Article

Cost-effectiveness of Olanzapine and Risperidone in Treatment of Patients with Behavioural and Psychological Symptoms of Dementia in Thailand

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Abstract

Aim: This research is aimed at examining the cost-effectiveness of olanzapine versus risperidone in dementia patients with behavioural and psychological symptoms in Thailand. Methods: An existing Markov model based on a critical review through the comprehensive literature search and a justification for the most appropriate model for a Thai setting was adapted to simulate the disease progression of patients with dementia with behavioural disturbances until their need for full-time care (FTC). The time to the FTC state was estimated by a predictive equation developed by Rive et al. (2010). The model was conducted to assess the expected costs and outcomes associated with olanzapine compared with risperidone for Thai patients with BPSD aged 60 years and above. This model performed over a five-year time horizon with a one-month cycle length based on a societal perspective. The incremental cost-effectiveness ratio was used as the estimated outcome. Sensitivity analyses were also conducted to demonstrate the robustness of the results. Results: Over 5 years, olanzapine was found to be a cost-effective therapeutic option for the treatment of behaviourally disturbed patients with dementia compared with risperidone, in Thailand from a societal perspective (ICER < THB 160,000). The model underwent extensive sensitivity analyses, which also confirmed that olanzapine was the dominant strategy following the base-case findings. Conclusions: By comparison with risperidone, the model suggests that olanzapine can be regarded as a cost-effective therapeutic strategy for the management of patients with behavioural and psychological symptoms in Thailand.

Keywords: Dementia, Olanzapine, Risperidone, BPSD, Markov model, Sensitivity analyses, Thailand

1. Introduction

In the last decades, dementia has become a leading cause of health problems in elderly people worldwide due to the rapid growth of older populations ([1.]). The decline in cognitive abilities is called the main illness of people with dementia; however, non-cognitive symptoms of dementia are also prominent difficulties, which take place in parallel to cognitive deteriorations during the progressive nature of the disease of these people ([2.]). Dementia has been identified as constituting significant burden of several countries, especially countries that are fast becoming ageing, including Thailand. This syndrome comes together with the behavioural and psychological symptoms of dementia (BPSD). These symptoms are related to several problems for those patients, caregivers and family members, resulting in a lesser quality of life as well as a higher incidence of both economic and clinical burdens for those people.

BPSD, sometimes called neuropsychiatric symptoms, non-cognitive symptoms or behavioural disturbances, are major problems in people with dementia, which frequently occur at some point during their illness ([3.], [4.], [5.]). These symptoms, such as agitation, aggression, psychosis, wandering, sleep disturbances and oppositional behaviour, significantly impact on caregiver burden and caregiver stress intensely beyond functional as well as cognitive impairment in those patients ([6.], [7.], [8.], [2.], [5.], [9.]).

Although, no treatments have been approved for the treatment of BPSD by the US FDA leading to a variety of treatments for those patients, antipsychotics, (especially atypical antipsychotics), have been widely used and recommended by many experts as a first-line therapy to treat BPSD in clinical practice. However, these drugs are off-label for use by patients with BPSD due to some levels of concern over drug safety. Furthermore, the newer atypical antipsychotics are likely to be costlier than the older ones, leading to a restriction on a physician's decision to prescribe these drugs for patients suffering from BPSD. This also has a significant impact on patients and their caregivers when deciding on the management of BPSD sufferers.

Confirming the above claim, [10.] and [11.] observe there is currently no cure for BPSD and no FDA-approved medications for the treatment of BPSD; and that BPSD-associated symptoms are the most significant problems encountered in clinical practice. The main treatment options are focused on problematic behavioural symptoms management. The non-drug interventions or non-pharmacological approaches are recommended as the first treatment options, however, drug interventions or pharmacological approaches are applied in cases where patients are unsuccessful or do not respond to first-line treatments ([12.], [9.]).

Atypical antipsychotics are one class of pharmacological approaches, which are favourable to prescribe in patients with BPSD as first-line therapy, even though there are serious concerns over the safety. These drugs and their prescriptions are an off-label fashion for BPSD patients ([13.], [2.], [14.], and [15.]). As previously, stated, behavioural disturbances in patients with dementia have a great impact on the economic burden and health care problems of caregiving for these people ([9.]).

To date, there are a limited number of studies conducted in health economic evaluations on atypical antipsychotics used in people with dementia. There are a variety of atypical antipsychotics, including olanzapine and risperidone, that are prescribed for patients with BPSD in Thailand but these are not well defined in terms of economic evaluations. Thus, this economic evaluation may provide the information potentially to enable decision-makers in making a better-informed decision in this area

The purpose of this study is to conduct a cost-utility analysis of olanzapine compared with risperidone, for the treatment of patients with behavioural and psychological symptoms of dementia in Thailand.

2. Methods, Materials and Design

A model-based cost-utility analysis was performed to assess the health and economic impact of atypical antipsychotics, olanzapine and risperidone, in the treatment of patients with behavioural and psychological symptoms of dementia in Thailand.

Model structure

The existing model-based economic evaluations in dementia have critically been reviewed through the comprehensive literature search. The most commonly used model frameworks were adopted for developing in the different model characteristics. Then, a comparison

amongst those models was conducted and justified, before selection of the most appropriate model that was applied to the cost-utility analysis of olanzapine, compared to risperidone in the treatment of patients with BPSD in Thailand.

The model adopted in this research was an adaptation of a Markov model based on the FTC conceptual framework developed by [16.] to simulate the disease progression in patients over time. The significant concept of the model was the patients' need for FTC. The definition of the FTC was based on either the dependency or the location of care, (community or institutions), ([17.]). The patients' dependency status was assessed based on physical and functional disability. Three states the model, called "health states," of the participating patients were identified as constituting of "Not requiring FTC (Pre-FTC)," "FTC" and "death" states.

In this study, the dependency status of patients was examined by physicians and through the Activities of Daily Living (ADL) rating as assessed by the Barthel Index-Thai. The scores were categorised into four levels: a total dependence (score ranging from 0 to 4), a severe dependence (score 5-8), a moderate dependence (score 9-11), and a mild dependence (score 12 and above ([18.]). Subsequently, the FTC and Pre-FTC states were defined by a score of 0-8 and 9 and over, respectively.

Given the model structure, all patients with BPSD were possibly starting treatment with one of the two available choices, (either olanzapine or risperidone), at the beginning of the model. Those patients were also assumed to start with the Pre-FTC state. The transition of patients from one health state to another state depended on the transition probabilities to simulate how patients progressed through the health states of the model over time. The possibility of transitions between health states of those patients is outlined below.

- From Pre-FTC, there were three possible transition states, which those patients might move to. Some patients remained in their current health state (Pre-FTC), whereas some transitioned to the other possible pathways of either FTC or death state.

- From FTC state, some patients remained in the same state whilst others progressed to death.

- Death is defined as an absorbing state.

The disease progression was conducted over a one-month cycle length and the time horizon of this analysis was five years, (60 Markov cycles). These were chosen because they covered the chronically progressive disease and reflected the natural history of the disease.

