Low	0.23	17,442	19,462	-2,020	70.55	64.56	5.99
	High	0.58	17,488	19,462	-1,974	67.43	64.56	2.87
Non drug specific clinical input probabilities								
Remission: after switch	Low	0.291	18,176	20,284	-2,108	64.19	58.39	5.8
	High	0.598	16,821	18,724	-1,903	73.86	70.07	3.79
Relapse: OR for antidepressant vs. real practice	Low	0.27	17,456	19,457	-2,001	69.6	64.89	4.71
	High	0.42	17,465	19,468	-2,003	69	64.17	4.83
Relapse after 4 months: real practice	Low	0.168	17,441	19,445	-2,004	70.62	65.74	4.88
	High	0.274	17,483	19,483	-2,000	67.72	63.12	4.6
Titration for lack of efficacy	Low	0.165	16,730	18,319	-1,589	69.56	66.53	3.03
	High	1	18,088	20,445	-2,357	69.11	62.86	6.25
Other pharmacological therapy in case of failure after titration	Low	0.24	17,481	19,435	-1,954	66.1	60.45	5.65
	High	1	17,445	19,481	-2,036	71.52	67.37	4.15
Other pharmacological therapy in case of failure after switch	Low	0	17,487	19,491	-2,004	67.2	62.29	4.91
	High	1	17,438	19,438	-2,000	71.08	66.45	4.63

shown in Table 7. Compared to venlafaxine, escitalopram remained cost saving under the ranges of all the parameters tested, and more effective in the majority of cases. However, the effectiveness and, to a lesser extent, cost outcome were sensitive to variations in the odds ratio of remission on escitalopram versus venlafaxine; effectiveness outcome was also somewhat sensitive to the OR of relapse for escitalopram and

Table 7. One-way sensitivity analysis on clinical input parameters (escitalopram vs. venlafaxine)

Variable		Value range	Effect on total costs			Effect on effectiveness		
			Escitalopram	Venlafaxine	Incremental	Escitalopram	Venlafaxine	Incremental
Drug specific clinical probabilities								
Remission: odds ratio of ESC vs. VLX	Low	0.84	17,180	17,762	-582	69.59	70.64	-1.05
	High	1.98	14,916	17,762	-2,846	77.56	70.64	6.92
Adverse events rate for ESC	Low	0.043	16,071	17,762	-1,691	74.06	70.64	3.42
	High	0.103	15,900	17,762	-1,862	73.4	70.64	2.76
Relapse: odds ratio of ESC vs. real practice	Low	0.23	15,973	17,762	-1,789	75.18	70.64	4.54
	High	0.58	16,026	17,762	-1,736	71.61	70.64	0.97
Non drug specific clinical input probabilities								
Remission: after titration	Low	0.249	16,139	17,867	-1,728	73.38	69.26	4.12
	High	0.492	15,827	17,642	-1,815	75.36	72.23	3.13
Remission: after switch	Low	0.291	16,556	18,426	-1,870	69.7	65.73	3.97
	High	0.598	15,487	17,159	-1,672	77.41	75.11	2.3
Relapse: OR for antidepressant vs. real practice	Low	0.27	15,991	17,758	-1,767	73.98	70.9	3.08
	High	0.42	15,998	17,767	-1,769	73.51	70.34	3.17
Relapse after 4 months: real practice	Low	0.168	15,974	17,743	-1,769	75.13	71.96	3.17
	High	0.274	16,018	17,786	-1,768	72.11	69.04	3.07
Titration for lack of efficacy	Low	0.165	15,495	17,070	-1,575	73.93	70.8	3.13
	High	1	16,423	18,358	-1,935	73.62	70.5	3.12
Other pharmacological therapy in case of failure after titration	Low	0.24	16,013	17,760	-1,747	71.56	68.45	3.11
	High	1	15,981	17,764	-1,783	75.27	72.14	3.13
Other pharmacological therapy in case of failure after switch	Low	0	16,015	17,802	-1,787	72.32	69.2	3.12
	High	1	15,977	17,729	-1,752	74.98	71.85	3.13

citalopram versus the real practice. However, overall, effectiveness and cost outcomes of the model did not demonstrate much variation with respect to changes in the input parameters tested.