This is also in line with previous studies regarding model-based economic evaluation in dementia, especially Alzheimer's disease, based on the FTC conceptual framework ([19.], [16.], [20.], [21.]). Further, Microsoft® Excel version 2013 was used to construct the decision-analytic model of this research.
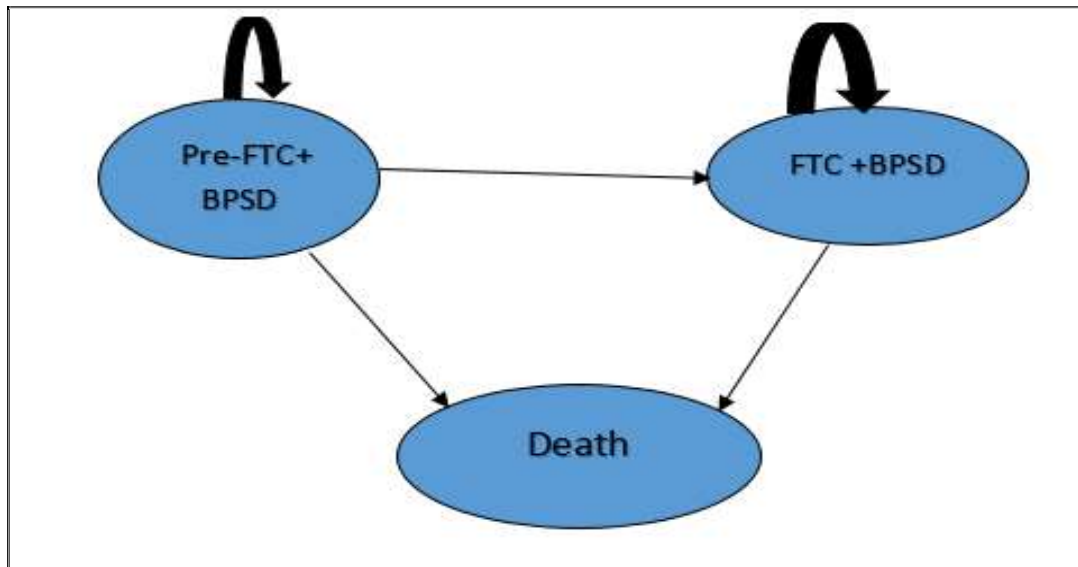
Figure 1: Diagram of the Markov Model based on the FTC Conceptual Framework for the Cost-Utility Analysis of Olanzapine compared with Risperidone

Data inputs of the model

The main parameters required for the developed model based on the FTC framework using the predictive equation to predict the time to the FTC state are outlined below.

The estimation of transition probabilities from the not requiring FTC state (Pre-FTC) to the FTC state

As stated above, the formulated model in this study reflected the disease progression, which was represented through three health states: Pre-FTC, FTC and death states. Due to unavailability of data required to predict time until patients' conditions deteriorate to a level requiring full-time care (FTC) in Thailand, we applied a new predictive equation, proposed by Rive et al., 2010. The model was developed using data from the UK longitudinal epidemiological study of 117 Pre-FTC patients with Alzheimer's disease, LASER-AD cohort ([22.]), to calculate the length of time to FTC in the model. Further, based on the LASER-AD cohort, the assessment in the cohort was at baseline, at six months and then every twelve months. Thus, the interval probabilities of reaching the FTC state were extrapolated over a five-year time horizon based on the assumption as to whether the risk of transitioning to the FTC state was constant in each time interval.

According to the predictive equation by [17.], the potential predictors for predicting the need for FTC were based on baseline values of (i.) cognition (by the Alzheimer's Disease Assessment Scale-cognitive subscale, ADAS-cog); (ii.) Function (by the Alzheimer's Disease Cooperate Study-Activities of Daily Living Scale total, ADCS-ADL); (iii.) Behaviour (as measured by the neuropsychiatric inventory total, NPI-total); and (iv.) the rates of change (slopes), in deterioration of ADAS-cog and ADCS-ADL scores.

Equations to be explored in predicting time to FTC are presented as follows:

$$p_j = 1 - \exp\left(-\exp\left(-11.1343 + 0.0330 \times ADAS - cog_{total-score}^{baseline} - 0.0877 \times ADCS - ADL_{total-score}^{baseline} + 0.0377 \times NPI_{total-scor}^{baseline} + 0.8122 \times ADAS - \right.\right.$$

$$cog_{total-scor}^{slope}\ (j) - 2.4072 \times ADCS - ADL_{total-scor}^{slope}\ (j)\big) \times \exp(3.3195 \times$$
$$\ln(interval_j))) \tag{1.}$$

Where p_j is the probability for the time interval j ; $ADAS - cog_{total-score}^{baseline}$ is the Alzheimer's Disease Assessment Scale-Cognitive Subscale at baseline; $ADCS - ADL_{total-score}^{baseline}$ is the Alzheimer's Disease Cooperative Study- Activities of Daily Living scale at baseline; $NPI_{total-scor}^{baseline}$ is the Neuropsychiatric Inventory total score at baseline; $ADAS - cog_{total-scor}^{slope}\ (j)$ is the Alzheimer's Disease Assessment Scale-Cognitive Subscale for the time interval $j;$

$ADCS - ADL_{total-score}^{slope}(j)$ is the Alzheimer's Disease Cooperative Study Activities of Daily Living Scale for the time interval j

Given the assumption of the constant risk of FTC within each time interval, the estimation of monthly transition probability to the FTC state was computed from:

$$p_{ji}^{FTC} = 1 - \sqrt[length(j)]{(1 - p_j)} \tag{2.}$$

Where p_{ji}^{FTC} is the monthly probability; p_j is the probability for the time interval j

Additionally, the calculation of the transition process from the Pre-FTC to FTC states due to drug treatments is based on three steps as follows:

a. The first step was associated with defining baseline parameters, (baseline values of ADAS-cog, ADCS-ADL and NPI and slopes of ADAS-cog, ADCS-ADL), in patients given the standard care. The standard care is defined as either patient having no pharmacological therapy or background therapy with ChEIs ([16.]).

b. At the second step, clinical effectiveness data of olanzapine and risperidone in dementia were derived from a critical review of published studies which ADAS-cog, ADCS-ADL and NPI were measured as the main clinical outcomes of such studies. For state-changes of the model, the probability was dependent on baseline parameters at the beginning and on the adopted treatment effects. Thus, the treatment effects of olanzapine and risperidone were adjusted to the baseline parameters of the standard care, providing the predictive equation parameters of each drug treatment.

c. The last step was that the predictive equation parameters of each drug were input into the predictive equation for calculating the interval probabilities of reaching the FTC state in the model.

Baseline Characteristics of Patients to Predict Time to FTC

The predictive equation to predict time to FTC was developed based on the LASER-AD cohort as this cohort was designed to be representative of the general Alzheimer's disease population (Rive et al. 2010). In addition, based on the LASER-AD cohort the distribution of patients was 30% with mild, 40% with moderate and 30% with severe symptoms of the disease. Mean age of Pre-FTC patients was 79.80 years. Approximately 69% of patients in the Pre-FTC state were women. Further, the mean ADAS-cog score was 27.20. Hypertension was predominant in the patients' medical history, (34%). The Laser-AD study also reported a prevalence of patients at 6 months post-baseline approximately 82% for agitation and 71% for psychosis ([23.], [17.]).

According to the primary data collected in Thailand, patients with BPSD were diagnosed with dementia, (ICD-10: F00-F03), or Alzheimer's disease, (G30), were included in this study (World Health Organization 2015). The cause of dementia profile of patients with BPSD was approximately 86.59% diagnosed with Alzheimer's disease, 10.98% with unspecified dementia and 2.44% with mixed dementia. Patient characteristics relevant to this study were distributed to 26.83% mild, 41.46% moderate and 31.71% with a severe classification of the disease. Associated with the Pre-FTC state, the mean age of BPSD patients was 77.54 years and mean ADAS-cog score was 29.40. A predominant comorbidity of patients with the Pre-FTC was hypertension (50.93%). Additionally, in this study, patients exhibiting signs of agitation/aggression and psychosis accounted for 60.98% and 53.66% of all cases respectively.

When considering the prediction of time to FTC, the data inputs to the equation were based on assessments on all core Alzheimer's disease domains: ADAS-cog, ADCS-ADL and NPI of patients at baseline. These assessments were frequently explored in Alzheimer's disease or dementia across several countries ([16.]). However, ADAS-cog, ADCS-ADL and NPI scores were not generally used in the routine clinical practice in Thailand. For instance, cognitive function was generally assessed using Thai Mental State Examination, (TMSE) or MMSE-Thai 2002. The "activities of living" was measured using basic activities of daily living, (bADL), and instrumental activities of daily living, (iADL), ([18.]). Whilst an assessment of BPSD was mostly based on the ABCs, approach and Four Ds approach ([24.], [18.]).

Due to a lack of data associated with baseline characteristics of patients in a Thai setting to exercise in the predictive equation, this model took baseline data from patients given the standard care in the LASER-AD study in the UK ([22.]). Further, other reasons are: (i.) the investigated patients' population in this research is similar, in characteristics to the patients' population, from which the predictive equation was developed; (ii.) the predictive equation is also applicable broadly in other settings because the developed equation was based on the general Alzheimer's disease population (Rive et al. 2010). This was consistent with the previous economic evaluation study in dementia, especially Alzheimer's disease, which used the baseline characteristics of patients given the standard care from the LASER-AD study in the UK as applied to the cost-effectiveness study in Norway ([21.]).

Estimating Transition Probabilities of dying

The transition probabilities between states to death in the study were calculated by multiplying the available data of the monthly probability on age-specific death, of 60 years and above population, and the relative risk (RR) of patients dying from Alzheimer's disease associated with the Pre-FTC and FTC health states. According to [25.], this study reveals that the relative risk of patients dying from Alzheimer's disease was 1.45 and 3.03 in the Pre-FTC and FTC states, respectively. This was in line with the cost-utility analysis of ChEIs in Alzheimer's disease in Thailand that used the same method to predict the probabilities of death of patients in the model based on the FTC conceptual framework ([20.]).

According to this study's assumption, regarding transition probabilities of death among BPSD patients receiving treatment with olanzapine or risperidone was that no treatment reflected an increased risk of mortality. This assumption was consistent with the study of olanzapine versus no treatment for the treatment of agitation and psychosis in patients with Alzheimer's disease ([26.]). Table 1 shows the monthly probabilities of dying for the general Thai population classified by age group, focusing on aged 60 and over

Table 1: Monthly probabilities of dying of the general Thai population classified by age group (The Thai working group on the burden of disease and injuries 2002)

Age group (years)	Probability
60-64	0.00119
65-69	0.00175
70-74	0.00267
75-79	0.00423
80-84	0.00667
> 85	0.01000

Clinical Effectiveness Data of Olanzapine or Risperidone

The effectiveness data were derived from a critical review of published studies through a comprehensive literature search from the electronic database between 1994 and July 2015. Clinical data for treatments were also extended to the relevant clinical trials from the references of the literature review.

In olanzapine and risperidone treated groups, the baseline characteristics of patients were adjusted with the treatment effects of both drugs derived from the clinical trials. The model assumed that patients started treatments immediately and benefits from treatments had immediate effects, resulting in modifying the time to progress from the Pre-FTC to FTC states of these patients. Further, treatment effects based on clinical trials did not evaluate the disease-modifying effects of the treatments on cognition and functioning ([27.], [28.]). Both drugs were then assumed to have no effect on the modifying of disease and on changing the rate in cognitive function and functioning over time. Based on this assumption, the treatment effects of olanzapine and risperidone did not affect or alter the speed of cognitive and functional decline, thus parameters associated with slopes of ADAS-cog and ADCS-ADL in the equation were the same values in both treatment groups. These parameters were taken data from the baseline characteristics of patients given the standard care as previously stated.

Consequently, the treatment effects of olanzapine and risperidone considered only the changes in ADAS-cog, ADCS-ADL, and NPI scores. The treatment effects from the two drugs were implemented by deducting those scores from the baseline data of patients at the beginning of the decision-analytic model. This was consistent with previous studies of the economic evaluation of memantine based on the FTC framework using the predictive equation by [16.] to estimate the time to the FTC state ([17.], [21.], [29.]).

According to the literature review, the effectiveness data of olanzapine and risperidone were obtained mainly from two published clinical trials ([27.], [28.]). Concerning cognitive function and functional ability, the effects of olanzapine and risperidone were derived from the Phase 1 outcomes. Such outcomes were measured as primary outcomes of the CATIE-AD study, which was a double-blind randomised controlled trial of 421 outpatients living with Alzheimer's disease, and are experiencing psychosis, aggression or agitation. Based on Phase 1 outcomes of the CATIE-AD study, at 12 weeks the changes in the cognition scores, (as measured by ADAS-cog), were 0.70 for olanzapine, 1.70 for risperidone and 1.30 for the placebo; however, these scores were not regarded as significant differences. For ADCS-ADL scores, the CATIE-AD study reported that the changes showed -6.10 in olanzapine-treated patients, -1.10 in risperidone-treated patients and 0.50 in the placebo group ([28.]). NPI-total scores were obtained from a study by [27.], which was a double-blind randomised controlled

trial of 496 patients with psychotic symptoms associated with dementia and are administered with either olanzapine, risperidone or placebo. According to [27.], the study reported that the changes in NPI-total scores was measured as a primary outcome of the treatment groups compared with the placebo group and were 0.50 in the olanzapine-treated group and 2.60 in the risperidone-treated group, respectively.

In addition, the study by [30.] suggested patients with Alzheimer's disease with more severe neuropsychiatric symptoms, especially agitation, aggression, or psychosis, responded well to long-term antipsychotic treatment. Consequently, the assumption of this model was that the effects of drugs were assumed to be constant over a five-year time horizon.

While **Table 2** details the baseline characteristics of patients and the clinical effectiveness data of olanzapine and risperidone, **Table 3** presents the predictive equation parameters based on treatment effects with olanzapine and risperidone were used in calculating the length of time to FTC in the model.

Table 2: Summary of the baseline characteristics of patients and the clinical effectiveness data of olanzapine and risperidone

Variable	Baseline	Olanzapine effect (Change in scores)	Risperidone effect (Change in scores)	Reference
Behavioural (NPI-total)	18.54	0.50	2.60	Deberdt et al. (2005), Rive et al. (2010)
Functioning (ADCS-ADL)	45.00	-6.60	-1.60	Sultzer et al. (2008), Rive et al. (2010)
Cognition (ADAS-cog)	36.30	-0.60	0.40	Sultzer et al. (2008), Rive et al. (2010)
ADAS-cog slope	0.6116	0.6116	0.6116	Rive et al. (2010)
ADCS-ADL slope	-0.7503	-0.7503	-0.7503	Rive et al. (2010)

* (+)/ (-), improvement of clinical outcomes from the treatments, olanzapine or risperidone

Table 3: The predictive equation parameters from treatment effects with olanzapine and risperidone for calculating the time to FTC in the model

Variable	Olanzapine	Risperidone	Reference
Behavioural (NPI-total)	19.04	21.14	Deberdt et al. (2005), Rive et al. (2010)
Functioning (ADCS-ADL)	38.40	43.40	Sultzer et al. (2008), Rive et al. (2010)
Cognition (ADAS-cog)	35.70	36.70	Sultzer et al. (2008), Rive et al. (2010)
ADAS-cog slope	0.6116	0.6116	Rive et al. (2010)
ADCS-ADL slope	-0.7503	-0.7503	Rive et al. (2010)