Sensitivity analysis on resource utilization

Escitalopram versus fluoxetine

Table 8 shows the univariate sensitivity analyses of resource utilization variables impact on the total costs difference between escitalopram and fluoxetine. There was little variation in the total incremental cost (escitalopram vs. citalopram) due to changes in input variables tested, suggesting that the results of the model were robust to uncertainty in the key input parameters tested. The model was only somewhat sensitive to duration of hospitalization, with total incremental cost varying from -1,502 Baht to -2,867 Baht with respect to variation of the above input parameter from its lower to higher boundary tested.

Escitalopram versus venlafaxine

Table 9 presents the univariate analyses on resource utilization between escitalopram and venlafaxine. The results were quite similar to those shown for the comparison of escitalopram to fluoxetine, with escitalopram being cost-saving. Varying the number of psychiatrist visits resulted in consistently higher total costs for patients treated with venlafaxine compared to those treated with escitalopram. The same trend was observed while varying hospitalization duration and sick leave parameters.

Probabilistic sensitivity analyses

The Monte Carlo sensitivity analyses[31] were performed on all drug-specific and cost variables. As shown on the cost-effectiveness plane (Fig. 2), escitalopram dominates fluoxetine (i.e., appears to be more effective and cost saving) in 99% of cases. Compared to venlafaxine, escitalopram appeared dominant in 88.2% of cases.

Discussion

The current study estimated cost-effectiveness of escitalopram *versus* fluoxetine and venlafaxine in treatment of major depressive disorder in Thailand from the perspectives of health-care provider and the

Table 8. One-way sensitivity analysis on resource use (escitalopram vs. fluoxetine)

Variable	Value	Effect on total costs		
		Escita-lopram	Fluo-xetine	Incre-mental
Psychiatrist visit				
Acute phase	1.0	17,220	19,222	-2,002
	3.2	17,880	19,882	-2,002
Follow-up phase	2.6	16,977	19,001	-2,024
	5.0	17,557	19,554	-1,997
Relapse	1.0	17,401	19,409	-2,008
	9.8	17,534	19,528	-1,994
Switch	2.0	17,330	19,299	-1,969
	10.0	17,781	19,866	-2,085
Titration	1.0	17,212	19,197	-1,985
	9.6	17,946	19,983	-2,037
Hospitalization/ECT				
Hospitalization -	7.0	14,710	16,212	-1,502
duration	41.4	22,218	25,085	-2,867
ECT	8.0	17,254	19,213	-1,959
	12.0	17,665	19,710	-2,045
Sick leave				
Proportion of	0.050	15,986	17,865	-1,879
patients	0.705	19,684	21,872	-2,188
Due to MDD	5.0	16,973	18,975	-2,002
	35.1	18,698	20,700	-2,002
Additional due to	3.0	16,899	18,839	-1,940
lack of efficacy	85.3	19,915	22,191	-2,276
Additional due to	1.0	17,445	19,438	-1,993
adverse events	20.0	17,493	19,514	-2,021

Table 9. One-way sensitivity analysis on resource use (escitalopram vs. venlafaxine)

Variable	Value	Effect on total costs		
		Escita-lopram	Venla-faxine	Incre-mental
Psychiatrist visit				
Acute phase	1.0	15,754	17,522	-1,768
	3.2	16,414	18,182	-1,768
Follow-up phase	2.6	15,341	17,130	-1,789
	5.0	16,094	17,860	-1,766
Relapse	1.0	15,933	17,703	-1,770
	9.8	16,071	17,837	-1,766
Switch	2.0	15,879	17,606	-1,727
	10.0	16,279	18,151	-1,872
Titration	1.0	15,824	17,593	-1,769
	9.6	16,328	18,094	-1,766
Hospitalization/ECT				
Hospitalization -	7.0	13,685	15,141	-1,456
duration	41.4	19,988	22,298	-2,310
ECT	8.0	15,826	17,568	-1,742
	12.0	16,162	17,957	-1,795
Sick leave				
Proportion of	0.050	14,761	16,479	-1,718
patients	0.705	17,856	19,700	-1,844
Due to MDD	5.0	15,507	17,275	-1,768
	35.1	17,232	19,001	-1,769
Additional due to	3.0	15,640	17,410	-1,770
lack of efficacy	85.3	17,708	19,468	-1,760
Additional due to	1.0	15,972	17,721	-1,749
adverse events	20.0	16,048	17,865	-1,817