Subsequently, monthly probabilities of the time to the FTC state were computed based on the predictive equation parameters of each treatment using the predictive equation as presented above. The estimated monthly probabilities time to the FTC state for both treatments, olanzapine and risperidone are displayed in **Table 4**

Table 4: Monthly transition probabilities of reaching FTC state of the treatments with olanzapine and risperidone

	Interval	Olanzapine	Risperidone
p_{1i}^{FTC}	0-6 months	0.00214	0.00154
p_{2i}^{FTC}	7-18 months	0.04020	0.02917
p_{3i}^{FTC}	19-30 months	0.20038	0.14901
p_{4i}^{FTC}	31-42 months	0.49502	0.38921
p_{5i}^{FTC}	43-54 months	0.79269	0.67871
p_{6i}^{FTC}	55-60 months	0.98849	0.96011

* Probability in each model cycle

Cost data for Olanzapine and Risperidone-treated Patients with BPSD within the Health States from a Societal Perspective

Data on Costs of patients with BPSD that are treated with olanzapine and risperidone were obtained primarily, from Thammasat Hospital University and Khon Kaen Rajanagarindra Psychiatric Hospitals in Thailand through a questionnaire completed by face-to-face interviews with the outpatients and/or their caregivers. In this study, data on cost included direct medical and direct non-medical costs from a societal perspective. The direct non-medical costs of patients with BPSD included informal care. Due to the concerns over safety and relapse of atypical antipsychotic use in patients with BPSD, costs associated with adverse events and relapses were considered in the cost analysis. Thereafter which the cost data (expressed in the Thai currency at 2017 values of 1£ =45 Baht) were classified into the Pre-FTC and FTC states. Cost parameters of olanzapine and risperidone treated patients with BPSD in the model are shown in **Table 5**.

Table 5: Cost parameters for the cost-utility analysis for olanzapine compared with risperidone in patients with BPSD

Parameter	Base-case value		Source
	Mean	**(SD)**	
Cost estimations (THB)			
Direct medical costs			
Monthly drug costs			
Pre-FTC, cost per month			
Risperidone	70.51	(34.13)	Collected data in a Thai setting
Olanzapine	939.29	(588.38)	Collected data in a Thai setting
FTC cost per month			

Parameter	Base-case value		Source
	Mean	**(SD)**	
Risperidone	76.24	(21.12)	Collected data in a Thai setting
Olanzapine	1,271.97	(544.42)	Collected data in a Thai setting
Total direct medical costs			
Pre-FTC, cost per month			
Risperidone	4,324.47	(2,030.91)	Collected data in a Thai setting
Olanzapine	4,782.94	(1,938.46)	Collected data in a Thai setting
FTC cost per month			
Risperidone	5,627.54	(3,003.93)	Collected data in a Thai setting
Olanzapine	9,905.50	(7,990.77)	Collected data in a Thai setting
Direct non-medical costs			
Pre-FTC, cost per month			
Risperidone	40,392.62	(14,412.45)	Collected data in a Thai setting
Olanzapine	39,564.34	(15,404.85)	Collected data in a Thai setting
FTC cost per month			
Risperidone	47,539.49	(10,245.71)	Collected data in a Thai setting
Olanzapine	48,388.70	(18,511.68)	Collected data in a Thai setting
Total monthly costs			
Pre-FTC, cost per month			
Risperidone	44,717.09	(14,573.74)	Collected data in a Thai setting
Olanzapine	44,347.28	(16,071.51)	Collected data in a Thai setting
FTC cost per month			
Risperidone	53,167.03	(11,251.27)	Collected data in a Thai setting

Parameter	Base-case value		Source
	Mean	**(SD)**	
Olanzapine	58,294.20	(19,227.41)	Collected data in a Thai setting

* Cost in 2017 Thai currency (THB); 1£ = 45 Baht

Health-related quality of life weights, (or utility weights), of olanzapine and risperidone, treated patients with BPSD at each health state of the model

The cross-sectional survey through face-to-face interviews using the EQ-5D-5L was conducted in the outpatient's departments with BPSD patients, treated with olanzapine or risperidone at the same setting. The resulting EQ-5D-5L scores were evaluated using Thailand tariffs, based on time trade-off (TTO) and the Discrete Choice Experiment (DCE) methods, to compute and capture individual utility weights for each health state, (Pre-FTC and FTC). Utility weight parameters of olanzapine- and risperidone-treated patients with BPSD in the model are shown in Table 6

Table 6: Utility weight parameters for cost-utility analysis for olanzapine and risperidone inpatients with BPSD

Parameter	Base-case value	Source
	Mean (SD)	
Health utility weights		
Pre-FTC, utility weights		
Risperidone	0.46 (0.26)	Collected data in a Thai setting
Olanzapine	0.63 (0.30)	Collected data in a Thai setting
FTC, utility weights		
Risperidone	0.12 (0.13)	Collected data in a Thai setting
Olanzapine	0.23 (0.22)	Collected data in a Thai setting

Discount rates of the study

A discount rate of 3% per annum was applied to both costs and health outcomes; subject to the recommendation in the guideline of health technology assessment in Thailand (HITAP 2014).

3. Presentation of Result, Discussions, Limitations and Conclusion

Base-case Analysis of the Model

At the base-case scenario, the results of the cost-utility analysis were calculated in terms of an incremental cost-effectiveness ratio (ICER) as measured by incremental costs, (a difference in costs between treatment groups), divided by incremental outcomes, (a difference in quality-adjusted life years, (QALYs), of both treatments). The QALYs was a measure of survival weighted by utility values, where the utility values indicated the desirability of living in

each health state. Costs, including direct medical and direct non-medical costs, were expressed in Thai currency, reporting in 2017 value, (1 £ = 45 Baht).

The incremental cost-effectiveness ratio (ICER) used to calculate as outlined below.

$$ICER = \frac{\text{Cost of Olanzapine} - \text{Cost of Risperidone}}{\text{QALY of Olanzapine} - \text{QALY of Risperidone}} \qquad (3.)$$

Where: ICER is the incremental cost-effectiveness ratio; QALY is the quality-adjusted life-year

Sensitivity Analyses of the Model

The model underwent deterministically and probability sensitivity analyses to examine the robustness of the base-case results and conclusions.

- The deterministic sensitivity analysis was performed based on the one-way sensitivity analysis across costs, utilities and discount rates by varying each parameter. Based on this method, the costs associated with each health state were analysed by varying between plausible extremes of data based on the primary data collected in a Thai setting. The utility weights were defined by varying ± 30%. In line with the recommendations of the guideline of health technology assessment in Thailand (HITAP 2014), discount rates for costs and health benefits were varied between 0% and 6% per annum.

- Probabilistic sensitivity analyses, (PSA), using a Monte Carlo simulation were performed by varying all key parameters in a plausible range according to a pre-defined distribution based on 1,000 repetitions. Beta distributions were assigned to health utility weights. Gaussian distributions were applied to transition probabilities, whereas gamma distributions were chosen for the cost data. Based on this approach, the expected costs and expected number of QALYs for that combination of parameter values were produced. The PSA in this study was performed using Microsoft® Excel version 2013.

In this research, the cost-effectiveness acceptability curve, (CEAC) was created from 1,000 approximations using the Monte Carlo simulation based on the net monetary benefit approach. At the given willingness to pay threshold, (WTP), the cost-effectiveness acceptability curve provided the probability of the cost-effectiveness of the treatment of interest compared with the current treatment, based on the uncertainty of sampling variations of costs and outcomes and the uncertainty of an acceptable level of cost-effectiveness ratio of a decision-maker. In this study, the willingness to pay, which was the valuation of the health benefit in monetary terms, is defined as a range between THB 0 - 500,000. This was the maximum price at which a consumer will definitely pay for their health benefit ([31.])

In Thailand, the cost-effectiveness, (CE), threshold was defined at THB 160,000 per QALY for consideration regarding a cost-effectiveness strategy, which was defined by the Sub-committee of the NLEM of Thailand ([32.]). However, a range of willingness to pay for an additional QALY in Thailand was suggested at THB 59,000-285,000 (valued in 2008) by [33.]. Thus, these values, adjusted to 2017 currencies by the Consumer Price Index, were also applied in this research to consider at the price society would be willing to pay to gain an additional QALY.

Base-case Results

As Table 7 shows, over the 5 years for an evaluation based on a societal perspective, the total expected cost per BPSD patient receiving risperidone was THB 1,918,257.12 and THB 2,015,958.43 for the BPSD patient receiving olanzapine. The incremental cost associated with the use of risperidone was lower than the use of olanzapine accounting for THB 97,701.31.

The total expected outcomes as addressed in terms of QALYs were 15.45 and 10.81 for the olanzapine treated patient and the risperidone treated patient, respectively. This showed that patients treated with olanzapine had an incremental improvement in QALYs compared with those treated with risperidone, (a corresponding QALY of 4.64).

At the base-case scenario, the treatment with olanzapine in the patient with BPSD was associated with an ICER of THB 21,039.45 per QALY compared with risperidone treatment from a societal perspective

Table 7: Cost-effectiveness results in a comparison of olanzapine relative to risperidone

Strategy	Cost (THB*)	Incremental cost	Effectiveness	Incremental effectiveness	ICER
Risperidone	1,918,257.12	-	10.81	-	
Olanzapine	2,015,958.43	97,701.31	15.45	4.64	21,039.45

* Costs, THB, the year 2017 values; perspective, a societal perspective; discount rate, at 3%; 1£ = 45 Baht

One-Way Sensitivity Analyses

Based on the results under the base-case analysis in a comparison of olanzapine to risperidone, the uncertainty around the model outcome or a central value, (corresponding to the base case analysis), was validated by varying each parameter, including costs, utility weights and discount rates.

One-way sensitivity analyses were executed from several scenarios as follows: costs associated with health state were varied between maximum and minimum values of each parameter from primary data collected in a Thai setting.

Utilities were tested by a variance of ± 30%. A variation of discount rates was performed between 0% and 6% per annum. Table 8 shows parameters for one-way sensitivity analysis.

The results of the one-way sensitivity analyses are presented in the Tornado diagram. Based on the diagram, the horizontal bar with the greatest spread and on the top of the diagram was the significant parameter having the most sensitivity and greatest influence on the model outcome. Whereas the horizontal bar that, was the least spread and at the bottom of the diagram had the least sensitivity and least influence on the model outcome.

According to Figure 2, with regard to cost parameters, informal care of the olanzapine-treated patient in the FTC state had the greatest influence on the model outcome. By comparison with the base-case scenario, an increase in 51.72% of the informal care cost of olanzapine in the FTC state significantly affected a 379.81% increase in the ICER, (THB 100,946.74 per QALY). By contrast, a 77.24% decrease in the cost of informal care of olanzapine in the FTC state, resulting in a decrease in the ICER accounting for 567.17%, (THB 98,288.75 per QALY). Other most sensitive parameters were also found in informal care cost of olanzapine in the Pre-FTC state. From the base-case analysis, a 100.00% decrease in the informal care cost of olanzapine in the Pre-FTC state, resulted in a change in decreasing by 531.23% of the ICER, (THB 90,726.04 per QALY). A 56.66% increase in the informal care cost of olanzapine in the

Pre-FTC state, lead to an increase in the ICER accounting for 300.99%, (THB 84,363.50 per QALY). For informal care cost of risperidone in the Pre-FTC state, a variation of costs by a reduction of 75.08% and an increase of 49.54% from the base-case scenario was associated with an increased ICER accounting for 411.74%, (THB 107,664.36 per QALY), and a decreased ICER accounting for 271.68%, (THB 36,118.80 per QALY), respectively.

When considering parameters that had the least influence on the model outcome, the medication cost of risperidone treatment in the FTC state was found to be a significant parameter. By comparing with the base-case scenario, if the medication cost of risperidone treatment in the FTC state decreased by 30.55%, it resulted in an increase in the ICER around 0.50%, (THB 21,144.33 per QALY). By contrast, a 38.90% increase in the medication cost of risperidone treatment in the FTC state increased, leading to a decrease in the ICER accounting for 0.63%, (THB 20,905.89 per QALY).

Additionally, a variation of utility weights by $\pm$ 30% found that the utility weights of olanzapine in the Pre-FTC state had the greatest influence on the model outcome. Based on the base-case scenario, a change in utility weights of olanzapine in the Pre-FTC state from 0.63 to 0.44, (-30%), and 0.83, (+30%), was associated with an increase in 206.72% of the ICER, (THB 64,530.75 per QALY), and a decrease in 40.26% of the ICER, (THB 12,568.65 per QALY), respectively. Conversely, a variation of utility weights of risperidone in the FTC state had the least influence on the model outcome. When comparing with the base-case analysis, the ICER decreased to THB 17,828.18 per QALY, (15.26% change), if the utility weights of risperidone in the FTC state decreased by 30%. In contrast with a 30% increase in the utility weights of risperidone in the FTC state, which found that the ICER had increased to THB 25,661.72 per QALY, (21.97% change).

By varying discount rates, the ICER had a 3.18% increase, (THB 21,708.90 per QALY), from the base-case analysis if the discount rate was changed at 0% per annum. Whilst the ICER had decreased by 3.15%, (THB 20,375.26 per QALY), from the base-case analysis if the discount rate was adjusted at 6% per annum. This showed that a variation of the discount rates had a less significant impact on the ICER, accounting for 3% changed from the base-case analysis.

Table 8: Parameter for the base-case and sensitivity analyses of olanzapine or risperidone treating patients with BPSD

Model Parameter	Base-case	Sensitivity Analysis
Medication use (THB)		
Risperidone in the Pre-FTC state	70.51	26.48 to 158.85
Risperidone in the FTC state	76.24	52.95 to 105.90
Olanzapine in the Pre-FTC state	939.29	462.53 to 1,850.10
Olanzapine in the FTC state	1,271.97	462.53 to 2,134.80
Comorbidity-associated costs (THB)		
Risperidone in the Pre-FTC state	4,087.41	0 to 11,700.00
Risperidone in the FTC state	4,789.58	0 to 16,423.13
Olanzapine in the Pre-FTC state	3,832.20	0 to 10,890.00
Olanzapine in the FTC state	6,477.18	60.00 to 21,020.00
Non-medical costs for OPD visits (THB)		