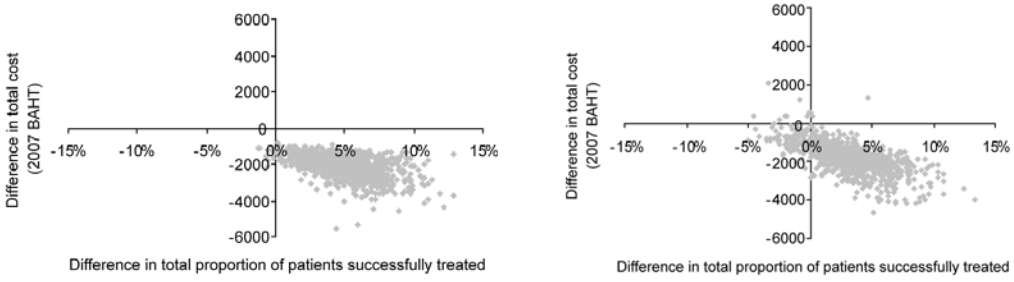

Fig. 2 Cost-effectiveness scattogram of the probabilistic sensitivity analysis of escitalopram vs. fluoxetine and escitalopram vs. venlafaxine

Thai society. The findings showed that escitalopram was more effective and cost-saving compared to fluoxetine and venlafaxine, suggesting that escitalopram can be a preferable choice of antidepressant for the treatment of patients with major depressive disorders in Thailand.

In the base-case analysis, escitalopram was associated with a higher overall success rate as well as the first-line success rate compared to fluoxetine and venlafaxine. Escitalopram was associated with lower switch and hospitalization rates compared to the alternatives. From an economic point of view, treatment

with escitalopram resulted in lower direct and indirect costs compared to the alternatives. The major driver of the cost savings observed with escitalopram was the lower resource utilization among patients on escitalopram vs. those on fluoxetine and venlafaxine. The results were supported by extensive one-way sensitivity analyses and probabilistic sensitivity analysis using Monte Carlo simulation; all findings were robust supporting the conclusion that escitalopram was a cost-effective first-line pharmacotherapy for major depressive disorders in Thailand.

Several published economic evaluations reported lower total expected costs and higher effectiveness of escitalopram vs. SSRIs [Fantino et al, 2007; Löthgren M et al, 2004; François et al, 2003][32,33,19] and cost-saving versus SNRI venlafaxine[14,15,34,35]. Although the authors' findings are consistent with these studies, some differences are worth noting that they may have resulted in somewhat different effectiveness and cost outcomes. Firstly, the present analyses took into account that most MDD patients in Thailand had a direct access to a psychiatrist, in contrast to other countries where MDD is widely treated by the primary care physician. Secondly, the original decision analytical model was adapted to reflect the local MDD treatment patterns, leading to certain differences in outcomes compared to other studies. In particular, although titration in case of lack of treatment response is recommended as a primary option by treatment guidelines in some countries[3], according to the Thai expert survey, other options (switch/combination/augmentation) are also common in Thailand in such a scenario (i.e., lack of response). Finally, the unit cost of the workdays lost due to depression in Thailand is substantially lower than in other countries, which explains a much lower contribution of the indirect cost to total estimated cost of depression.