| Model Parameter	Base-case	Sensitivity Analysis
Risperidone in the Pre-FTC state	2,173.87	912.98 to 11,212.98
Risperidone in the FTC state	2,433.69	1,062.98 to 4,862.98
Olanzapine in the Pre-FTC state	1,975.05	300.00 to 3,300.00
Olanzapine in the FTC state	2,106.62	1,012.98 to 5,460.00
Non-medical costs for IPD visits (THB)		
Risperidone in the Pre-FTC state	2,618.66	0 to 54,489.60
Risperidone in the FTC state	1,557.10	0 to 17,395.84
Olanzapine in the Pre-FTC state	592.65	0 to 17,779.52
Olanzapine in the FTC state	8,589.39	0 to 41,642.70
Other treatments (THB)		
Risperidone in the Pre-FTC state	1,867.41	0 to 10,000.00
Risperidone in the FTC state	3,567.29	1,200.00 to 10,000.00
Olanzapine in the Pre-FTC state	1,161.67	0 to 5,000.00
Olanzapine in the FTC state	3,190.91	500.00 to 9,500.00
Costs associated with paid caregivers (THB)		
Risperidone in the Pre-FTC state	7,861.11	0 to 20,000.00
Risperidone in the FTC state	9,382.86	4,000.00 to 15,000.00
Olanzapine in the Pre-FTC state	6,189.67	0 to 13,000.00
Olanzapine in the FTC state	10,800.00	6,000.00 to 18,000.00
Informal care costs (THB)		
Risperidone in the Pre-FTC state	29,708.61	7,404.30 to 44,425.80
Risperidone in the FTC state	33,143.06	19,744.80 to 44,425.80
Olanzapine in the Pre-FTC state	31,508.35	0 to 49,360.34
Olanzapine in the FTC state	32,532.95	7,404.05 to 49,360.34
Utility weights (± 30%)		
Risperidone in the Pre-FTC state	0.46	0.32 to 0.60
Risperidone in the FTC state	0.12	0.08 to 0.16
Olanzapine in the Pre-FTC state	0.63	0.44 to 0.82
Olanzapine in the FTC state	0.23	0.16 to 0.30
Discount rate (at 0% and 6%)	3%	0% to 6%

* Cost in 2017 Thai currency (THB); 1£ = 45 Baht
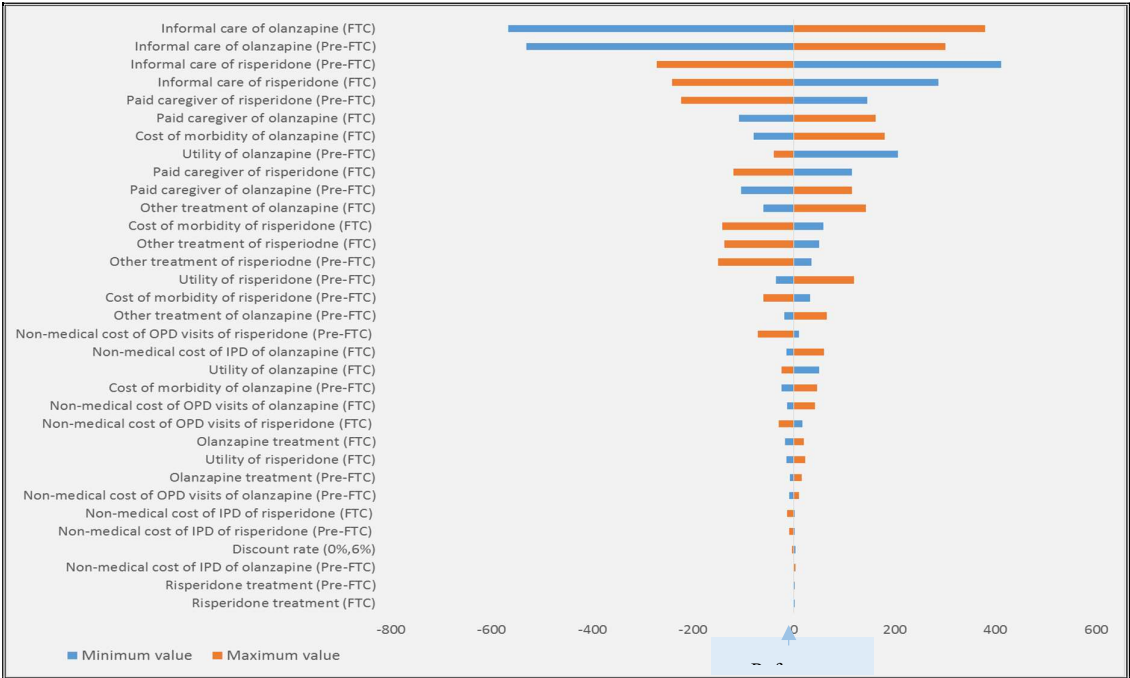
Figure 2: The Tornado diagram based on the one-way sensitivity analysis of parameters in the model

* At the base case, (or reference case): THB 21,039.45 per QALY

Probability Sensitivity Analysis (PSA)

According to **Figure 3** associated with the cost-effectiveness plane for olanzapine versus risperidone, the probability sensitivity analysis showed that olanzapine was more effective than risperidone in 98.80% at the given willingness to pay for an additional QALY at THB 500,000 based on 1,000 repeated random computations.
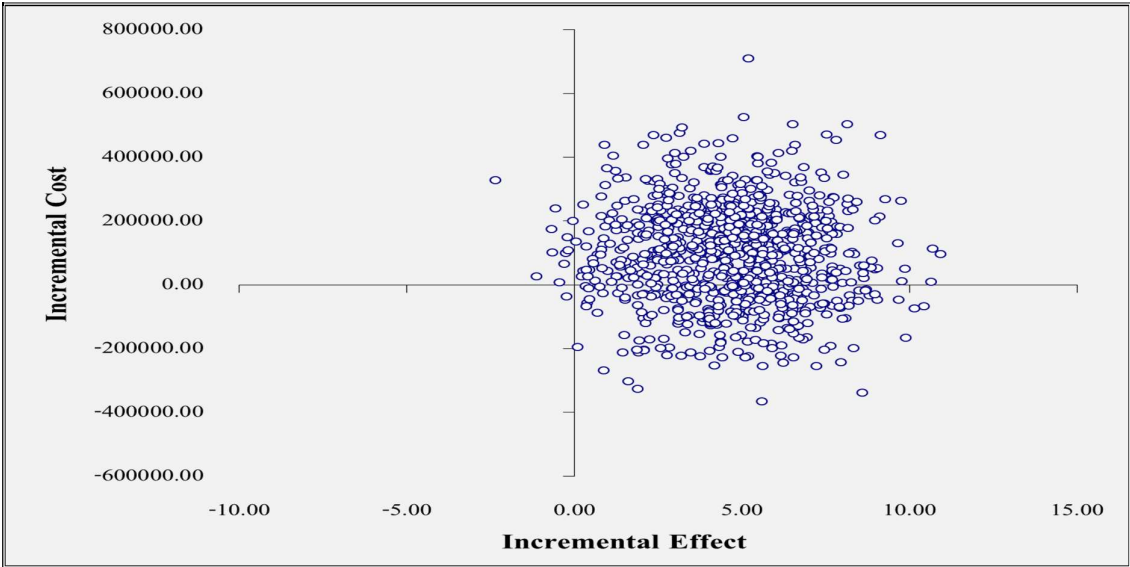

Figure 3: Cost-effectiveness plane for olanzapine and risperidone based on 1,000 PSA iterations of willingness to pay for an additional QALY at THB 500,000

Figure 4 displays the cost-effectiveness acceptability curve for the willingness to pay threshold for an additional QALY at THB 500,000. From the societal perspective, at a willingness to pay

threshold of THB 0 per QALY, risperidone had a greater probability of a cost-effective treatment than olanzapine accounting for 73% of PSA iterations. If the willingness to pay was approximately THB 21,000, this showed that the probability of olanzapine being the cost-effectiveness treatment option for BPSD patients was only 50% when compared with risperidone. Where decision-makers aimed to increase the willingness to pay threshold for an additional QALY to more than THB 21,000, olanzapine progressively increased the probability of being the cost-effective treatment. Conversely, the probability of the cost-effectiveness of risperidone was continuously decreasing as the willingness to pay more than THB 21,000 by decision-makers increased.

When considering the willingness to pay threshold per QALY at THB 59,885-289,275 (at the year 2017 values) suggested for Thailand (Thavorncharoensap et al. 2013), olanzapine was considered as the dominant therapeutic option for the treatment of patients with BPSD based on a societal perspective associated with 82.80%-98.20%.

According to the cost-effectiveness threshold for the policy-makers in Thailand, the treatment option was considered more effective, less costly and cost-effective at THB 160,000 per QALY, defined by the Sub-committee of the NLEM of Thailand ([32.]). The results showed that olanzapine was a cost-effective treatment for patients with BPSD compared with risperidone from a societal perspective, accounting for 96.6%.
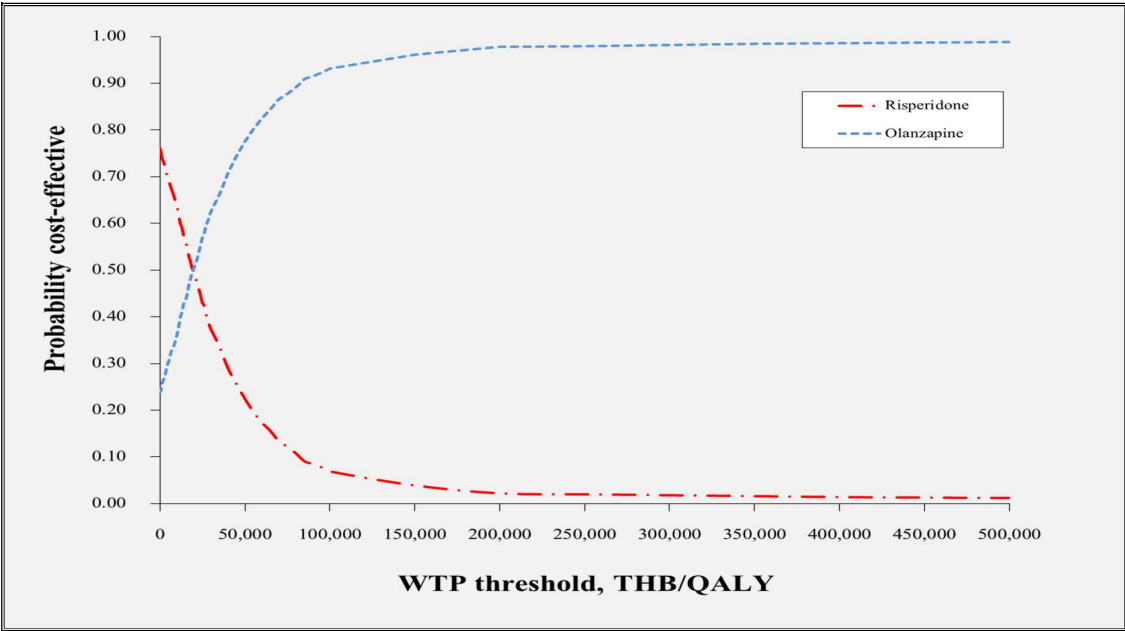
Figure 4: Cost-effectiveness acceptability curve of willingness to pay for an Additional QALY at THB 500,000 based on the societal perspective
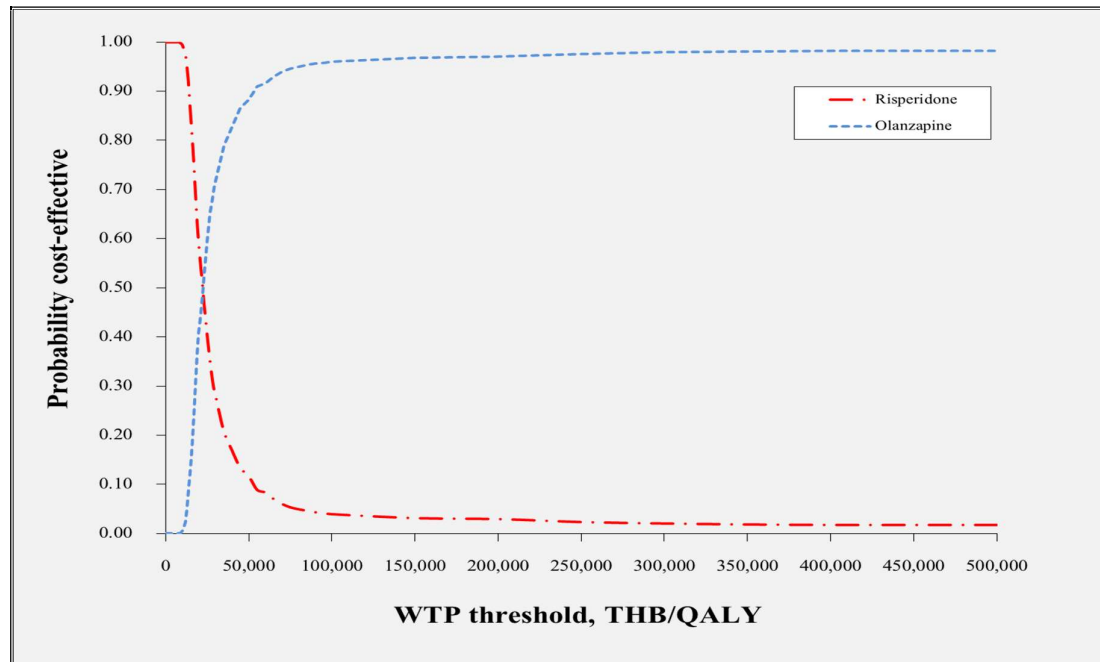** WTP, willingness to pay for an additional QALY in Thai currency, (THB), 1£ = 45 Baht

Figure 5 shows a cost-effectiveness acceptability curve from a healthcare perspective considering only direct-medical costs. This shows that risperidone had a greater probability of cost-effectiveness at a willingness to pay of THB 0 per QALY. However, at more than THB 21,867.09 per QALY of a willingness to pay, olanzapine had a greater probability of cost-effectiveness than the option treatment of risperidone. At a willingness to pay of THB 500,000 per QALY, olanzapine provided the probability of cost-effectiveness at around 98.20% compared with risperidone.

Given the willingness to pay thresholds per QALY for Thailand at a range of THB 59,885-289,275, (in the year 2017 values), according to the proposal by [33.], olanzapine was

the dominant treatment for treating of BPSD patients based on a healthcare perspective, accounting for 91.60%-97.80%.

Furthermore, based on the cost-effectiveness threshold in Thailand for policy-makers, it was defined at THB 160,000 per QALY ([32.]). The results showed that olanzapine was a cost-effective treatment for patients with BPSD compared with risperidone from a healthcare perspective, accounting for 96.80%.

Figure 5: Cost-effectiveness acceptability curve of willingness to pay for an additional QALY at THB 50,000 based on a healthcare perspective
** WTP, willingness to pay for an additional QALY in Thai currency, (THB), 1£ = 45 Baht

Discussion

The analyses presented in this study have provided information comparing the cost-effectiveness of olanzapine compared with risperidone for patients with behavioural and psychological symptoms of dementia in Thailand, using the cost-utility analysis based on the decision-analytic model, which had not been conducted previously, in Thailand and Asia in general.

From a societal perspective over five years, the results suggest that treatment of patients with BPSD with olanzapine is cost-effective, in terms of cost per QALY gained, when compared with risperidone in Thailand, accounting for THB 21,039.45 per QALY based on the cost-effectiveness threshold at THB 160,000 per QALY in Thailand.