The present study is subject to a number of limitations. 1) Bias, bias may be present due to different data sources used. To minimize the effect of this weakness, the model was largely built on local data collected through the Thai expert survey. The clinical parameters were derived from the published international clinical trials conducted in Western countries, assuming applicability of these parameters to Asian populations. 2) Three-armed comparison, limitation was the absence of a three-armed comparison of escitalopram to fluoxetine and venlafaxine; due to lack of data, two parallel analyses were conducted, comparing escitalopram with fluoxetine and escitalopram with venlafaxine. 3) Head-to-head comparison, due to unavailability of published clinical evidence from head-to-head comparison of escitalopram with fluoxetine at the time of the present analysis, the data on escitalopram vs. citalopram was used as a proxy, taking into account the published evidence of clinical equivalence between citalopram and fluoxetine[18]. Finally, since the modeling approach to the economic comparison is associated with necessary unavoidable simplification of the real-life treatment patterns, extrapolation of short-term clinical data, assumptions, etc., the long-term real-life evidence is warranted to confirm our findings.

Conclusion

The results from these analyses demonstrate that treatment with escitalopram results in superior health outcomes and substantial cost savings to patients and society compared to fluoxetine and venlafaxine, suggesting that escitalopram can be a preferred treatment option in Thailand. The reported evidence can be considered as a tool to assist in decision-making in the financing and management of pharmaceutical products in the health care system of Thailand.

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การวิเคราะห์ต้นทุนทางเศรษฐศาสตร์ การรักษาโรคซึมเศร้าในคนไทย: เปรียบเทียบระหว่างยาเอสซิตาโลเพรม ฟลูอ๊อกซิทีน และเวนลาแฟกซีน

รณชัย คงสกนธ์, ชาญชัย บัญชาพัฒนศักดา

วัตถุประสงค์: *เปรียบเทียบผลทางด้านเศรษฐศาสตร์ ในการรักษาผู้ป่วยโรคซึมเศร้า โดยเปรียบเทียบระหว่างยา SSRI ใหม่ escitalopram กับ ยาในกลุ่ม SSRI ตัวอื่น คือ fluoxetine และ ยาในกลุ่ม SNRI คือ venlafaxine*

วัสดุและวิธีการ: *การประเมินทางเภสัชเศรษฐศาสตร์ครั้งนี้ ใช้ decision analytical model เพื่อการวัดประสิทธิภาพและมูลค่าทางเศรษฐศาสตร์ของการรักษาข้อมูลรูปแบบของการรักษาผู้ป่วยซึมเศร้า และ resource utilization ได้จากการสำรวจจากจิตแพทย์ไทยและแพทย์ทั่วไป*

ค่าใช้จ่ายในการรักษา ประมาณค่าจากค่าใช้จ่ายในการรักษาโดยตรง (ราคายา, ค่าธรรมเนียมแพทย์, ค่าใช้จ่ายผู้ป่วยนอกของโรงพยาบาล, ค่าใช้จ่ายผู้ป่วยในของโรงพยาบาล, และค่ารักษาด้วยการกระตุ้นไฟฟ้า) และค่าใช้จ่ายโดยอ้อม (ค่าสูญเสียจากการหยุดงาน ค่าเสียรายรับจากการตกงาน)

ผลการศึกษา: *escitalopram ได้ผลการรักษาในอัตราที่สูงกว่า และค่าใช้จ่ายโดยรวมในการรักษาต่ำกว่ายา fluoxetine และยา venlafaxine จากการศึกษาระยะเวลา 6 เดือนในผู้ป่วยโรคซึมเศร้าพบว่า escitalopram สามารถประหยัดค่าใช้จ่ายได้ 2,002 บาท เมื่อเปรียบเทียบกับ fluoxetine, และ 1,768 บาท เมื่อเปรียบเทียบกับ venlafaxine*

สรุป: *การรักษาโรคซึมเศร้าในคนไทยด้วยกลุ่มยาต้ านเศร้า escitalopram มีความคุ้มทุนในเชิงเศรษฐศาสตร์มากกว่าเมื่อเปรียบเทียบกับ fluoxetine และ venlafaxine*