To date, very few studies have assessed the economic impact of atypical antipsychotics for patients with BPSD. For example, in the previous study, a Markov model was constructed to examine the cost-effectiveness of olanzapine for the treatment of agitation and psychosis in adults aged 65 and above with Alzheimer's disease in the US ([26.]). The study by [26.]reported that olanzapine was the cost-effective treatment, (ICER= US 13,230 per QALY), however, the comparator used for analysis was no treatment. Thus, findings from the Kirbach's study might not be directly compared with our study because of the difference in the scope of an economic evaluation. In another study, [34.] conducted a cost-benefit analysis of atypical antipsychotics, (risperidone, olanzapine, quetiapine), compared with a placebo in Alzheimer's disease outpatients with psychosis, aggression, or agitation, based on a clinical trial with nine-month

follow up in the US. The results from Rosenheck's study suggested the placebo group had lower health costs compared with the atypical antipsychotic group, whereas the QALYs had no differences between treatments. By comparing the findings, it is evident that Rosenheck's study provided the results differ from our study. This might be partly due to the differences in medical costs and healthcare services provided between Thailand and the US as well as the methods conducted in both studies. Furthermore, the instrument used to assess health-related quality of life is different between the two studies. This study uses EQ-5D-5L, whereas the study by Rosenheck et al. (2007) applies HUI-3. This could be associated with the differences in the results, on the QALYs of both studies.

Additionally, the model in this study is constructed by adapting from the FTC model framework; however, it is different from the original model ([17.]) due to this research focusing more on patients with BPSD and requiring atypical antipsychotics for their treatments. In the previous study by Rive et al., 2010, the probabilities of dying derived data from the LASER-AD study in the UK. However, the transition probabilities of dying used in the research are estimated from the mortality rates of the available epidemiological data of the general Thai population, multiplied by the relative risks due to Alzheimer's disease from a previous study ([25.], [35.]). This might lead to more accuracy and be more reflective of data analysis within a Thai setting.

According to a sensitivity analysis, the informal care costs are the significant parameters, which have the greatest influence on the ICER. Therefore, an alteration of informal care costs of both treatments will result in the dramatic changes of the ICER. For instance, based on a comparison of olanzapine to risperidone, if the informal care cost of olanzapine in the FTC state increases as in a worst-case scenario by THB 16,827.39 from the base-case analysis, the ICER is estimated to increase at THB 100,946.74 per QALY from the base-case analysis (ICER=THB 21,039.45/QALY). Conversely, a decrease in the informal care cost of olanzapine in the FTC state as in a worst-case scenario, (THB 7,404.05), would lead to a decrease in ICER, which is associated with lower costs and higher QALYs compared to risperidone. Consequently, it indicates that as the informal care cost of olanzapine in the FTC state decreased it would be expected to see a decrease in additional costs to gain one QALY.

Furthermore, this is in line with reporting from [1.] that the informal care costs were the predominant cost of dementia in lower-and upper-income countries accounting for 40-65%. Mean informal care costs per patient with BPSD in this research are THB 31,425.84 and THB 32,020.65 for the Pre-FTC and FTC state, accounting for 62.39%-64.21% of a total cost. However, a previous study conducted in the Thai elderly with dementia in a Thai University hospital by Turongkaravee (2008), reported the informal care costs of patients with the Pre-FTC and FTC states were THB 4,814.00 and THB 25,872.00, respectively. Based on [36.], informal care costs of both states, (Pre-FTC and FTC), had lower costs when compared with our study. This might be associated with a difference in time spent in patients' care of both studies as contained in this study, focused on patients with BPSD. In addition, several studies also suggested patients with BPSD correlated with increased caregiver burden ([37.], [38.], [39.], [40.], [41.]). Therefore, we imply in this study that the occurrence of BPSD was a significant factor, leading to a greater cost of informal care for patients with dementia.

Furthermore, much of the informal care costs of patients with BPSD are associated with care inputs by caregivers and their families, which have a significant influence on the societal costs of patients with dementia. Therefore, policy-makers should exercise or interpret the results with caution if this information is adopted in the decision-making process of the reimbursement system.

However, when considering the information based on a healthcare perspective focusing only on direct medical costs, the results still show that olanzapine is the dominant treatment for

BPSD patients compared with risperidone, accounting for THB 21,867.09 per QALY under the cost-effectiveness threshold at THB 160,000 per QALY. Comparing findings between the viewpoints of societal perspective (focusing on direct medical and non-medical costs), and healthcare perspective (considering only direct medical costs), shows that ICER per QALY of olanzapine versus risperidone from the healthcare perspective has a higher value than the societal perspective, with THB 827.64 per QALY (THB 21,867.09 per QALY versus THB 21,039.45 per QALY). This might be caused by direct non-medical costs, (such as informal care costs, paid caregivers, and other treatment costs), between treatments show no significant differences. Therefore, the differences in the ICERs per QALY between a societal and healthcare perspective mainly depend on the differences in the direct medical costs of both drugs.

When considering the utility weights by varying at ±30%, the changes in values of the Pre-FTC state of both treatments show more subtle changes in ICER than the FTC state. The utility weight in the Pre-FTC state of the olanzapine treatment is the significant factor, which is related to the greatest changes in ICERs. If the utility weight in the Pre-FTC state of olanzapine changes to the plausible minimum value, the ICER has increased to THB 64,530.75 per QALY. By contrast, if it changes to the plausible maximum value, the ICER has decreased to THB 12,568.65 per QALY. Implying that if the olanzapine-treated patient in the Pre-FTC state has a more health-related quality of life it would be expected to see a decrease in additional costs to gain one QALY.

The cost-utility analysis shows that olanzapine is a cost-effective choice in the management of behaviourally disturbed patients with dementia. Validity and robustness of the results were performed by a probabilistic sensitivity analysis using the Monte Carlo simulation by randomly sampling each parameter according to pre-defined distribution for a total of 1,000 iterations.

Study Limitations

As with any model, economic evaluation has its limitations. Firstly, the predictive equation used in this research is based on the LASER-AD study deriving from the UK population ([22.]). However, that study was designed to be representative of the general Alzheimer's disease population.

Secondly, data relating to relapse requiring hospitalisation and relapse not requiring hospitalisation used to calculate the costs of patients being on olanzapine or risperidone are derived from studies of schizophrenia, due to a paucity of data of these drugs being used for the treatment of dementia patients.

Thirdly, adverse event-related costs from atypical antipsychotic drug use consider only constipation, falls and EPSs. An underestimation of costs from other hidden adverse events might occur, such as weight gain, somnolence, prolactin increase, urinary infection and cerebrovascular events ([27.], [42.]and [43.]).

Finally, a further limitation is that utility data derived from a cross-sectional survey using the EQ-5D. This then might be associated with a limitation of the study to know how changes over time were due to the two drugs. Due to this limitation, the study might be unable to answer how the drugs affect the health-related quality of life or utility weights over time, how long patients benefit from drugs after taking them and the time until patients had discontinued drugs for any reason, namely lack of efficacy, intolerability and undesirable effects. Further, current utility weights might be due to other conditions, such as improvement of co-conditions of patients.

Conclusion

The model-based economic evaluation adopted in this study suggests that olanzapine is a cost-effective treatment for patients with BPSD in Thailand when compared with risperidone, (the cost-effectiveness threshold at THB 160,000 per QALY). In essence, to the researcher's best knowledge, this research is the first study to highlight and contribute new evidence on the analysis of the cost-effectiveness of olanzapine compared with risperidone for behavioural disturbances related to patients with dementia in Thailand. In addition, the findings of this study provide useful information for behaviourally disturbed patients with dementia and support to the decision making of physicians, patients, caregivers and policymakers in providing improved treatments and suitably allocated resources for sufferers from behavioural disturbances in Thailand.

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